POTENTIAL RISK FACTORS FOR

ADVERSE DRUG REACTIONS IN ELDERLY PATIENTS

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Dekan

ES KOMMT NICHT DRAUF AN,

WIE ALT MAN IST,

SONDERN WIE MAN ALT IST.

(JOHANNES HEESTERS)

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ABBREVIATIONS

ACE	Angiotensin-converting enzyme
ADE	Adverse drug effect
ADR	Adverse drug reaction
ANF	Atrial natriuretic factor
ATC	Anatomical Therapeutic Chemical classification system
Cl_{hep}	Hepatic clearance
Cl_i	Intrinsic hepatic clearance
CNS	Central nervous system
COX	Cyclooxygenase
CYP	Cytochrome P450
DDI	Drug-drug interaction
E	Hepatic extraction of a drug
EPS	Extrapyramidal symptoms
F_u	Fraction unbound
GABA	γ-Aminobutyric acid
GFR	Glomerular filtration rate
GW	Geriatric ward
ICD-10	International Classification of Diseases, tenth revision
ICH	International Conference on Harmonization
ICU	Intensive care unit
INR	International normalized ratio
LMWH	Low-molecular-weight heparin
MW	Medical ward
NSAID	Nonsteroidal anti-inflammatory drug
OTC drugs	Over-the-counter drugs

pAI	Potentielle Arzneimittelinteraktion
pDDI	Potential drug-drug interaction
PGE_2	Prostaglandin E_2
Pgp	P-glycoprotein
PIM	Potentially inappropriate medication
PUM	Potentiell ungeeignetes Medikament
Q	Liver blood flow
SIADH	Syndrome of inappropriate antidiuretic hormone secretion
SSRI	Selective serotonin reuptake inhibitor
UAW	Unerwünschte Arzneimittelwirkung
WHO	World Health Organization

SUMMARY

Because of demographic aging the proportion of elderly persons in the population is increasing, especially in industrialized countries. Increasing age is associated with a higher prevalence of comorbidities possibly necessitating pharmacotherapy. Elderly persons are not only treated with more drugs than younger ones, but they are also more vulnerable to adverse drug reactions (ADRs). The aim of the thesis was to elucidate potential risk factors that increase the risk for ADRs in the elderly with the purpose to improve safety of medical treatment. First, the literature was reviewed in order to get an overview on the potential risk factors already known. It has been shown that not only physiological changes that affect pharmacokinetic and/or pharmacodynamic effects of drugs, but also specific drugs and drug classes may increase the risk for ADRs. Two studies were then performed to evaluate specific aspects of drug prescribing, which may enhance the risk for ADRs.

In the first study age-specific differences in the prevalence of clinically relevant potential drug-drug interactions (pDDIs) in ambulatory dyslipidemic patients treated with a statin were evaluated. Practitioners from different parts of Switzerland collected data for a total of 2'742 patients treated with a statin which attended their practice. Medical treatment was screened for clinically relevant pDDIs, defined as a DDI that could have had a potential serious outcome, using an interactive electronic drug interaction program. The prevalence of clinically relevant pDDIs was significantly higher in patients aged ≥75 years than in patients aged ≤54 years (18.4% versus 7.9%; $p < 0.001$). This was ascribed to a higher number of diseases (3.5 versus 2.8; $p < 0.001$) and pharmacologically active substances prescribed (5.8 versus 3.8; $p < 0.001$). Beside polypharmacy, also heart failure and arrhythmia have been identified as risk factors for pDDIs in elderly patients. The more frequent prescription of cardiovascular drugs with a high potential for drug interactions (e.g. amiodarone and digoxin) was mainly responsible for the observed increase in statin and non statin pDDIs.

The aim of the second study was to retrospectively evaluate and compare the prevalence of potentially inappropriate medication (PIM) use and prescription of drugs with strong anticholinergic properties in 800 elderly patients hospitalized on general medical or geriatric wards throughout hospital stay. PIMs as defined by the

Beers criteria and anticholinergic drugs have been associated with a higher risk for ADRs in patients aged ≥65 years. At hospital discharge, geriatric patients had a lower prevalence of use of PIMs that should generally be avoided than at admission (15.9% versus 22.1%; $p < 0.05$), whereas no difference was observed in medical patients. Overall, the three most prevalent inappropriate drugs/drug classes were amiodarone, long-acting benzodiazepines and anticholinergic antispasmodics. On the other hand, geriatric patients were discharged with a higher prevalence of use of PIMs that should be avoided in the presence of specific underlying diseases compared to medical patients (23.7% versus 11.7%; $p < 0.001$). The main reason was the higher prescription rate of benzodiazepines to patients with a history of falls and syncope. There was neither a difference in the prevalence of patients with anticholinergic drugs at admission nor at discharge between medical and geriatric patients. Compared with internists, geriatricians appeared to be more aware of PIMs that should generally be avoided. However, the results of this study should be interpreted with caution, because some of the drugs identified as potentially inappropriate may in fact be beneficial when the patient's individual clinical condition is taken into consideration.

Finally, a patient with lithium intoxication as a result of a drug-drug interaction (DDI) with rofecoxib is presented. This 68-year-old woman had several risk factors that finally resulted in the clinical manifestation of the DDI, illustrating well the problems of pharmacotherapy in the elderly. The already impaired renal function (calculated creatinine clearance 40 mL/min) deteriorated after the addition of rofecoxib, a selective cyclooxygenase 2 (COX-2) inhibitor. As a consequence, renal clearance of lithium was impaired, leading to an accumulation of the drug and symptoms of lithium intoxication such as vomiting, hypokinesia and tremor. Selective COX-2 inhibitors seem therefore not to be safer than conventional nonsteroidal anti-inflammatory drugs concerning their effect on renal function, especially in patients with renal insufficiency.

Depending on the underlying disease, medical treatment with drugs associated with a high potential for DDIs and/or ADRs may not always be avoided. Knowledge of the potential risk can help to take appropriate measures to lower the probability for an adverse outcome, e.g. close monitoring of the patient, dose adjustment or selection of an alternative drug.

ZUSAMMENFASSUNG

Der Anteil älterer Personen in der Bevölkerung nimmt speziell in industrialisierten Ländern stetig zu. Höheres Alter ist verbunden mit einer Zunahme von Erkrankungen und Einnahme von Medikamenten. Ältere Patienten sind allerdings häufiger von unerwünschten Arzneimittelwirkungen (UAW) betroffen. Das Ziel der vorliegenden Dissertation war es, Risikofaktoren für UAW bei älteren Patienten näher zu untersuchen, um so zu einer höheren Arzneimittelsicherheit beizutragen. In einem ersten Schritt wurden in einem Review der bestehenden Literatur mögliche Risikofaktoren eruiert. Es zeigte sich, dass nicht nur physiologische Veränderungen, welche zu einer Veränderung der Pharmakokinetik und/oder Pharmakodynamik von Medikamenten führen können, sondern auch bestimmte Medikamente respektive Medikamentengruppen mit einem erhöhten Risiko für UAW assoziiert sind. In einem weiteren Schritt wurden zwei Studien durchgeführt, um spezifische Risiken für UAW in der Pharmakotherapie älterer Patienten zu untersuchen.

In der ersten Studie wurden altersabhängige Unterschiede in der Prävalenz von klinisch relevanten potentiellen Arzneimittelinteraktionen (pAI) bei 2'742 ambulanten dyslipidämischen Patienten mit einer Statin-Therapie untersucht. Als klinisch relevant galten Interaktionen, die mit dem Auftreten schwerwiegender UAW verbunden sein können. Die Prävalenz klinisch relevanter pAI war signifikant höher in der ältesten im Vergleich zur jüngsten Patientengruppe (18.4% versus 7.9%; $p < 0.001$). Das war auf die höhere Anzahl Diagnosen (3.5 versus 2.8; $p < 0.001$) und verschriebener Substanzen (5.8 versus 3.8; $p < 0.001$) zurückzuführen. Nebst der Polypharmazie, wurden auch Herzinsuffizienz und Arrhythmie als Risikofaktoren für pAI bei älteren Patienten identifiziert. Die Zunahme an pAI mit und ohne Statinbeteiligung war hauptsächlich auf die Verschreibung von kardiovaskulären Medikamenten mit einem hohen Interaktionspotential (z.B. Digoxin und Amiodaron) zurückzuführen.

Ziel der zweiten Studie war es, retrospektiv die Prävalenz der Verschreibung von potentiell ungeeigneten Medikamenten (PUM) gemäss Beers Kriterien und Medikamenten mit anticholinergen Eigenschaften bei 800 Patienten ≥65 Jahre, welche auf medizinischen und geriatrischen Abteilungen hospitalisiert waren, während des gesamten Spitalaufenthalts zu erfassen und miteinander zu

vergleichen. Die Prävalenz der Patienten mit PUM, welche generell zu vermeiden sind, war bei geriatrischen Patienten bei Austritt im Vergleich zu Eintritt signifikant geringer (15.9% versus 22.1%; $p < 0.05$). Bei medizinischen Patienten war keine Abnahme zu verzeichnen. Die drei häufigsten PUM waren in beiden Patientengruppen Amiodaron, langwirksame Benzodiazepine und anticholinerge Spasmolytika. Im Vergleich zu medizinischen Patienten war die Prävalenz von PUM, welche aufgrund gewisser Erkrankungen vermieden werden sollten, bei geriatrischen Patienten bei Spitalaustritt signifikant höher (23.7% versus 11.7%; $p < 0.001$). Dies war hauptsächlich auf die Verschreibung von Benzodiazepinen an Patienten mit Stürzen oder Synkopen in der Anamnese zurückzuführen. Medizinische und geriatrische Patienten unterschieden sich weder bei Eintritt noch bei Austritt in der Prävalenz der Verschreibung von anticholinergen Medikamenten. Im Vergleich zu Internisten, schienen Geriater Medikamente, welche generell nicht an ältere Patienten verschrieben werden sollten, besser zu kennen. Allerdings können gewisse Medikamente, welche gemäss Beers Kriterien als potentiell ungeeignet definiert wurden (z.B. Amiodaron), durchaus einen Benefit für den Patienten bringen, wenn das Risiko individuell für den Patienten abgeschätzt wird.

Der Fallbericht einer 68-jährigen Patientin zu Lithiumintoxikation als Folge einer Interaktion mit Rofecoxib zeigte ein Zusammentreffen verschiedener Risikofaktoren, welche letztendlich zur klinischen Manifestation der Interaktion führten. Die Patientin hatte bereits eine eingeschränkte Nierenfunktion (Schätzclearance 40 mL/min), welche sich nach Gabe von Rofecoxib massiv verschlechterte. In der Folge kam es zur Akkumulation von Lithium, welches hauptsächlich renal eliminiert wird, und zum Auftreten von Nausea, Erbrechen, Hypokinesie und Tremor. Selektive Cyclooxygenase-2 Inhibitoren, wie z.B. Rofecoxib, scheinen demnach bezüglich UAW auf die Niere bei Patienten mit bestehender Niereninsuffizienz nicht sicherer zu sein als konventionelle nichtsteroidale Antirheumatika.

Es ist zu beachten, dass bei der Behandlung von Erkrankungen gewisse Risiken für UAW nicht zu vermeiden sind, welche von pAI oder dem Medikament selbst ausgehen. Dieses Risiko lässt sich allerdings durch geeignete Massnahmen wie Dosisanpassung, engmaschige Überwachung des Patienten oder Wahl eines anderen geeigneten Medikamentes erheblich reduzieren.

AIMS OF THE THESIS

The major goal of the thesis was to elucidate potential risk factors for adverse drug reactions (ADRs) in elderly patients, with the purpose to contribute to safer drug prescribing. The elderly are a growing population especially in industrialized countries and it is known that they are at higher risk for adverse effects resulting from medical treatment.

First, the literature was reviewed in order to define potential risk factors for ADRs in the elderly resulting from physiological changes as well as from polymorbidity and associated polypharmacy. From this overview, two topics were selected to be studied more in detail by two individual projects.

In the first project the association between polymorbidity as a risk factor for polypharmacy and consequently also potential drug-drug interactions (pDDIs) that may result in ADRs was investigated. The main objective of the study was to evaluate differences in the prevalence and risk factors of clinically relevant pDDIs with age in ambulatory dyslipidemic patients treated with a statin. Potentially serious and clinically relevant pDDIs with and without involvement of a statin were evaluated. This patient population was selected because of the high risk for polymorbidity, especially for the manifestation of cardiovascular diseases, and therefore also polypharmacy with increasing age. Drugs associated with a high risk for pDDIs, but often prescribed to elderly patients, were identified. The results of this study may help to recognize potentially dangerous drug combinations in order that appropriate measures can be taken in the future to minimize the risk for ADRs resulting from these drug-drug interactions (DDIs).

In the second project the prevalence of potentially inappropriate medication (PIM) use as defined by the Beers criteria and use of drugs with anticholinergic properties was evaluated in hospitalized patients aged ≥65 years. Because of age-related physiological changes and impaired homeostatic mechanisms some drugs including drugs with anticholinergic properties are associated with a higher risk for ADRs due to alterations of their pharmacokinetic and/or pharmacodynamic properties. Such drugs should therefore be replaced by safer alternatives in the elderly. Also underlying diseases or conditions were considered for the evaluation of appropriateness of treatment. The identification of frequently prescribed potentially inappropriate and anticholinergic drugs could contribute to the development of

recommendations for safer drug prescribing and selection of alternative drugs. The prevalence of use of PIMs and anticholinergic drugs of patients hospitalized to a medical and geriatric ward was compared at hospital admission, during hospitalization as well as at discharge in order to additionally elucidate the potential impact of the specific knowledge of geriatricians considering drug treatment and associated problems in elderly patients.

A case of lithium intoxication in an elderly woman with renal impairment as a result of a drug interaction between rofecoxib and lithium was included in the thesis, because several of the risk factors for ADRs identified in the review and the two studies performed predisposed the patient for the clinical manifestation of ADRs. It emphasizes the need to assess the patient's clinical condition carefully in order to avoid ADRs.

INTRODUCTION

PHYSIOLOGICAL CHANGES AND POLYMORBIDITY IN THE ELDERLY: ASSESSMENT OF THE POTENTIAL RISK FOR ADVERSE DRUG REACTIONS

Demographic aging

The process of demographic aging observed in Switzerland and other industrialized countries is mainly caused by a falling in birth rate and a simultaneous increase of life expectancy.[1,2] While in the year 2000 the proportion of individuals aged ≥65 years was 16% it will reach 28% by the year 2050 (figure 1). The oldest old (individuals aged ≥85 years) is the fastest growing segment of the older population. In the year 2000 about 141'400 individuals aged ≥85 years lived in Switzerland (2% of the total population) and it is expected that this number will increase to 554'900 inhabitants or 6.9% of the total population in Switzerland by the year 2050.[1]

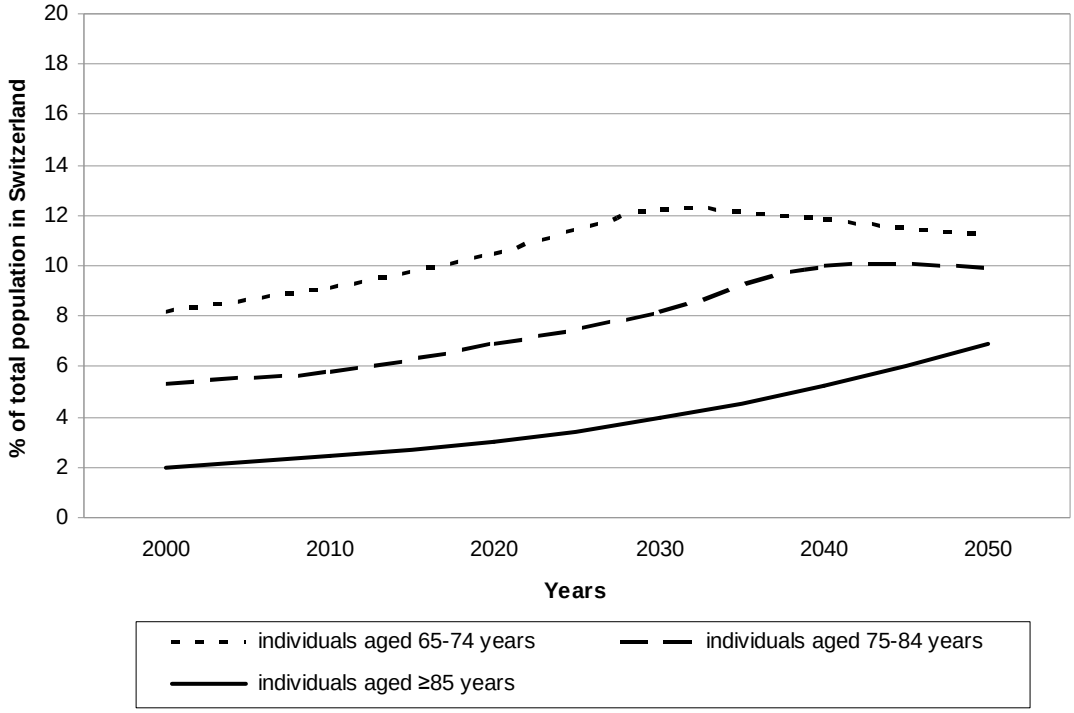

Figure 1. Demographic development of the elderly population in Switzerland based on data from the Federal Office for Statistics[1] according to the reference scenario.

The prevalence of individuals with long term diseases increases with higher age and amounts to 66-75% in individuals aged ≥65 years.[3] As a consequence healthcare costs per inhabitant raise continuously with age.[2] Considering only medication costs, prescription drugs to individuals aged >65 years accounted for 40% of the medication costs in Switzerland in the year 2002.[2] This is similar to findings in other

industrialized countries, where elderly patients constitute only 13-20% of the population, but consume 30-50% of the drugs prescribed.[3-5]

The administration of drugs may be related with adverse drug events (ADEs) or ADRs. According to the World Health Organization (WHO) an ADR is defined as any noxious and unintended reaction caused by a drug that is used at appropriate human doses for prophylaxis, diagnosis or therapy.[6] This definition does not include events resulting from medication errors, overdosage, and drug abuse, or therapeutic failure because of poor adherence, which are defined as ADEs.[7] In 80-90% of the cases an ADR can be explained by the pharmacological effect of the drug and occurs dose-dependent.[7,8] This type of reaction is defined as type A (augmented) reaction. About 10-20% of the ADRs are not foreseeable and occur normally not dose-dependent such as allergic, pseudoallergic or idiosyncratic reactions.[7,8] These ADRs are classified as type B (bizarre) reactions. It is estimated that ADRs would be the fifth leading cause of death in the United States, if they were ranked as a disease by cause of death.[9]

Elderly patients at risk for ADRs

Due to age-related physiological changes, the pharmacokinetics (absorption, distribution, metabolism and elimination) and/or the pharmacodynamics of a drug may be altered in elderly patients. These changes may be responsible for the more frequent occurrence of ADRs in the elderly, if drug therapy is not adapted (figure 2). ADRs are responsible for 6-12% of hospital admissions in the elderly.[10-12] During hospitalization, the risk to experience an ADR is further increased because of the administration of multiple drugs during a short period of time and because of treatment with drugs associated with a high potential for ADRs used only in a hospital setting.[13] As a result, up to 61% of elderly patients may experience ADRs of various severities during hospital stay.[10,13]

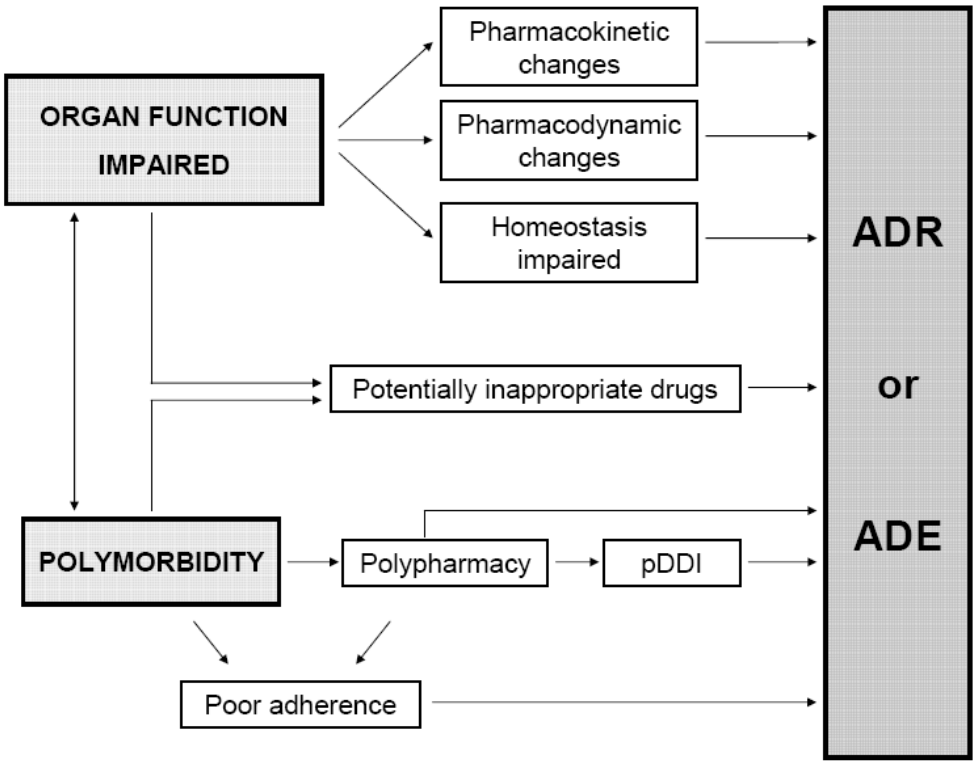

Figure 2. Age-related impairment of organ function and polymorbidity as primary factors leading to an increased risk of adverse drug reactions in the elderly. Some drugs may not be appropriate for elderly patients, because of a negative benefit-risk-ratio, or because they may exacerbate underlying diseases. ADR = adverse drug reaction; ADE = adverse drug event; pDDI = potential drug-drug interaction.

In addition to age-related physiological changes the prevalence of diseases is also increasing with age.[14] The presence of multiple diseases is correlated with polypharmacy, which is a risk factor for DDIs that may result in ADRs (figure 2). DDIs may be classified, according to their underlying mechanism, in pharmacodynamic and pharmacokinetic interactions.[15] In case of a pharmacokinetic interaction absorption, distribution, metabolism or elimination of a drug is altered by another drug. Of particular importance is the inhibition or induction of the cytochrome (CYP) P450 isozymes in the gut and liver by drugs. This is relevant for substrates whose metabolism is mainly dependent on one specific CYP isozyme. But also drugs that influence the activity of P-glycoprotein (Pgp) may play an important role.[15] Pgp is a transporter localized in intestinal epithelial cells, in the liver, kidney and blood brain barrier protecting cells from xenobiotics and toxic substances. Drug-induced inhibition of Pgp may lead to a substantial increase of the concentration of a Pgp

substrate and to dose-dependent ADRs (e.g. inhibition of Pgp-mediated transport of digoxin by quinidine). However, most of the DDIs in the elderly are pharmacodynamic interactions, resulting in a potentiation (or loss) of the pharmacological effect in a direct or indirect way. One example for a direct interaction is the antagonism of the opiate effect by naloxone, whereas the increased risk for bleeding due to concomitant treatment with nonsteroidal anti-inflammatory drugs (NSAIDs) and oral anticoagulants is an example for an indirect pharmacodynamic interaction.

The mean number of diagnoses in the elderly ranges between 2 and 7, and the mean number of drugs prescribed between 3 and 14, depending on the patient setting.[10,13,16] The prevalence of clinically relevant pDDIs increases continuously with the number of drugs administered, affecting approximately 40% of the patients if ≥7 drugs are prescribed concomitantly.[16] DDIs are responsible for up to 24% of the ADRs observed in the elderly.[10,13]

Polypharmacy and various diseases may also affect adherence (figure 2). Poor adherence may result in an exacerbation of the underlying disease, ADEs, death and an increase in health care costs.[17] Between 7-12% of hospital admissions or visits to emergency departments because of ADEs result from poor adherence.[18-20] It is estimated that the prevalence of poor adherence in elderly patients ranges between 26-59%.[20,21]

Age-related changes in organ functions and body composition affecting drug effects

Body composition

The distribution of drugs may be altered due to changes in body composition. Generally, there is a decrease in muscle mass and total body water and an increase in adipose tissue with age.[22,23] The relative changes may vary between males and females being more accentuated in males. Variations in body composition influence

the volume of distribution of drugs. An increase in body fat may increase the volume of distribution of lipophilic drugs, as shown for diazepam, and prolong their elimination half-life and duration of action.[14,24]

Age-related changes in protein binding are not considered to be of great clinical importance.[25] In the Normative Aging Study, albumin levels decreased by 0.54 g/L per decade in healthy men, but mean albumin levels of individuals in the eighth decade were still within the normal range, averaging 42.5 ± 2.6 g/L in this study.[26] More important reasons for lower albumin concentrations than age are underlying diseases such as liver cirrhosis, neoplasms, heart failure, pulmonary infections and/or malnutrition.[25,27] Displacement from albumin binding sites, e.g. through endogenous substances in patients with severe renal insufficiency, as well as low albumin levels, may increase the free fraction of drugs highly bound to albumin (e.g. oral anticoagulants, phenytoin, valproate). Since the total (free plus albumin-bound) plasma concentration of such drugs is decreased in such situations, the dosage of such drugs has to be adjusted according to their clinical effect (e.g. international normalized ratio [INR]) or to the free drug concentration.[25]

Gastrointestinal system

Gastric emptying seems to be delayed in the elderly, whereas the total gastrointestinal transit time is similar to younger adults.[28-30] Absorption of most drugs is not much affected with increasing age, except for some substances transported by active transport mechanisms such as protein-bound vitamin B_{12} or calcium.[27,31-33] Because of a slowed esophageal peristalsis, drugs ingested orally may remain longer in contact with the mucosa and may cause mucosal irritations and possibly ulcers.[27] This may be relevant for the administration of bisphosphonates or other drugs with irritant effects on the gastrointestinal mucosa such as potassium tablets. Gastric acid secretion seems not to decrease with age, but chronic atrophic gastritis has to be considered as pathological condition, leading to the exclusion of patients with this disorder.[34-36] On the other hand, mucosal protective mechanisms, e.g. mucosal prostaglandin concentrations and duodenal bicarbonate secretion, as well as gastric mucosal blood flow decrease with age.[37-39] As a consequence, the risk for gastric

mucosal injury is higher with age, especially for patients treated with NSAIDs.[37] Ibuprofen has generally been associated with the lowest risk, followed by diclofenac ≈ acetylsalicylic acid < indomethacin < naproxen < piroxicam < ketoprofen.[40,41] In addition, the risk for gastrointestinal complications following treatment with NSAIDs seems to be dose dependent.[40,41]

Liver

Liver size and hepatic blood flow both decrease with age.[15,42] Hepatic clearance (Cl_{hep}) for a given drug can be expressed as the product of the blood flow across the liver (Q) and the extraction of this drug (E) during its first passage across the liver (see formula).[43] The hepatic extraction of a drug (E) is dependent on the fraction of a drug not bound to serum proteins and the intrinsic hepatic clearance (Cl_i) that reflects the capacity of the liver to metabolize a certain drug.

$$Cl_{hep} = Q \times E = Q \times \frac{f_u \times Cl_i}{Q + (f_u \times Cl_i)}$$

For high extraction drugs (f_u x Cl_i) >> Q and the above equation can be simplified to

$$Cl_{hep} \approx Q$$

Hepatic clearance for high extraction drugs is therefore limited by the blood flow across the liver, and the decline in hepatic blood flow by up to 40% in elderly persons require dose adjustment of such drugs (table 1).[15,42-44] Hepatic metabolism of drugs consists of phase I reactions (e.g. oxidation, hydrolysis, dealkylation, reduction; many of them CYP P450-dependent) and phase II reactions (e.g. conjugation, acetylation, methylation). While phase II metabolism does not appear to be significantly reduced with age, data about phase I metabolism are not consistent.[42] In vitro, no relationship between age and the activity of various CYP isozymes isolated from microsomal preparations from liver resection specimens could be found.[15,42,45] On the other hand, data from pharmacokinetic studies indicate a reduced clearance of drugs that undergo phase I metabolism with age.[15,42,46] It can be hypothesized that a reduction

in oxygen supply to the CYP system due to age-related alterations in blood flow to the liver and diffusion of oxygen to the hepatocytes may be responsible for the impairment of phase I metabolism.[42,47] It has to be considered that pharmacokinetic parameters from in vivo studies can be influenced by many more variables than CYP isozymes assessed in vitro, including altered protein binding and volume of distribution, extrahepatic metabolism, and comedications.[15,44] A reduced activity of phase I reactions decreases the hepatic clearance of drugs with a low hepatic extraction and can be associated with an increased bioavailability of drugs with a high hepatic extraction, as demonstrated for propranolol.[48]

Table 1. Drugs with high hepatic extraction[43]

Drug class	**Examples of drugs with hepatic extraction ≥60%**
Analgesics	Morphine, pentazocine, propoxyphene
Anthelmintics	Praziquantel
Antianginal agents	Isosorbide dinitrate, nitroglycerine
Anticholinesterases	Tacrine
Antidepressants	Dibenzepin, doxepin, imipramine, mianserin, sertraline, trimipramine, venlafaxine
Antihyperlipidemic drugs	Fluvastatin, lovastatin
Antimigraine agents	Sumatriptan
Antineoplastic and immunosuppressive agents	Cyclosporine, fluorouracil, idarubicin, mercaptopurine, sirolimus, tacrolimus, vinorelbine
Antiparkinson drugs	Bromocriptine, levodopa, selegiline, biperiden
Antipsychotics	Chlorpromazine, chlorprothixene, flupenthixol, quetiapine, perphenazine, sulpiride
Beta-adrenoceptor antagonists	Labetalol, metoprolol, propranolol
Calcium channel blockers	Nicardipine, nisoldipine, verapamil
Histamine H1 receptor antagonists	Promethazine
Hypnotics, sedatives, anxiolytics	Buspirone, clomethiazole, midazolam, zaleplon
Phosphodiesterase inhibitors	Sildenafil

Heart

There are several changes in cardiac and vascular structures with age.[49,50] However, left ventricular end-diastolic volume and ventricular ejection fraction at rest are preserved with advancing age, providing adequate organ perfusion.[49,51] Elderly patients show a poor blood pressure regulation in response to orthostasis.[52-54] Impairment of baroreflex sensitivity and attenuation of the vestibulosympathetic reflex with age have been discussed as possible underlying mechanisms.[53,54] As a consequence, elderly patients are more susceptible to postural hypotension in response to drugs that lower arterial blood pressure such as antihypertensive drugs, antiparkinson drugs, tricyclic antidepressants and antipsychotics with a high affinity to α1-receptors (e.g. clozapine, chlorpromazine, risperidone).[55,56]

Kidney

Several reviews about changes in renal function with advancing age have been published.[57-59] Renal plasma flow and glomerular filtration rate (GFR) generally decline with age.[57,58] The number of functioning glomeruli declines in the elderly, while the number of sclerotic glomeruli increases.[57,58,60,61] Because of a loss of muscular mass with increasing age and a parallel decrease of urinary creatinine excretion, concentration of serum creatinine remains nearly constant with age and is therefore not a precise indicator of GFR (see also figure 3).[27,57,58,62,63] A widely used formula for the estimation of GFR, also recommended by the National Kidney Foundation, is the Cockcroft-Gault formula:[63,64]

$$\text{Creatinine clearance (mL/min)} = \frac{(140 - \text{age}) \times \text{weight (kg)}}{72 \times \text{serum creatinine (mg/dL)}} \times 0.85 \text{ for females}$$

However, the prediction of the creatinine clearance with the Cockcroft-Gault formula may not be accurate in healthy elderly individuals, for whom the creatinine clearance may be underestimated, and for malnourished patients.[63]

There is generally a decline in GFR by approximately 0.75 mL/min per year between the fourth and the eighth decade of life in healthy individuals, but GFR may remain within the normal range.[65,66] On the other hand, the mean calculated creatinine clearance of 1'837 patients aged ≥70 years admitted to an acute care geriatric medical unit was 35 ± 15 mL/min (range 5-115 mL/min), indicating that the prevalence of renal impairment may be high in elderly individuals with underlying diseases (figure 3).[27] Important risk factors for a decline in GFR are hypertension, heart failure and/or diabetes mellitus.[57,66] The high prevalence of renal impairment in elderly patients emphasizes the need to assess renal function and to perform dose adaptation of renally eliminated drugs in the elderly (table 2), since renal impairment is an important risk factor for ADRs.[5,14,57,67] Tubular function of the kidney tends to parallel the age-dependent decrease in GFR and may therefore also be approximated by calculating creatinine clearance.[59]

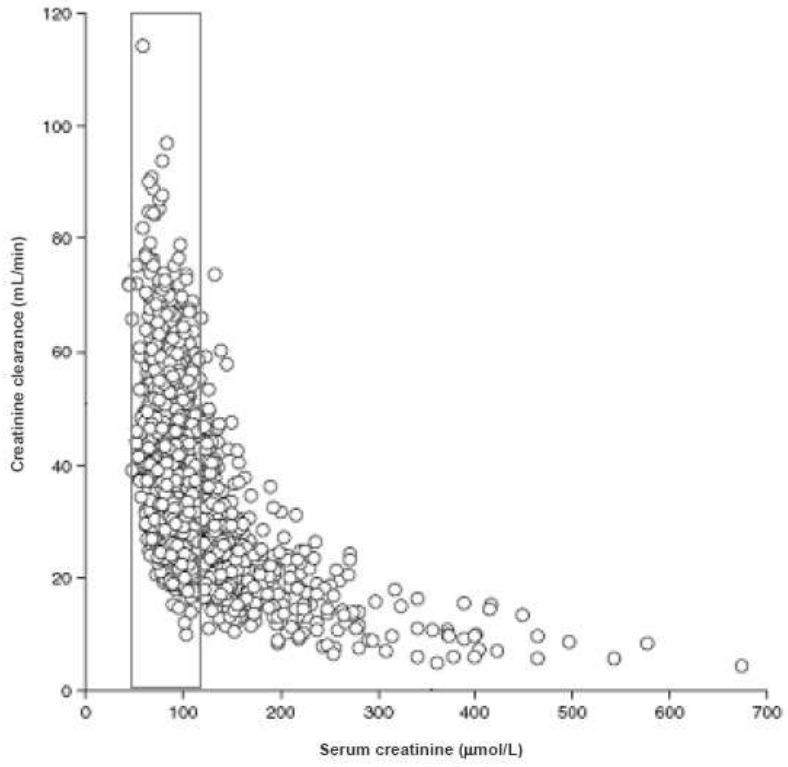

Figure 3. Creatinine clearance versus serum creatinine in 1'837 patients aged 70-103 years adapted from Merle L et al.[27]. The bar indicates the normal range of serum creatinine (45-117 µmol/L), whereas the normal range for women is 45-93 µmol/L and for men 60-117 µmol/L, respectively.

Table 2. Drugs mostly cleared unchanged through the kidney

Drug class	Drugs with a fraction of ≥60% excreted unchanged through the kidney
ACE inhibitors	Cilazapril, enalapril, lisinopril, quinapril, ramipril
Aminoglycosides	Amikacin, gentamicin, netilmicin, tobramycin
Antiallergics	Acrivastine, cetirizine, levocetirizine
Antidiabetics	Metformin
Antiepileptics	Gabapentin, levetiracetam, pregabalin, topiramate, vigabatrin
Antigout agents	Oxypurinol (major active metabolite of allopurinol)
Antimycotics	Fluconazole, flucytosine, terbinafine
Beta-adrenoceptor antagonists	Atenolol, esmolol, nadolol, sotalol
Betalactam antibiotics	Penicillins, cephalosporins, others: aztreonam, imipenem, meropenem
Cytostatics	Carboplatin, cisplatin, dacarbazine, methotrexate, pemetrexed
Digitalis glycosides	Digoxin
Fluorochinolons	Ciprofloxacin, levofloxacin, lomefloxacin, ofloxacin
Glycopeptid antibiotics	Teicoplanin, vancomycin
Histamine H2 receptor antagonists	Cimetidine, famotidine, nizatidine, ranitidine
Lithium	
Low-molecular-weight heparins	Dalteparin, enoxaparin, nadroparin, tinzaparin
Opioids	Morphine-6-glucuronide (active metabolite of morphine)
Tetracyclines	Tetracycline
Virostatics	Aciclovir, ganciclovir, foscarnet, NRTIs: adefovir, tenofovir

NRTIs = nucleoside/nucleotide reverse transcriptase inhibitors.

With advancing age, adaptive mechanisms responsible for water and electrolyte homeostasis are impaired.[57,58] Dehydration may occur more frequently in the elderly because the renal tubular response to arginine vasopressin, a hormone principally responsible for the regulation of water balance, is diminished and the perception of thirst is decreased.[68,69] Especially treatment with diuretics may markedly affect water and electrolyte homeostasis and is one of the most common reasons for electrolyte disturbances, dehydration and acute prerenal failure in the elderly.[3,58] Hyponatremia and hyperkalemia occur more frequently in the elderly due to a decrease in plasma

renin activity resulting in low aldosterone levels.[68,70] Aldosterone regulates sodium reabsorption and potassium secretion in the collecting tubule.[71] In addition, secretion of atrial natriuretic factor (ANF) is increased in the elderly.[68,72] ANF is responsible for natriuresis and inhibits the renal renin secretion, contributing to a further decrease in aldosterone levels. On the other hand, several drugs are associated with hyperkalemia, e.g. potassium-sparing diuretics, NSAIDs, angiotensin-converting enzyme (ACE) inhibitors, cyclosporine, and tacrolimus.[70,71] Serum sodium concentrations should be monitored closely when patients are treated with substances known to be associated with hyponatremia and/or the syndrome of inappropriate antidiuretic hormone secretion (SIADH) such as selective serotonin reuptake inhibitors (SSRIs), tricyclic antidepressants, carbamazepine, oxcarbazepine, vasopressin and analogues, oxytocin, vinca alkaloids, cyclophosphamide, chlorpropamide, tolbutamide, thiazide diuretics, NSAIDs and antipsychotics.[57,73,74]

Central nervous system

There is a decrease in cholinergic function in the central nervous system (CNS) with age, contributing to cognitive impairment and Alzheimer's disease.[75,76] Results from post mortem and ante mortem studies in aged humans and patients with Alzheimer's disease, as well as animal experiments, suggest that a loss of cholinergic neurons in the basal forebrain, alterations in choline transport and acetylcholine release, and muscarinic receptor expression may all contribute to the observed cognitive impairment.[75] These changes in cholinergic function could explain the higher susceptibility of elderly patients to central anticholinergic drug effects resulting from treatment with highly anticholinergic drugs such as some of the antipsychotic agents (e.g. clozapine, chlorpromazine), tri- and tetracyclic antidepressants, first generation histamine H1 receptor antagonists, anticholinergic antiparkinson agents and antispasmodics.[77]

Regarding benzodiazepines, it is not fully established, if pharmacokinetic and/or pharmacodynamic changes lead to the observed higher risk for ADRs in the elderly.[33] Nevertheless, it is suggested that changes in the affinity of benzodiazepines to the

γ-aminobutyric acid type A ($GABA_A$) receptor due to age-related alterations in the expression of its subunits could influence the effects of benzodiazepines that are mediated by distinct $GABA_A$ receptor subunits.[78]

Dopaminergic neurotransmission in the CNS is involved in many aspects of human behavior including motor function, cognitive performance and mood.[79] Ascending dopaminergic neurons degenerate with age, along with postsynaptic dopamine receptors as shown for D1 and D2 receptors in the striatum.[80] These changes in dopaminergic neurotransmission may contribute to the occurrence of Parkinson's disease, cognitive impairment, and more frequent manifestation of extrapyramidal symptoms (EPS) following treatment with conventional antipsychotics in the elderly.[79-82] It is assumed that a 60-70% occupancy of D2 receptors is required for an antipsychotic response.[83] On the other hand, a rise above 80% seems to increase the incidence of EPS. In comparison with conventional agents, the risk of tardive dyskinesia during treatment with atypical antipsychotics is lower, which may be explained by a lower D2 occupancy at usual therapeutic doses.[83] However, D2 occupancy increases with the dosage of atypical antipsychotics used.[84] Atypical antipsychotics are associated with other ADRs than EPS, namely weight gain, diabetes, cardiac effects or sexual adverse effects.[83]

Polymorbidity and polypharmacy increasing the risk for ADRs in the elderly

Treatment of cardiovascular diseases and associated risk for ADRs

The most frequent diagnoses in the elderly are hypertension, ischemic heart disease, heart failure, cerebrovascular diseases, atrial fibrillation, and diabetes mellitus.[10,85,86] Age-related changes in vascular and cardiac structures may contribute to the high prevalence of cardiovascular diseases observed in the elderly, lowering the threshold for the manifestation of rhythm disorders such as atrial fibrillation and heart failure

that are induced by other factors.[49] For the treatment of cardiovascular diseases, often several drugs are needed, predisposing the patients to polypharmacy and related problems. In addition, patients with cardiovascular diseases often have predisposing risk factors such as type 2 diabetes mellitus and/or hyperlipidemia that also require medical treatment and further increase the risk for polypharmacy and pDDIs.

Drugs used in the treatment of cardiovascular and associated disorders such as amiodarone, diuretics, calcium channel blockers, digoxin, ACE inhibitors, oral anticoagulants, insulin or oral antidiabetics are often involved in ADRs observed in the elderly.[5,10,12,67,87] These are the same drugs that are also often causing DDIs, potentially resulting in ADRs (table 3).[88-90] Most of these ADRs observed in the elderly are dose-dependent reactions that may at least partially arise from age-related physiological changes.[18,87] Equally, most of the DDIs identified are pharmacodynamic interactions that result in a potentiation (or loss) of the pharmacological effect of the affected drug (table 3).[89] Because of impaired homeostatic mechanisms, the elderly may be particularly sensitive to this kind of DDIs.

A potentially serious pharmacodynamic DDI is the combination of ACE inhibitors with potassium sparing diuretics or potassium supplements, increasing the risk for hyperkalemia in predisposed elderly patients (see also age-related changes of the kidney).[91] The combination of ACE inhibitors with 25 mg spironolactone has proven to reduce mortality in patients with severe congestive heart failure.[92] However, more than 15% of the patients treated with spironolactone on top of an existing treatment for heart failure will develop clinically relevant hyperkalemia, especially patients with impaired renal function and poor monitoring.[93,94]

Digoxin toxicity has also been reported as a frequent ADR leading to hospital admission.[10,67,87] An important risk factor for digoxin toxicity is impairment of renal function, leading to reduced digoxin clearance and accumulation of the substance.[95] DDIs may also be responsible for the enhanced toxicity observed. Thiazide/loop diuretics may enhance the inhibition of Na-K-ATPase associated with digoxin secondary to diuretic induced hypokalemia and hypomagnesemia.[91] Digoxin serum

Table 3. Common drug-drug interactions (DDIs) and potential adverse drug reactions (ADRs) in the elderly[88-91,96,97]

Drug or drug class	Interacting drugs	Mechanism	Expected ADR due to DDI
Digoxin	Loop/thiazide diuretics	Enhanced inhibition of Na-K-ATPase	Digoxin toxicity
	Pgp inhibitors e.g. clarithromycin, quinidine, verapamil, amiodarone	Pgp inhibition	Digoxin toxicity
	Beta-adrenoceptor antagonists	Additive effects	Bradycardia, AV block
ACE inhibitors	Potassium sparing diuretics/potassium supplements	Additive effects	Hyperkalemia
	NSAIDs	Additive impairment of kidney function	Hyperkalemia, renal failure
Oral anticoagulants	CYP inhibitors e.g. amiodarone, cimetidine, clarithromycin, cotrimoxazole, fluconazole, metronidazole	Decreased metabolism	Bleeding
	CYP inducers e.g. barbiturates, carbamazepine, rifampicin, St. John's wort	Increased metabolism	Thromboembolism due to reduced anticoagulant effect
	Low dose acetylsalicylic acid, clopidogrel, NSAIDs	Additive effects (platelet aggregation inhibition, gastric erosion for NSAIDs)	Bleeding
Insulin/oral antidiabetics (sulfonylureas, glinides)	Beta-adrenoceptor antagonists	Masking of hypoglycemic effect	Severe hypoglycemia
	Other antidiabetics or insulin	Additive effects	Hypoglycemia
	CYP 2C8/9 inhibitors e.g. cotrimoxazole, gemfibrozil, fluconazole	Decreased metabolism	Hypoglycemia
Tricyclic antidepressants Antipsychotics[a]	Other anticholinergic drugs e.g. some antispasmodics, antiparkinson agents (biperiden, amantadine), first generation histamine H1 receptor antagonists	Additive anticholinergic effects	Xerostomia, blurred vision, urinary retention, tachycardia, confusion, cognitive impairment, delirium
Sedative hypnotics	Other sedative drugs e.g. first generation histamine H1 receptor antagonists, antipsychotics with high affinity to histamine H1 receptors (e.g. chlorpromazine, chlorprothixene, clozapine, quetiapine), maprotiline	Additive sedative effects	Excessive sedation, confusion, falls

[a]Antipsychotics with high affinity to muscarinic receptors e.g. clozapine and phenothiazines.

AV = atrioventricular; CYP = cytochrome P450; NSAIDs = nonsteroidal anti-inflammatory drugs; Pgp = P-glycoprotein.

concentrations may also indirectly be raised due to NSAID-induced renal failure.[98] Inhibitors of Pgp increase digoxin serum levels, because digoxin is a Pgp substrate.[95]

The calcium channel blockers diltiazem and verapamil, and the antiarrhythmic agent amiodarone are often involved in pharmacokinetic pDDIs. Diltiazem and verapamil are inhibitors of CYP 3A4 and Pgp (verapamil > diltiazem).[99-101] Amiodarone and its active metabolite desethylamiodarone are potent inhibitors of various CYP isozymes (CYP 1A1/2, 2A6, 2B6, 2C9, 2C19, 2D6, 3A4) as well as of Pgp, and may like diltiazem and verapamil enhance the risk for dose-dependent ADRs of CYP and Pgp substrates such as lipophilic statins.[97,102,103]

The bleeding risk during treatment with oral anticoagulants seems to be increased in the elderly as suggested by a hazard ratio of 2.7 (95% confidence interval (CI) 1.7-4.4) in patients older than 80 years compared to patients younger than 60 years, without major differences in achieved intensities of anticoagulant treatment.[104] It has been hypothesized that comorbidities may play a role, because potential bleeding sites may be a consequence of other diseases or because actual bleeding may be worsened, e.g. by hypertension.[104] In addition, the comedication and changes in the pharmacokinetics of coumarins may be reasons for higher bleeding rates in the elderly.[104] Amiodarone is known to inhibit the metabolism of warfarin resulting in prolongation of the INR and increased risk of bleeding,[105] if the warfarin dose is not adapted. The dosage of warfarin has to be reduced by 25-40%, depending on the amiodarone maintenance dose. The relative risk for a hemorrhagic gastrointestinal ulcer is increased by 12.7 (95% CI 6.3-25.7) in elderly patients using oral anticoagulants in combination with NSAIDs as compared to patients not using NSAIDs.[106] Additive pharmacological effects and/or ADRs such as impairment of platelet aggregation, NSAID-induced gastric erosions or ulcers may primarily contribute to the increased risk of gastrointestinal hemorrhagic complications in NSAID users.[106]

Hypoglycemia occurs more often in elderly patients treated with secretagogue antidiabetics such as sulfonylureas or glinides (nateglinide, repaglinide) as compared to non secretagogue oral antidiabetics, because glucose counterregulation seems to

be impaired with age.[107] Hypoglycemia may also result from DDIs with other hypoglycemic agents or CYP inhibitors, especially inhibitors of CYP 2C8/9 (table 3).[96]

Treatment with centrally acting drugs and associated risk for ADRs

Beside cardiovascular drugs, elderly patients are also often treated with drugs affecting the CNS, namely benzodiazepines, antidepressants (including SSRIs), antipsychotics or analgesics.[13]

Drug-induced cognitive impairment in the elderly has been associated with tricyclic antidepressants, other drugs with anticholinergic properties, pethidine and benzodiazepines.[108,109] Additionally, these drugs may contribute to the manifestation of delirium in predisposed elderly patients, e.g. those with cognitive impairment.[109,110] The prevalence of delirium may be high in a hospital setting, ranging between 14-24% at hospital admission, whereas the incidence of delirium arising during hospital stay may reach up to 56%.[111] About two thirds of cases of delirium occur in patients with dementia.[111] Patients treated with long-acting benzodiazepines at high doses are at higher risk for delirium as compared to those exposed with short-acting benzodiazepines at low doses.[110] Delirium has also been associated with elevated serum anticholinergic activity that results often from additive anticholinergic effects of different drugs.[112] In accordance, also antipsychotics with strong anticholinergic properties such as clozapine and phenothiazines have been reported to induce delirium.[113] This is not the case for haloperidol and some atypical antipsychotics (e.g. risperidone, olanzapine, quetiapine), which are used for prophylaxis and treatment of delirium.[56,111] Less serious peripheral manifestations of drugs with anticholinergic effects include dry mouth, tachycardia, blurred vision, urinary retention, and obstipation. Nevertheless, these ADRs may exacerbate underlying clinical conditions such as obstipation, xerostomia, glaucoma, and urinary retention that are common in elderly patients.[114] Administration and especially combination of drugs with strong anticholinergic properties (e.g. antipsychotics such as clozapine or chlorpromazine, tricyclic antidepressants, first generation histamine H1 receptor antagonists) should therefore be avoided in the elderly.[89]

Another ADR of special concern in the elderly associated with the use of centrally acting drugs such as antidepressants, antipsychotics and benzodiazepines (long- and short-acting) is the increased risk of falls and fractures.[115-119] Falls are a serious problem in the elderly and are associated with increased morbidity and mortality.[120] About 30-40% of community-dwelling adults aged ≥65 years fall each year, what may lead to serious injuries such as hip fractures or head trauma.[120] Clinical conditions contributing to the increased risk of falls in the elderly are gait disturbance, muscle weakness, dizziness, vertigo, drop attacks, visual impairment, confusion, or postural hypotension.[120] Use of centrally acting drugs such as tricyclic antidepressants, antipsychotics and benzodiazepines (with long and short half-life) may additionally increase the risk of falls and fractures.[115-119] Some studies also report an association with SSRIs.[115,116] However, the risks reported for the individual members of these drug classes markedly vary between different studies, probably due to the multifactorial etiology of falls.[120] The combination of drugs with additive sedative effects should be avoided in the elderly, because the risk for falls and confusion may be further enhanced.[89]

Potentially inappropriate medications increasing the risk for ADRs

Some drugs may not be appropriate for the treatment of elderly patients, because the risk for ADRs outweighs the possible clinical benefit.[121] The Beers criteria provide a list of drugs that should generally be avoided in patients aged ≥65 years or that should not be given to elderly patients with specific underlying diseases.[121] The expected increase in ADRs in elderly patients treated with such drugs results from age-related, physiological changes, favoring the manifestation of dose-dependent reactions. Examples of drugs listed by Beers and commonly prescribed to elderly patients include nitrofurantoin (concern: renal adverse effects), long-acting benzodiazepines (concern: prolonged sedation, increased risk of falls and fractures), amitriptyline (concern: strong anticholinergic and sedation properties), doxazosin (concern: potential for hypotension, dry mouth, urinary problems), amiodarone (concern: prolongation of QT interval, torsade de pointes) and estrogens (concern: carcinogenic potential).[122-124]

Poor adherence following polymorbidity and polypharmacy

Polymorbidity and polypharmacy are not only associated with an increased risk for ADRs and DDI-related ADRs, they may also lead to poor adherence and cause additional ADEs in the elderly. Some predisposing factors for poor adherence in elderly patients include type of disease, severity and duration of the illness, the number of comorbidities as well as the number of drugs prescribed.[21] The presence of psychological problems, impairment of cognitive functions, vision and/or hearing, decrease of manual dexterity and occurrence of ADRs may significantly contribute to poor adherence.[17,21] In addition, adherence for a specific drug is inversely proportional to the frequency of doses per day.[17] Problems of adherence have especially been reported for the treatment of chronic cardiovascular diseases such as hypertension or heart failure, type 2 diabetes, hyperlipidemia, as well as for psychiatric disorders such as depression.[17,125-128]

STUDY I

AGE-RELATED DIFFERENCES IN THE PREVALENCE OF POTENTIAL DRUG-DRUG INTERACTIONS IN AMBULATORY DYSLIPIDEMIC PATIENTS TREATED WITH A STATIN

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Abstract

Background and objective: Elderly patients may be at higher risk of DDIs due to polypharmacy. This study evaluated age-specific differences in the prevalence of clinically relevant pDDIs in ambulatory dyslipidemic patients treated with a statin. We hypothesized that elderly patients are at higher risk for pDDIs due to the presence of more drugs and drugs with a higher potential for DDIs.

Methods: In this cross-sectional study, a total of 2'742 dyslipidemic ambulatory patients treated with a statin were included. Drug treatment was screened for clinically relevant pDDIs using an electronic drug interaction program (Drug Reax®).

Results: There were 483 (17.6%) patients aged ≤54 years, 732 (26.7%) aged 55-64 years, 924 (33.7%) aged 65-74 years, and 603 (22.0%) patients aged ≥75 years. Patients ≥75 years had significantly more pharmacologically active substances prescribed than patients aged ≤54 years (5.8 versus 3.8; $p < 0.001$). Cardiovascular diseases such as coronary heart disease, heart failure or arrhythmias were significantly more prevalent in patients aged ≥75 years than in younger patients. The overall prevalence of pDDIs increased significantly from 7.9% in those aged ≤54 years to 18.4% in patients aged ≥75 years ($p < 0.001$). The frequency of both pDDIs associated with statins and non statin pDDIs increased with age. Risk factors for pDDIs in patients aged ≥75 years were arrhythmias, heart failure, and the number of pharmacologically active substances prescribed. The more frequent prescription of cardiovascular drugs with a high potential for pDDIs (e.g. amiodarone and digoxin) was mainly responsible for the observed increase in statin and non statin pDDIs.

Conclusion: As compared to younger patients, elderly dyslipidemic patients are at a higher risk for clinically relevant pDDIs, mainly due to a higher number of drugs prescribed. In addition, patients aged ≥75 years were prescribed more drugs with a high potential for DDIs, especially drugs used for the treatment of arrhythmias and heart failure. The risk for adverse reactions following pDDIs may often be reduced by dose adjustment, close monitoring or selection of an alternative drug.

Introduction

Concomitant administration of two or more drugs may lead to alterations of the therapeutic effect of one drug by another due to pharmacokinetic and/or pharmacodynamic interactions. The prevalence of pDDIs in patients with polypharmacy may be as high as 68%, depending on the patient setting and the definition of pDDIs.[13,90,129,130] However, the fraction of pDDIs actually resulting in serious negative consequences for the affected patient, is relatively small.[15,129,131] The proportion of hospital admissions due to DDIs ranges between 0-3%.[132] In geriatric inpatients, up to 15% of the patients hospitalized may experience mild to moderate ADRs due to DDIs.[13] Known risk factors for pDDIs are the number of drugs prescribed and advanced age.[89,129,133] Due to reduced homeostatic mechanisms and age-related pharmacodynamic and pharmacokinetic changes, elderly patients may be more sensitive to adverse effects resulting from DDIs.[89]

Dyslipidemic patients treated with a statin are likely to receive several other drugs due to the presence of various comorbidities such as cardiovascular diseases or diabetes mellitus. Potential DDIs may therefore be quite common in this group of patients. The aim of our study was to explore age-related differences in diagnoses, associated prescription of drugs and pDDIs in ambulatory dyslipidemic patients treated with a statin. We hypothesized that pDDIs were more prevalent in the elderly not only because of exposure to a higher number of drugs, but also because of the prescription of drugs with a higher potential for DDIs.

Methods

Study population and data collection

Between February and April 2002 practitioners from different parts of Switzerland participated in the cross-sectional Swiss Analysis Focused on the Evaluation of potential drug interactions (SAFE) trial. They collected data during five consecutive

days for all dyslipidemic patients treated with a statin which attended their practice. The study is described in detail elsewhere.[16,91] For all patients, demographic data such as age, sex, actual diagnoses, the statin and comedication prescribed were recorded. Physicians were asked also to record over-the-counter (OTC) preparations taken by the patients. Diagnoses were coded according to the International Statistical Classification of Diseases version 10 (ICD-10) and drugs were coded according to the WHO Drug Dictionary (version 01-3, third quarter 2001). The medication profiles of all patients were screened for pDDIs using the online version of DrugReax®, an interactive database for drug interactions.[134]

Classification of clinically relevant potential DDIs

A pDDI involving a statin was considered clinically relevant if a) the prescribed statin was combined with a known inhibitor of its metabolism and/or transport, or b) at least one case report has been published describing a harmful reaction caused by the specific drug combination, and c) the combination could have had a potential serious outcome. A serious outcome was defined according to the International Conference on Harmonization (ICH) guidelines for clinical safety data management of ADRs[135] as an event that may result in death, be life-threatening, require or prolong hospitalization and/or result in persistent or significant disability. Potential DDIs not involving a statin were considered to be clinically relevant if the expected outcome could have been serious (definition see above for statins). These included pDDIs of 'major severity' according to the drug interaction program DrugReax® or, if not recognized by DrugReax®, according to other information sources such as standard literature,[136,137] an additional online drug interaction database[138] and/or Medline. In addition, each pDDI identified was checked by a pharmacist and a clinical pharmacologist if the criteria for clinical relevance were fulfilled. A pDDI was not considered clinically relevant, despite a rating of 'major severity' according to DrugReax®, if the interaction did not correspond to the actual clinical situation. For example, the interaction between ACE inhibitors and diuretics was not considered clinically relevant in patients under long-term treatment. The indicated risk of first-dose hypotension (classification: 'major severity') does no longer exist in this case

and does therefore not reflect the actual clinical situation. Also topical treatment with ketoconazole in a patient treated with a CYP 3A4 substrate was not considered to be clinically relevant.

Statistical analysis

Patients were classified into four different age groups, i.e. ≤54 years, 55-64 years, 65-74 years and ≥75 years. Potential differences of numerical variables between age groups were analyzed with one-way ANOVA, or with Pearson's chi-square test for categorical variables. Because of multiple testing, the significance level was adjusted according to Bonferroni-Holm.[139] Significance was assessed for the corrected 5%, 1% and 0.1% significance levels. The exact method was used to calculate 95% CI for proportions.[140] Differences in the number of specific pDDIs between age groups were not analyzed statistically, because of the limited number of pDDIs identified.

Logistic regression analyses using a backward elimination procedure with Wald statistics and likelihood-ratio statistics were performed to identify risk factors for the occurrence of clinically relevant pDDIs separately for each of the 4 different age groups. As explanatory dichotomous variables sex, German-, French- or Italian-speaking part of Switzerland, professional specialty of the practitioner (internist, cardiologist or other), diagnosis of hypertension, diabetes mellitus, coronary heart disease, heart failure, arrhythmias, depression/psychiatric disorders, cerebrovascular diseases, rheumatic diseases, disorders of the musculoskeletal system, gout/hyperuricemia, epilepsy or other diagnoses, and use of pravastatin were included in the model. Continuous numerical variables included in the model were age, number of diagnoses, number of pharmaceutical preparations and number of pharmacologically active substances prescribed. Explanatory variables with a p-value <0.1 were included in the final model. Relative risk estimates are expressed as odds ratios (OR) with 95% CI.

Statistical analyses were performed with SPSS for Windows version 13.0 (SPSS Inc., Chicago, USA).

Results

Of the 2'753 patients initially registered in this cross-sectional study, 11 patients were excluded (10 patients were not receiving a statin, 1 patient was prescribed cerivastatin, which was withdrawn from the market in 2000). The mean age (± SD) of the study population (n = 2'742; 61.6% male) was 65.1 ± 11.2 years. There were 483 (17.6%) patients aged ≤54 years, 732 (26.7%) patients aged 55-64 years, 924 (33.7%) patients aged 65-74 years and 603 (22.0%) patients aged ≥75 years. Patient characteristics are presented in table 4. The proportion of female patients increased significantly from 27.1% in the ≤54 years-old to 46.3% in the group of patients ≥75 years ($p < 0.001$). On average, patients ≥75 years of age had significantly more diagnoses (3.5 versus 2.8; $p < 0.001$) and more pharmacologically active substances prescribed (5.8 versus 3.8; $p < 0.001$) than patients aged ≤54 years. However, the number of active compounds prescribed to older patients is not only a function of the number of diagnoses, since the average number of substances per diagnosis increased with higher age (1.52 ± 0.90 in the group of patients aged ≤54 years versus 1.88 ± 1.10 in the group of patients aged ≥75 years; $p < 0.001$). Hypertension, coronary heart disease and diabetes mellitus were the three most prevalent comorbidities in the whole study population with overall prevalences of 52.1%, 42.5% and 19.0%, respectively. There was a significant increase in the prevalence of hypertension, coronary heart disease, heart failure, arrhythmias and cerebrovascular diseases with increasing age, whereas the prevalence of depression and/or psychiatric disorders was significantly decreased in older as compared to younger patients.

Cardiovascular drugs were most often prescribed concomitantly with a statin (see table 5). The prescription frequency for low dose acetylsalicylic acid, beta-adrenoceptor antagonists, thiazides and/or loop diuretics, ACE inhibitors, calcium channel blockers (dihydropyridines, verapamil, diltiazem), oral anticoagulants (phenprocoumon and acenocoumarol; warfarin is not marketed in Switzerland), potassium-sparing diuretics, amiodarone, and digoxin increased significantly with advancing age. Only the prescription of antidepressants was significantly lower in patients aged ≥75 years compared to patients aged ≤54 years ($p < 0.01$), reflecting

Table 4. Patient characteristics and comorbidities of 2'742 patients with dyslipidemia stratified by age groups

Characteristics	Total (n = 2'742)	Age groups (years) ≤54 (n = 483)	55-64 (n = 732)	65-74 (n = 924)	≥75 (n = 603)	p-value
Female, n (%)	1'052 (38.4)	131 (27.1)	251 (34.3)	391 (42.3)	279 (46.3)	<0.001
Number of diagnoses, mean ± SD	3.3 ± 1.55	2.8 ±1.42	3.1 ± 1.54	3.4 ± 1.54	3.5 ± 1.56	<0.001
Number of active substances prescribed including statins, mean ± SD	4.9 ± 2.37	3.8 ± 2.15	4.5 ± 2.22	5.2 ± 2.36	5.8 ± 2.34	<0.001
Number of active substances per diagnosis, mean ± SD	1.71 ± 0.98	1.52 ± 0.90	1.70 ± 1.00	1.70 ± 0.93	1.88 ± 1.10	<0.001
Hypertension, n (%)	1'428 (52.1)	187 (38.7)	363 (49.6)	537 (58.1)	341 (56.6)	<0.001
Diabetes mellitus, n (%)	520 (19.0)	74 (15.3)	132 (18.0)	211 (22.8)	103 (17.1)	<0.01
Coronary heart disease, n (%)	1'166 (42.5)	137 (28.4)	271 (37.0)	428 (46.3)	330 (54.7)	<0.001
Heart failure, n (%)	130 (4.7)	15 (3.1)	21 (2.9)	42 (4.5)	52 (8.6)	<0.001
Arrhythmia, n (%)	188 (6.9)	6 (1.2)	40 (5.5)	68 (7.4)	74 (12.3)	<0.001
Cerebrovascular disease, n (%)	461 (16.8)	38 (7.9)	85 (11.6)	184 (19.9)	154 (25.5)	<0.001
Depression/psychiatric disorder, n (%)	423 (15.4)	119 (24.6)	140 (19.1)	102 (11.0)	62 (10.3)	<0.001
Rheumatic disease/disorder of musculoskeletal system, n (%)	416 (15.2)	52 (12.5)	110 (26.4)	149 (35.8)	105 (25.2)	NS
Gout/hyperuricemia, n (%)	103 (3.8)	13 (2.7)	24 (3.3)	44 (4.8)	22 (3.6)	NS
Epilepsy, n (%)	16 (0.6)	7 (1.4)	4 (0.5)	4 (0.4)	1 (0.2)	NS
Other diagnoses, n (%)	244 (8.9)	93 (19.3)	75 (10.2)	59 (6.4)	17 (2.8)	<0.001

NS = not significant; SD = standard deviation.

the observed decrease in the prevalence of depression and other psychiatric disorders with increasing age. With increasing number of pharmacologically active substances prescribed per patient, also the prevalence of patients with clinically relevant pDDIs increased. In patients aged ≤54 years, the prevalence of pDDIs increased from 3.4% (95% CI 1.3-7.2%) when 2-3 active substances were prescribed to 22.7% (95% CI 11.5-37.8%) in patients receiving ≥7 substances concomitantly (figure 4). This increase was even more pronounced in patients aged ≥75 years, reaching 33.8% (95% CI 27.4-40.7%) when ≥7 substances were prescribed.

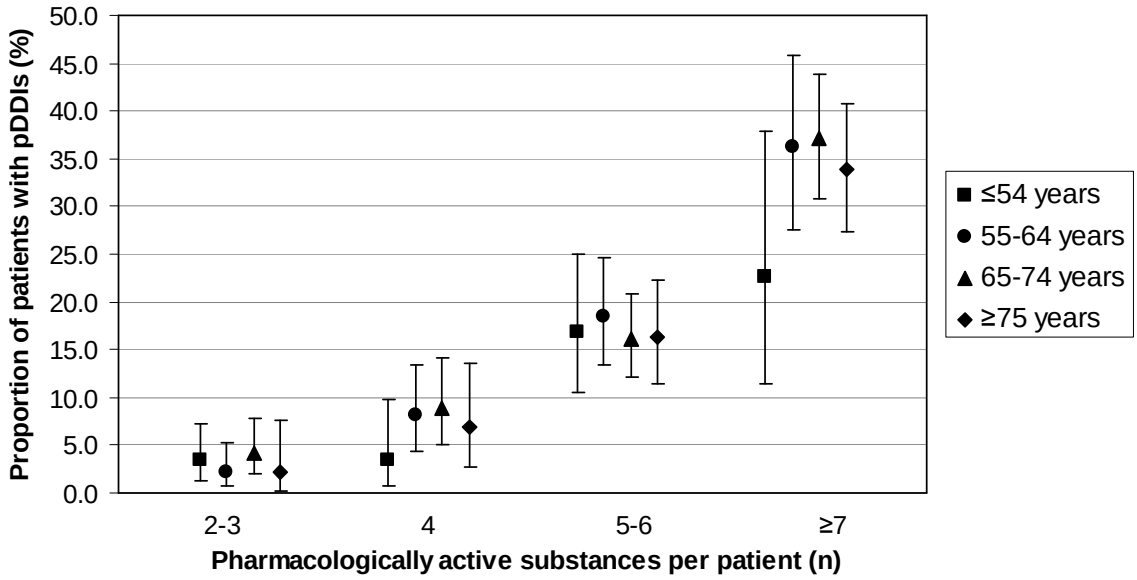

Figure 4. Number of pharmacologically active substances prescribed and prevalence of potential drug-drug interactions (pDDIs) stratified by age group. The figure shows the proportion (± 95% confidence interval) of patients with a pDDI stratified by age and number of active substances prescribed. While the proportion of patients with a pDDI increases with the number of active substances prescribed, there is no significant increase with age. A total of 704 patients were prescribed 2-3 active substances (range: 92-221 patients in the different age groups), 519 patients 4 substances (range: 87-169 patients), 807 patients 5-6 substances (range: 113-298 patients), and 590 patients were prescribed ≥7 active substances concomitantly (range: 44-226 patients).

Logistic regression analysis identified male sex (OR 2.9; 95% CI 1.1-7.5), number of pharmaceutical preparations prescribed (OR 1.8; 95% CI 1.5-2.2) and psychiatric disorders (OR 2.4; 95% CI 1.1-5.3) as risk factors for clinically relevant pDDIs in

Table 5. Prevalence of the most frequently prescribed comedications in 2'742 dyslipidemic patients stratified by age groups

	Age groups (years)					
Substances or therapeutic groups	**Total (n = 2'742) n (%)**	**≤54 (n = 483) n (%)**	**55-64 (n = 732) n (%)**	**65-74 (n = 924) n (%)**	**≥75 (n = 603) n (%)**	**p-value**
Acetylsalicylic acid (low dose)	1'258 (45.9)	173 (35.8)	323 (44.1)	439 (47.5)	323 (53.6)	<0.001
Beta-adrenoceptor antagonists	1'145 (41.8)	169 (35.0)	291 (39.8)	408 (44.2)	277 (45.9)	<0.01
Thiazide or loop diuretics	900 (32.8)	82 (17.0)	195 (26.6)	333 (36.0)	290 (48.1)	<0.001
ACE inhibitors	778 (28.4)	91 (18.8)	183 (25.0)	288 (31.2)	216 (35.8)	<0.001
Angiotensin II receptor antagonists	551 (20.1)	83 (17.2)	156 (21.3)	193 (20.9)	119 (19.7)	NS
Oral antidiabetics	533 (19.4)	73 (15.1)	142 (19.4)	231 (25.0)	87 (14.4)	NT
Benzodiazepines	499 (18.2)	79 (16.4)	112 (15.3)	175 (18.9)	133 (22.1)	NS
Nonsteroidal anti-inflammatory drugs	427 (15.6)	85 (17.6)	128 (17.5)	132 (14.3)	82 (13.6)	NS
Calcium channel blockers (dihydropyridines)	403 (14.7)	29 (6.0)	90 (12.3)	171 (18.5)	113 (18.7)	<0.001
Antidepressants (incl. St John's wort)	363 (13.2)	80 (16.6)	115 (15.7)	96 (10.4)	72 (11.9)	<0.01
Oral anticoagulants (phenprocoumon, acenocoumarol)[a]	320 (11.7)	19 (3.9)	52 (7.1)	135 (14.6)	114 (18.9)	<0.001
Potassium-sparing diuretics	161 (5.9)	11 (2.3)	34 (4.7)	59 (6.4)	57 (9.5)	<0.001
Clopidogrel	136 (5.0)	17 (3.5)	36 (4.9)	46 (5.0)	37 (6.1)	NS
Insulin	133 (4.9)	16 (3.3)	31 (4.2)	51 (5.5)	35 (5.8)	NT
Allopurinol	122 (4.5)	12 (2.5)	28 (3.8)	51 (5.5)	31 (5.1)	NT
Calcium channel blockers (verapamil or diltiazem)	100 (3.7)	2 (0.4)	25 (3.4)	47 (5.1)	26 (4.3)	<0.01
Antipsychotics	98 (3.6)	22 (4.6)	29 (4.0)	31 (3.4)	16 (2.7)	NT
Amiodarone	82 (3.0)	2 (0.4)	15 (2.1)	36 (3.9)	29 (4.8)	<0.001
Digoxin	67 (2.4)	0	8 (1.1)	27 (2.9)	32 (5.3)	<0.001
Antiepileptics	56 (2.0)	16 (3.3)	12 (1.6)	16 (1.7)	12 (2.0)	NT
Tramadol	24 (0.9)	4 (0.8)	10 (1.4)	5 (0.5)	5 (0.8)	NT
Other lipid lowering drugs: fibrates and nicotinic acid	20 (0.7)	5 (1.0)	6 (0.8)	8 (0.9)	1 (0.2)	NT
Ginkgo	18 (0.7)	1 (0.2)	1 (0.1)	7 (0.8)	9 (1.5)	NT
Potassium	16 (0.6)	1 (0.2)	4 (0.6)	7 (0.8)	4 (0.7)	NT

[a]Only the oral anticoagulants phenprocoumon and acenocoumarol are marketed in Switzerland (but not warfarin).

NS = not significant; NT = not tested to avoid multiple testing on the same sample.

patients ≤54 years (see table 6). In ≥55 years-old patients, in addition to the number of pharmaceutical preparations or pharmacologically active substances prescribed a diagnosis of arrhythmia or heart failure was associated with a higher risk for pDDIs (table 6). In each model, either the number of pharmaceutical preparations or pharmacologically active substances resulted to be a significant risk factor, demonstrating the collinearity between these two variables.

Table 6. Factors significantly associated with an increased risk of clinically relevant potential drug-drug interactions using age-specific multivariate logistic regression analysis

	Age groups			
Risk factors	**≤54 years (n = 483) OR [95% CI]**	**55-64 years (n = 732) OR [95% CI]**	**65-74 years (n = 924) OR [95% CI]**	**≥75 years (n = 603) OR [95% CI]**
Male sex	2.9 [1.1-7.5]	NS	NS	NS
Number of preparations or active substances[a]	1.8 [1.5-2.2]	1.7 [1.5-1.9]	1.5 [1.4-1.6]	2.4 [1.5-3.9]
Psychiatric disorders	2.4 [1.1-5.3]	NS	NS	-[b]
Arrhythmia	NS	9.1 [4.2-19.6]	4.7 [2.6-8.4]	5.6 [3.1-10.1]
Heart failure	NS	3.8 [1.3-10.7]	3.6 [1.8-7.4]	2.7 [1.3-5.4]

[a]In each model either the number of pharmaceutical preparations or pharmacologically active substances resulted as a significant risk factor due to collinearity problems using multivariate logistic regression analysis.
[b]Odds ratio for psychiatric disorders indicated a significantly reduced risk (OR 0.3 [95% CI 0.1-0.8]; $p < 0.05$) in patients aged ≥75 years.
NS = not significant; OR = odds ratio.

Table 7 lists the most prevalent of the 591 clinically relevant pDDIs found in 401 patients (14.6% of all patients studied) stratified by age. The prevalence of total pDDIs increased significantly ($p < 0.001$) from 7.9% in the group of patients aged ≤54 years to 18.4% in those aged ≥75 years (figure 5). Accordingly, taking into account only patients with pDDIs, the mean number of pDDI per patient increased from 1.21 ± 0.84 in the group of patients aged ≤54 years to 1.56 ± 0.99 in the group of patients aged ≥75 years. While almost all of the 198 pDDIs involving statins were pharmacokinetic interactions, in 65% of the 393 non statin pDDIs, the underlying

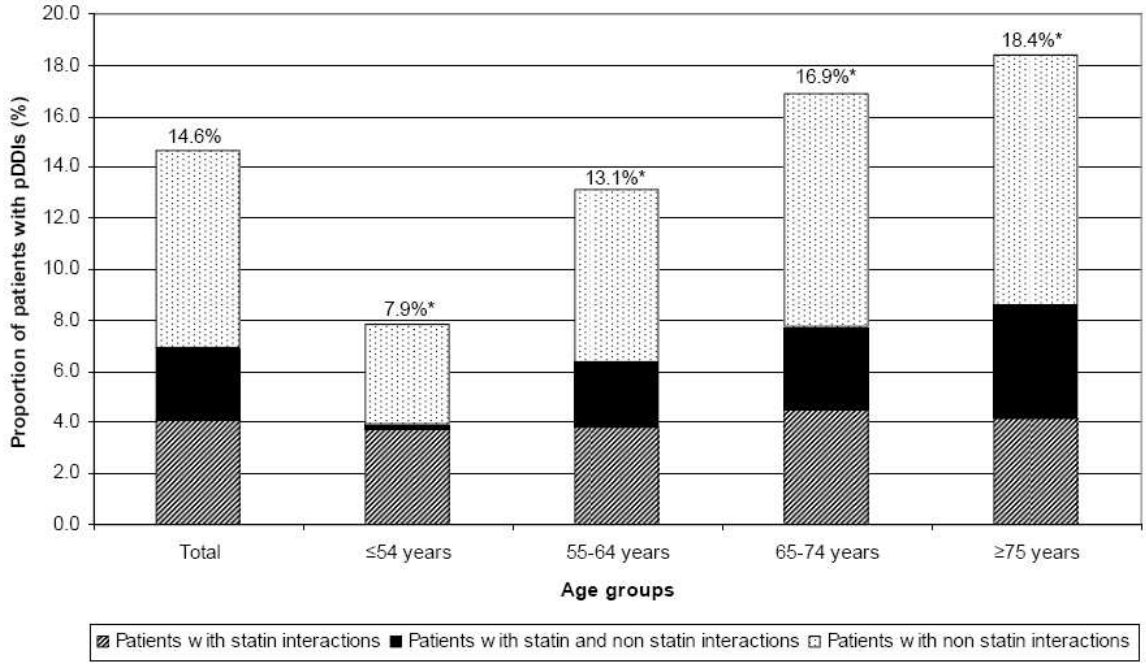

Figure 5. Prevalence of potential drug-drug interactions (pDDIs) stratified by age groups. Also the proportion of patients with statin and non statin pDDIs, respectively both of them, contributing to the total amount of clinically relevant pDDIs is indicated. * indicates a significant difference in the prevalence of total pDDIs between the age groups.

mechanism was pharmacodynamic. The prevalence of both statin and non statin pDDIs increased with age, whereas the proportion of statin interactions in relation to the total number of pDDIs decreased from 41.3% in patients aged ≤54 years to 30.6% in patients aged ≥75 years. Overall, the most common pDDI involving a statin was the combination of amiodarone with atorvastatin or simvastatin, increasing the risk for rhabdomyolysis.[103] Compared to younger patients, those aged ≥75 years were more likely to be exposed to this potentially harmful drug combination. Also the pDDI between atorvastatin or simvastatin and digoxin, which is associated with increased digoxin serum concentrations and potential digoxin toxicity, was more frequent in the elderly. On the other hand, the prevalence of the pharmacokinetic interaction between fluoxetine in combination with atorvastatin, fluvastatin, or simvastatin decreased with age. The only pharmacodynamic pDDI involving statins was the combination with other lipid-lowering drugs, in particular with nicotinic acid. Non statin interactions commonly implicated cardiovascular drugs such as ACE

inhibitors, amiodarone, beta-adrenoceptor antagonists, digoxin or oral anticoagulants, which were more often prescribed to elderly patients.

Discussion

Dyslipidemic patients treated with a statin were selected as a study population, because treatment with statins can be associated with potentially serious adverse reactions such as rhabdomyolysis that are frequently associated with underlying DDIs.[141] Statins are commonly used as a long-term treatment and elderly patients are at special risk for pDDIs because of polymorbidity and consequent prescription of multiple drugs.[141,142] In addition, patients with dyslipidemia have a high risk for cardiovascular diseases[143] and the prevalence of cardiovascular disorders is known to increase with age.[50] Drugs used for the treatment of cardiovascular disorders are frequently involved in pDDIs, especially in elderly patients.[89]

Our study shows that the prevalence of clinically relevant pDDIs significantly increased with advancing age. This is consistent with the findings in the literature.[89,133,144] Only 7.9% of the patients aged ≤54 years have been identified with serious pDDIs, whereas the prevalence reached 18.4% in patients aged ≥75 years. Importantly, the frequency of both statin and non statin pDDIs increased with age.

Using logistic regression analysis, the number of pharmaceutical preparations or pharmacologically active substances prescribed were identified as risk factors for pDDIs, independently of the patient's age. Polypharmacy is a well known risk factor for pDDIs.[89,129,144] The higher number of comorbidities and pharmacologically active substances per diagnosis prescribed may partly explain the higher prevalence of pDDIs observed in patients aged ≥75 years compared to younger patients. An additional explanation for the observed increase in the prevalence of pDDIs with advancing age may be the prescription of drugs with a higher potential for DDIs. Especially drugs used for the treatment of heart failure and/or arrhythmias were often involved in clinically relevant pDDIs. These drugs have previously been described to be commonly responsible for pDDIs in the elderly.[89,130] As surrogate parameters for

Table 7. List of the most prevalent clinically relevant potential drug-drug interactions (pDDIs) identified in statin-treated patients with dyslipidemia stratified by age group. When applicable, the second listed drug or drug class is the one affected by the pDDI.

Interacting drugs	Mechanism	Number of pDDIs, n (%)				
		All patients	**≤54 years**	**55-64 years**	**65-74 years**	**≥75 years**
Total number of pDDIs		*591 (100.0)*	*46 (100.0)*	*140 (100.0)*	*232 (100.0)*	*173 (100.0)*
Interactions involving a statin (total)		*198 (33.5)*	*19 (41.3)*	*47 (33.6)*	*79 (34.1)*	*53 (30.6)*
Amiodarone – atorvastatin or simvastatin	k	52 (8.8)	1 (2.2)	10 (7.1)	22 (9.5)	19 (11.0)
Diltiazem/verapamil – atorvastatin or simvastatin	k	45 (7.6)	-	10 (7.1)	25 (10.8)	10 (5.8)
Atorvastatin/simvastatin – digoxin	k	43 (7.3)	-	4 (2.9)	18 (7.8)	21 (12.1)
Fluoxetine/norfluoxetine – atorvastatin, fluvastatin or simvastatin	k	29 (4.9)	10 (21.7)	15 (10.8)	3 (1.3)	1 (0.6)
Other lipid-lowering drugs[a] – all statins	k/d	18 (3.0)	5 (10.9)	5 (3.6)	7 (3.0)	1 (0.6)
Other pDDIs involving a statin		11 (1.9)	3 (6.5)	3 (2.1)	4 (1.7)	1 (0.6)
Interactions not involving a statin (total)		*393 (66.5)*	*27 (58.7)*	*93 (66.4)*	*153 (65.9)*	*120 (69.4)*
ACE inhibitor – potassium sparing diuretic or potassium	d	57 (9.6)	5 (10.9)	17 (12.1)	21 (9.0)	14 (8.1)
Loop/thiazide diuretic – digoxin	d	42 (7.1)	-	5 (3.6)	15 (6.5)	22 (12.7)
ACE inhibitor – allopurinol	u	40 (6.8)	2 (4.3)	9 (6.4)	18 (7.8)	11 (6.4)
Amiodarone – oral anticoagulant[b]	k	33 (5.6)	1 (2.2)	6 (4.3)	17 (7.3)	9 (5.2)
Amiodarone – beta-adrenoceptor antagonist	d	31 (5.3)	-	7 (5.0)	14 (6.0)	10 (5.8)
ASS – oral anticoagulant[b] or heparin	d	29 (4.9)	7 (15.3)	6 (4.3)	10 (4.3)	6 (3.5)
Beta-adrenoceptor antagonist – antidiabetic agents	d	22 (3.7)	2 (4.3)	4 (2.9)	9 (3.9)	7 (4.0)
Beta-adrenoceptor antagonist – digoxin	d/(k)	21 (3.6)	-	3 (2.1)	6 (2.6)	12 (7.0)
Diltiazem/verapamil – beta-adrenoceptor antagonist	d/(k)	18 (3.0)	-	6 (4.3)	8 (3.4)	4 (2.3)
Ginkgo – oral anticoagulant[b] or ASS	d	16 (2.7)	-	1 (0.7)	6 (2.6)	9 (5.2)
NSAID – ASS	d	13 (2.2)	2 (4.3)	5 (3.6)	3 (1.3)	3 (1.7)
Other non statin interactions		71 (12.0)	8 (17.4)	24 (17.1)	26 (11.2)	13 (7.5)

[a]Other lipid-lowering drugs: fibrates, nicotinic acid.

[b]Oral anticoagulants available in Switzerland are phenprocoumon and acenocoumarol; the pDDIs identified for these substances are also relevant for warfarin.

ASS = Acetylsalicylic acid (low dose); d = pharmacodynamic interaction; k = pharmacokinetic interaction; NSAID = nonsteroidal anti-inflammatory drug; SD = standard deviation; u = mechanism of interaction is unknown.

these drugs the diagnoses heart failure and arrhythmia have been identified as risk factors for pDDIs in patients aged ≥55 years in our study. The increase in the proportion of interactions involving cardiovascular drugs related to the total number of pDDIs with age supports the importance of the potential risk associated with this drug class.

The most frequent non statin pDDI of major severity in all age groups in our study was the combination of ACE inhibitors with potassium-sparing diuretics, which increases the risk for hyperkalemia. The combination of ACE inhibitors with 25 mg spironolactone has proven to reduce the mortality in patients with severe congestive heart failure.[92] However, in 13% of the patients, the addition of spironolactone to an existing treatment with ACE inhibitors may lead to hyperkalemia.[93] Other risk factors identified are age, renal impairment, diabetes mellitus type 2 and spironolactone doses >25 mg daily.[145] Close monitoring of renal function and serum potassium concentrations may help to prevent the development of hyperkalemia.

In our study, the frequency of digoxin prescription and the prevalence of pDDIs involving digoxin increased with advancing age (table 7). Because of its pharmacological properties and narrow therapeutic range, digoxin is a drug frequently implicated in serious pharmacodynamic and/or pharmacokinetic pDDIs.[89] In the elderly, digoxin toxicity may be further enhanced due to an age-related decline in renal function and subsequent decrease in digoxin clearance, but also due to an enhanced susceptibility to digoxin, even at therapeutic concentrations.[95,146,147] Potential DDIs identified more often in elderly patients treated with digoxin included the combination with loop/thiazide diuretics, beta-adrenoceptor antagonists, atorvastatin or simvastatin. By inducing hypokalemia or hypomagnesemia, loop and thiazide diuretics may enhance the inhibitory effect of cardiac glycosides on Na-K-ATPase through indirect pharmacodynamic mechanisms.[148] Concomitant use of beta-adrenoceptor antagonists and digoxin may be associated with the risk of bradycardia due to additive pharmacological effects.[134] Pharmacokinetic pDDIs associated with digoxin toxicity include inhibition of Pgp-mediated transport of digoxin, possibly leading to increased intestinal digoxin absorption and decreased renal and biliary excretion, leading to increased serum concentrations. Recently, it has been shown in vitro that carvedilol, propranolol and bisoprolol may inhibit the

activity of Pgp.[149] In human pharmacokinetic studies, carvedilol, the most efficient Pgp inhibitor of the beta-adrenoceptor antagonists tested, has shown to increase bioavailability of digoxin, but the clinical relevance has to be determined.[150,151] In analogy, concomitant administration of simvastatin, lovastatin and atorvastatin may increase digoxin serum concentrations up to 20%, because of the inhibition of Pgp-mediated transport.[141,152] On the other hand, pravastatin did not show alterations in the pharmacokinetics of digoxin,[152,153] and the effect of fluvastatin seems not to be clinically relevant.[154] Therapeutic drug monitoring may help to prevent toxic effects associated with higher digoxin concentrations.

Drugs used in the treatment of arrhythmias were also often involved in pDDIs. The most common pDDIs with antiarrhythmics identified in our study were the pharmacokinetic interactions involving amiodarone, diltiazem or verapamil in combination with atorvastatin or simvastatin. Amiodarone, diltiazem and verapamil are inhibitors of different hepatic CYP isozymes, in particular CYP 3A4.[100-102] CYP 3A4 is primarily responsible for the metabolism of simvastatin, atorvastatin and lovastatin. Since the occurrence of myotoxicity associated with statins is considered to be dose-dependent,[142,155-157] pDDIs of CYP 3A4 inhibitors with simvastatin, atorvastatin or lovastatin are associated with an increased risk for rhabdomyolysis.[158] In addition, older patients, particularly thin or frail women, or those with multisystem diseases, in particular patients with renal failure, seem to be at higher risk for statin-associated myopathy and should therefore be monitored carefully for early signs of muscle discomfort or weakness.[142,155]

In our study, the prevalence of depression and psychiatric disorders was highest in patients aged ≤54 years and was identified as a risk factor for pDDIs in this age group. Several reasons may contribute to this observation, which may not accurately reflect the age-dependent prevalence of depression.[159] Considering the low prevalence of psychiatric disorders compared with the amount of centrally acting drugs prescribed, it can be assumed that the physicians did not report all psychiatric disorders in elderly patients. In addition, depression is often underdiagnosed and undertreated in the elderly, because somatic symptoms may predominate or dementia and/or comorbid medical illnesses may complicate the recognition of depressive symptoms.[160,161] Patients aged ≤54 years had a higher prevalence of

pDDIs between fluoxetine and atorvastatin, fluvastatin or simvastatin than elderly patients. Fluoxetine and its active metabolite norfluoxetine may increase the risk for rhabdomyolysis through inhibitory effects on the metabolism of these statins. The lower prescription rate of fluoxetine in the elderly probably reflects the awareness of the physicians that this drug should better be avoided in this patient group, because of the long half-life of the drug and of its active metabolite, increasing the risk for dose-dependent ADRs.[121]

The identification of male sex as a risk factor for pDDIs in patients aged ≤54 years may be related to the earlier onset of cardiovascular disorders requiring drug treatment in men as compared to women.[143]

While this study demonstrates the frequency and the type of pDDIs in different age groups, it has also several limitations. According to the inclusion criteria, all patients studied had dyslipidemia and were treated with a statin. Since dyslipidemia is often associated with the metabolic syndrome, most patients had more than one diagnosis and were treated with multiple drugs, possibly decreasing the difference in the frequency of pDDIs between younger and older patients. In addition, since pDDIs of lower severity were excluded, the significance of pDDIs may have been underestimated. Adherence to the prescribed medication, which may influence the clinical impact of an identified pDDI, has not been assessed in the current study. The study was not designed to evaluate adverse outcomes resulting from pDDIs, decreasing the clinical relevance of our results. Furthermore, the use of a drug interaction program is helpful to identify pDDIs, but it has also limitations. It is for example not possible to control for factors influencing the relevance of a pDDI, e.g. dosage, time of administration, beginning and duration of treatment, and underlying diseases.[16,144]

Conclusion

Our study demonstrates that elderly dyslipidemic patients treated with a statin are at a higher risk for clinically relevant pDDIs than younger ones, irrespective whether a

statin is involved in the pDDI or not. The principle reason for this finding is the prescription of a higher number of drugs in the elderly, due to an increased number of diagnoses and due to the prescription of more drugs per diagnosis. Cardiac arrhythmias and heart failure are two diagnoses with a higher prevalence in the elderly and both are risk factors for pDDIs in this patient group. Beside the higher number of active substances prescribed, the prescription of cardiovascular drugs with a high potential for DDIs, e.g. digoxin or amiodarone, may also contribute to the observed higher prevalence of pDDIs with age. The combination of amiodarone with atorvastatin or simvastatin was the most frequent statin interaction in patients aged ≥75 years.

Elderly patients may be more prone to ADRs resulting from pDDIs, due to impaired homeostatic mechanisms and age-related pharmacodynamic and pharmacokinetic changes. In order to avoid the occurrence of ADRs associated with DDIs, the number of drugs prescribed should be minimized as much as possible. Drugs with a high potential for pDDIs must be recognized as such in order to take appropriate measures to minimize the risk for pDDIs such as choosing an alternative treatment with a lower risk for pDDIs, adjusting the dosage or close monitoring of therapy.

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STUDY II

PREVALENCE OF POTENTIALLY INAPPROPRIATE MEDICATION USE IN ELDERLY PATIENTS: COMPARISON BETWEEN GENERAL MEDICAL AND GERIATRIC WARDS

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Abstract

Background and objective: Inappropriate drug use is one of the risk factors for ADRs in the elderly. We hypothesized that, in elderly patients, geriatricians are more aware of PIMs and may replace or stop PIMs more frequently as compared with internists. We therefore evaluated and compared the prevalence of PIMs as well as anticholinergic drug use throughout hospital stay in elderly patients admitted to a medical or geriatric ward.

Methods: In this retrospective cross-sectional study, 800 patients aged ≥65 years admitted to a general medical or geriatric ward of a 700-bed teaching hospital in Switzerland during 2004 were included. PIMs were identified using the Beers criteria published in 2003. The prevalence of anticholinergic drug use was assessed based on drug lists published in the literature.

Results: The prevalence of use of PIMs that should generally be avoided was similar in medical and geriatric inpatients both at admission (16.0% versus 20.8%, respectively; $p = 0.08$) and at discharge (13.3% versus 15.9%, respectively; $p = 0.31$). In contrast to medical patients, the reduction in the prevalence of use of PIMs between admission and discharge in geriatric patients reached statistical significance ($p < 0.05$). Overall, the three most prevalent inappropriate drugs/drug classes were amiodarone, long-acting benzodiazepines and anticholinergic antispasmodics. At admission the prevalence of use of PIMs related to a specific diagnosis was not significantly different between patients hospitalized to a medical or a geriatric ward (14.0% versus 17.5%, respectively; $p = 0.17$), as compared with the significant difference evident at hospital discharge (11.7% versus 23.7%, respectively; $p < 0.001$). This was largely because of a higher prescription rate of platelet aggregation inhibitors in combination with low-molecular-weight heparins (LMWHs) and benzodiazepines in patients with a history of falls and syncope. The proportions of patients taking anticholinergic drugs in medical and geriatric patients at admission (13.0% versus 17.5%, respectively; $p = 0.08$) and discharge (12.2% versus 16.5%, respectively; $p = 0.10$) were similar.

Conclusion: Inappropriate drug use as defined by the Beers criteria was common in both medical and geriatric inpatients. Compared with internists, geriatricians appear

to be more aware of PIMs that should generally be avoided, but less aware of PIMs related to a specific diagnosis, and of the need to avoid anticholinergic drug use. However, the results of this study should be interpreted with caution because some of the drugs identified as potentially inappropriate may in fact be beneficial when the patient's clinical condition is taken into consideration.

Introduction

Because of age-related polymorbidity, drug regimen for elderly patients regularly consist of more than one drug. In addition to polypharmacy and related problems such as increased risk of DDIs and ADRs, various other factors (including age-related changes in pharmacokinetics and pharmacodynamics or underlying diseases) must be considered when prescribing drugs to elderly patients. Inappropriate drug use is one important aspect of suboptimal prescribing in the elderly.[162]

A drug prescription is defined as potentially inappropriate when the potential risk for ADRs outweighs the possible clinical benefit.[121] The Beers criteria provide a list of potentially inappropriate drugs or drug classes that should generally be avoided in the treatment of patients aged ≥65 years or when a specific underlying disease is present.[121] It has been estimated that in elderly patients, approximately 12% of hospital admissions are caused by ADRs.[10,11] In some studies, use of PIMs according to the Beers criteria was identified as a risk factor for ADRs.[10,163,164] Avoiding PIMs and using safer alternatives instead could therefore contribute to improved drug safety in the elderly.

Drugs with anticholinergic properties pose a special risk to elderly patients. The elderly are more susceptible to anticholinergic effects because acetylcholine levels decrease with advanced age and are typically reduced in patients with Alzheimer's disease and other dementias.[112] In particular, combining two or more drugs with anticholinergic properties may enhance the risk of peripheral anticholinergic effects such as dry mouth, blurred vision or increased heart rate. Anticholinergic load can also often induce severe central nervous ADRs, ranging from sedation and confusion

to delirium and cognitive impairment,[108,112,165] which, in the elderly, may often go unrecognized as such.

Recently, Laroche et al.[166] showed that hospitalization on geriatric wards can result in a decrease in prescription of PIMs as well as anticholinergic drugs. Potentially inappropriate drugs were identified using the Beers criteria published in 1997 and medications with anticholinergic properties other than those listed in the Beers criteria were added. However, these investigators did not evaluate drugs that should not be used in the presence of specific underlying diseases. Similarly, Saltvedt et al.[167] also showed that hospitalization in a geriatric ward improved the appropriateness of drug treatment in elderly patients. Compared with patients on a medical ward, patients on a geriatric ward were prescribed fewer drugs with anticholinergic properties and experienced fewer pDDIs.

The aim of this retrospective cross-sectional study was to assess and compare the prevalence of use of PIMs, taking into account underlying diseases, and the exposure prevalence of anticholinergic drug use in medical and geriatric patients aged ≥65 years throughout hospital stay. It was hypothesized that geriatricians are more aware of PIMs and would therefore replace or stop PIMs more frequently than internists.

Methods

Study population and data collection

Eight hundred patients aged ≥65 years consecutively admitted either to a general medical or a geriatric ward of the University Hospital of Basel, Basel, Switzerland, in the year 2004 were retrospectively identified. This hospital is a 700-bed teaching institution providing primary and tertiary care to an urban population of approximately 200'000 inhabitants. The main emphasis of the 45-bed general medical ward selected for the study is treatment of patients with gastroenterological, hematological, infectious, nephrological, oncological, and/or rheumatological diseases. The 28-bed

geriatric ward specializes in the treatment of patients with complex geriatric diseases, with particular emphasis on decubitus ulcers, senile delirium, dementia and malnutrition. Patients were excluded if they were discharged on the same day they were admitted or if the medical record was not complete. If patients were hospitalized more than once, only the first hospital stay in 2004 was considered.

Demographic information (age, sex, length of hospital stay, residence before and after hospitalization), main diagnoses (ICD-10[168]) and information on drug treatment at hospital admission, during hospitalization and at discharge, were retrieved from the clinical records and from the hospital discharge letter. Pharmacologically active substances were coded according to the Anatomical Therapeutic Chemical (ATC) classification.[169] Only drugs administered on a regular basis were recorded; drugs applied on an on-demand basis were not included. Topically applied drugs with presumed topical effects were not evaluated, other than inhaled drugs for the treatment of airway diseases. Drugs present at hospital admission were considered to have been taken as long-term treatment unless otherwise noted; similarly, a drug was considered to be taken for >2 weeks after discharge unless treatment duration was specified.

Inappropriate drugs

PIMs were identified according to the updated Beers criteria published in 2003[121] adapted to drugs available in Switzerland. The original list contains 48 active substances or drug classes that should generally be avoided in patients aged ≥65 years, including some substances for which appropriateness depends on the daily dose administered or the duration of the therapy. The Beers criteria also contain a list of substances or drug classes that should be avoided in the presence of specific underlying diseases or conditions. Several of the drugs listed are not marketed in Switzerland and were therefore excluded from the analysis (see appendix). For drug classes listed in the Beers criteria, individual substances belonging to this drug class that are available in Switzerland, but not listed in the original drug list, were added. For example, six benzodiazepines with a half-life of the parent drug or of an active

metabolite of ≥20 hours were added to the five long-acting benzodiazepines originally listed. Only drugs with a systemic action were checked for inappropriateness according to these modified Beers criteria.

Anticholinergic drugs

Additional to the anticholinergic substances listed in the Beers criteria,[121] the list was completed with drugs and drug classes defined in other studies as having anticholinergic properties.[108,170] The final list used in the current study contained the following drug classes with anticholinergic properties: conventional antipsychotics, tri- and tetracyclic antidepressants, first-generation histamine H1 receptor antagonists, anticholinergic antiparkinson agents (biperiden and amantadine) and antispasmodics (including belladonna alkaloids).

Statistical analysis

The Pearson's chi-square test (for categorical variables) and the independent two-sided Student's t-test (for log-transformed not normally distributed numerical variables) were used to detect differences between the two groups regarding demographic characteristics, number of diagnoses and number of pharmacologically active substances prescribed. The Pearson's chi-square test was used to compare the prevalence of inappropriate medication or anticholinergic drug use between medical and geriatric patients at hospital admission, during hospital stay and at discharge. The prevalence at discharge was calculated excluding patients who died during hospitalization. McNemar's test was used to analyze potential differences between exposure prevalences of PIMs and anticholinergic drugs at hospital admission and discharge within each patient group, excluding patients who died during hospital stay. This resulted in slightly different prevalences of PIMs and anticholinergic drugs at hospital admission. A p-value < 0.05 was considered to be statistically significant. All analyses were performed using SPSS for Windows version 12.0 (SPSS Inc., Chicago, IL, USA).

Results

Patient characteristics

Table 8. Principal characteristics of the study population

Characteristic	Medical ward (n = 400)	Geriatric ward (n = 400)	p-value
Age (years), median (range)	*76 (65-96)*	*84 (65-98)*	*<0.001*
65-74 years, n (%)	163 (40.8)	33 (8.3)	
75-84 years, n (%)	187 (46.7)	176 (44.0)	
≥85 years, n (%)	50 (12.5)	191 (47.7)	
Sex			
female, n (%)	185 (46.3)	285 (71.3)	<0.001
Number of diagnoses, median (range)	*6 (2-9)*	*7 (2-9)*	*<0.001*
Number of pharmacologically active substances, median (range)			
admission	5.5 (0-20)	6 (0-23)	0.31
hospitalisation	10 (0-38)	11 (1-28)	<0.05
discharge	6 (0-16)	7 (0-17)	0.67
Length of hospital stay (days), median (range)	*11 (1-59)*	*16 (2-190)*	*<0.001*
1-7 days, n (%)	123 (30.7)	54 (13.5)	
8-14 days, n (%)	143 (35.7)	109 (27.3)	
15-21 days, n (%)	83 (20.8)	125 (31.3)	
≥22 days, n (%)	51 (12.8)	112 (28.0)	
Residence before admission, n (%)			
community dwelling	358 (89.5)	305 (76.2)	
nursing home	20 (5.0)	71 (17.8)	
transferred from another hospital	20 (5.0)	21 (5.2)	
others	2 (0.5)	3 (0.8)	
Residence after discharge, n (%)			
death	24 (6.0)	42 (10.5)	
community dwelling	267 (66.8)	153 (38.3)	
nursing home	24 (6.0)	104 (26.0)	
transferred to another hospital or rehabilitation center	85 (21.2)	100 (25.0)	
others	-	1 (0.2)	

A total of 800 patients aged ≥65 years were included in the analysis. The characteristics of the study population are presented in table 8. Main differences were higher age (84 versus 76 years; $p < 0.001$), higher proportion of female patients

(71.3% versus 46.3%; $p < 0.001$) and longer duration of hospital stay (16 versus 11 days; $p < 0.001$) in geriatric compared with medical patients, respectively. Approximately four times more geriatric patients resided in nursing homes before admission, or were discharged to a nursing home after hospitalization, compared with medical patients, and almost twice as many patients admitted to the geriatric ward died during the hospital stay.

The main reasons for hospital admission for patients of both study groups were diseases of the circulatory system (26.5% in medical and 22.0% in geriatric patients), which mainly presented as ischemic heart disease, heart failure or cerebrovascular disease. Additional common reasons for hospitalization to the geriatric ward were injuries to various parts of the body (12.3%) most often as a result of falls and unspecified symptoms (11.3%) such as syncope or collapse.

The median number of pharmacologically active substances at hospital admission was similar for both groups (5.5 in the medical ward versus 6 in the geriatric ward; $p = 0.31$), as was the exposure prevalence to various drug classes. The drug classes most often prescribed according to the ATC classification in both patient groups were drugs acting on the cardiovascular system (diuretics, ACE inhibitors or angiotensin II receptor antagonists and beta-adrenoceptor antagonists), drugs to treat disorders of the gastrointestinal tract or metabolic diseases (mineral supplements, antihyperglycemic agents and proton pump inhibitors), and drugs affecting the CNS system (analgesics, antidepressants and benzodiazepines).

Prevalence of PIMs and anticholinergic drugs at hospital admission

As shown in figure 6, the prevalence of use of PIMs that should generally be avoided according to the Beers criteria was not different between geriatric and medical patients (20.8% versus 16.0%, respectively; $p = 0.08$). A total of 75 and 96 PIMs were identified on admission in medical and geriatric patients, respectively (table 9). Of these, the most prevalent inappropriate substances in both groups were drugs with anticholinergic effects (anticholinergic antispasmodics and biperiden), amiodarone and long-acting benzodiazepines.

Table 9. Number of potentially inappropriate medications (PIMs) that should generally be avoided according to the Beers criteria published in 2003[121] identified in the study

Drugs or drug classes	Number of PIMs, n (%)					
	admission		hospitalization		discharge	
	MW 75 (100.0)	GW 96 (100.0)	MW 94 (100.0)	GW 77 (100.0)	MW 53 (100.0)	GW 67 (100.0)
Anticholinergic antispasmodics[a] or anticholinergics[b]	18 (24.0)	23 (24.0)	13 (13.8)	16 (20.8)	9 (16.9)	14 (20.9)
Amiodarone	15 (20.0)	15 (15.6)	24 (25.5)	16 (20.8)	20 (37.7)	15 (22.4)
Long-acting benzodiazepines	7 (9.3)	10 (10.4)	8 (8.5)	10 (13.0)	5 (9.4)	4 (5.9)
Estrogens only	5 (6.7)	3 (3.1)	4 (4.3)	3 (3.9)	3 (5.7)	3 (4.5)
First-generation histamine H1 receptor antagonists	5 (6.7)	4 (4.2)	1 (1.1)	2 (2.6)	1 (1.9)	1 (1.5)
Paraffin	4 (5.3)	6 (6.3)	9 (9.5)	11 (14.2)	1 (1.9)	5 (7.5)
Amitriptyline	3 (4.0)	2 (2.1)	5 (5.3)	4 (5.2)	4 (7.5)	4 (5.9)
Non-COX-selective NSAIDs with long half-life, long-term use of high doses	3 (4.0)	2 (2.1)	-	-	-	-
Barbiturates (except phenobarbital and except to control seizures)	2 (2.7)	-	2 (2.1)	-	1 (1.9)	-
Doxepin	2 (2.7)	-	2 (2.1)	-	2 (3.8)	-
Digoxin >0.125 mg/day (except to treat atrial arrhythmia)	2 (2.7)	3 (3.1)	-	1 (1.3)	-	1 (1.5)
Short-acting benzodiazepines in high doses	2 (2.7)	7 (7.3)	8 (8.5)	5 (6.5)	-	1 (1.5)
Stimulant laxatives for >2 weeks (except when opioid analgesics are used)	2 (2.7)	8 (8.3)	-	4 (5.2)	-	11 (16.4)
Amphetamines and anorexic agents	1 (1.3)	-	1 (1.1)	-	1 (1.9)	-
Clonidine	1 (1.3)	-	4 (4.3)	-	2 (3.8)	-
Doxazosin	1 (1.3)	1 (1.0)	1 (1.1)	1 (1.3)	1 (1.9)	2 (3.0)
Fluoxetine	1 (1.3)	-	3 (3.1)	-	2 (3.8)	-
Iron >200 mg/day	1 (1.3)	2 (2.1)	4 (4.3)	-	1 (1.9)	-
Ergot mesyloids	-	4 (4.2)	-	1 (1.3)	-	3 (4.5)
Meperidine (pethidine)	-	2 (2.1)	4 (4.3)	-	-	-
Thioridazine	-	2 (2.1)	-	1 (1.3)	-	1 (1.5)
Indomethacin	-	1 (1.0)	-	1 (1.3)	-	1 (1.5)
Short-acting nifedipine	-	1 (1.0)	-	1 (1.3)	-	1 (1.5)
Pentazocine	-	-	1 (1.1)	-	-	-

[a]Anticholinergic antispasmodics: belladonna alkaloids, butylscopolamine, tolterodine, trospium, oxybutynin, isometheptene, drofenine.

[b]Anticholinergics: biperiden.

COX = cyclooxygenase; GW = geriatric ward; MW = medical ward; NSAID = nonsteroidal anti-inflammatory drugs; PIM = potentially inappropriate medication.

A total of 79 and 97 PIMs associated with a specific diagnosis were detected on admission in 56 medical (14.0%) and 70 geriatric patients (17.5%), respectively (table 10, figure 6). Often identified in both groups was the administration of NSAIDs or platelet aggregation inhibitors to patients with pre-existing blood clotting disorders or anticoagulant therapy, which consisted most often of LMWHs in prophylactic doses. Prescription of benzodiazepines to patients with depression or a history of syncope and/or falls was also common.

At admission, 61 substances with anticholinergic properties were identified as having been prescribed to 52 medical patients (table 11; figure 6). Of these, tricyclic antidepressants were most often prescribed (see table 11). Geriatric patients were taking more drugs with anticholinergic properties (81 substances), but overall the prevalence was not different compared with medical patients (17.5% versus 13.0%, respectively; p = 0.08). Conventional antipsychotics were the most prevalent anticholinergic drug class in this population (39.5% of all anticholinergic drugs).

Prevalence of PIMs and anticholinergic drugs during hospital stay

In medical patients the exposure prevalence of PIMs that should generally be avoided was 20.5% during hospital stay (figure 6). Contributing to this nonsignificant increase compared with hospital admission was the addition of amiodarone in nine patients and the administration of short-acting benzodiazepines in inadequate high doses in additional six patients (see table 9). In contrast, the proportion of geriatric patients receiving a PIM during hospital stay decreased nonsignificantly from 20.8% to 17.3%, despite an increase in the number of pharmacologically active substances administered (increasing from a median of 6 to a median of 11 substances per patient). In both groups, anticholinergic antispasmodics as well as first-generation histamine H1 receptor antagonists were most often stopped.

There was an almost 3-fold increase in the exposure prevalence of PIMs associated with a specific disease in both groups compared with admission, rising to 40.5% in medical patients and 51.8% in geriatric patients. This increase is mainly explained by

Table 10. Number of potentially inappropriate medications (PIMs) associated with a specific underlying disease or condition identified in the study

		Number of PIMs, n(%)					
		admission		hospitalization		discharge	
Disease or condition	**Drugs or drug classes**	**MW 79 (100.0)**	**GW 97 (100.0)**	**MW 252 (100.0)**	**GW 304 (100.0)**	**MW 51 (100.0)**	**GW 109 (100.0)**
Depression	Benzodiazepine use >2 weeks, sympatholytic agents[a]	16 (20.3)	27 (27.8)	11 (4.4)	27 (8.9)	10 (19.6)	21 (19.2)
Blood clotting disorders or anticoagulant therapy[b]	NSAIDs, platelet aggregation inhibitors	14 (17.7)	20 (20.6)	198 (78.5)	194 (63.8)	25 (49.0)	34 (31.2)
Bladder outflow obstruction	Anticholinergics[c], first-generation histamine H1 receptor antagonists, anticholinergic antispasmodics[d], tricyclic antidepressants	12 (15.2)	5 (5.2)	9 (3.6)	3 (1.0)	3 (5.8)	2 (1.8)
Syncope or falls	Short-/intermediate-acting benzodiazepines, tricyclic antidepressants	9 (11.4)	22 (22.6)	14 (5.5)	55 (18.1)	5 (9.8)	37 (33.9)
Arrhythmias	Tricyclic antidepressants	6 (7.6)	6 (6.2)	4 (1.6)	6 (2.0)	1 (2.0)	5 (4.6)
Chronic constipation	Calcium channel blockers, tricyclic antidepressants	6 (7.6)	3 (3.1)	5 (2.0)	3 (1.0)	3 (5.8)	3 (2.8)
Gastric or duodenal ulcers (history and actual)	NSAIDs and aspirin (acetylsalicylic acid) [>325 mg]	6 (7.6)	3 (3.1)	-	3 (1.0)	-	-
COPD	Long-acting benzodiazepines, propranolol	3 (3.8)	-	1 (0.4)	-	1 (2.0)	-
Parkinson's disease	Metoclopramide, conventional antipsychotics	3 (3.8)	-	4 (1.6)	3 (1.0)	1 (2.0)	-
Cognitive impairment	Barbiturates, anticholinergics[c], anticholinergic antispasmodics[d], centrally acting muscle relaxants[e]	2 (2.5)	5 (5.2)	1 (0.4)	5 (1.6)	1 (2.0)	4 (3.7)
SIADH/hyponatremia	SSRIs	2 (2.5)	6 (6.2)	2 (0.8)	4 (1.3)	1 (2.0)	3 (2.8)
Heart failure	High sodium content drugs[f]	-	-	3 (1.2)	1 (0.3)	-	-

[a]Sympatholytic agents: clonidine.

[b]Proportion of prescriptions concerning the combination of heparins or low-molecular-weight heparins with NSAIDs or platelet aggregation inhibitors: at admission: MW 9/14 (64.3%), GW 11/20 (55.0%); during hospitalization: MW 182/198 (91.9%), GW 180/194 (92.8%); at discharge: MW 20/25 (80.0%), GW 28/34 (82.4%).

[c]Anticholinergics: biperiden.

[d]Anticholinergic antispasmodics: tolterodine, trospium, oxybutynin.

[e]Centrally acting muscle relaxants: tizanidine, baclofen.

[f]High sodium content drugs: sodium polystyrene sulfonate, piperacillin sodium/tazobactam sodium.

COPD = chronic obstructive pulmonary disease; GW = geriatric ward; MW = medical ward; SIADH = syndrome of inappropriate antidiuretic hormone; SSRI = selective serotonin reuptake inhibitor.

the addition of LMWHs for thrombosis prophylaxis to an existing therapy of platelet aggregation inhibitors (see table 10). In geriatric patients, the increase was also due to initiating treatment with short-acting benzodiazepines in patients with a history of falls or syncope.

There was also an increase in the exposure prevalence of drugs with anticholinergic properties by a factor of 2.6 in geriatric patients. This increase was largely explained by the prescription of haloperidol to 150 patients (37.5%), mainly for delirium prophylaxis or treatment. Use of conventional antipsychotics, mainly pipamperone or haloperidol, also increased in medical patients; overall, however, use of anticholinergic drugs was significantly lower in medical patients than in geriatric patients (16.5% versus 45.5%, respectively; $p < 0.001$).

Prevalence of PIMs and anticholinergic drugs at hospital discharge

During hospital stay, 24 medical patients and 42 geriatric patients died and were therefore excluded from the analyses at hospital discharge. The prevalence of treatment with inappropriate substances in the remaining 358 patients discharged from the geriatric ward was 15.9% compared with 22.1% at admission ($p < 0.05$). In comparison, there was no difference between the prevalence of treatment with inappropriate substances at discharge and admission in the remaining 376 medical patients (13.3% versus 16.0%, respectively; $p = 0.10$). Overall, there was no difference in the exposure prevalences of PIMs between geriatric and medical patients at discharge (figure 6). The most often prescribed inappropriate drugs or drug classes at discharge for both groups were the same as at admission, namely amiodarone, anticholinergic antispasmodics including the anticholinergic antiparkinson agent biperiden, long-acting benzodiazepines and, in geriatric patients, paraffin and stimulant laxatives (table 9).

At discharge, the exposure prevalence of PIMs associated with a specific disease was significantly higher in geriatric than in medical patients (23.7% versus 11.7%, respectively; $p < 0.001$). In geriatric patients, this exposure prevalence was 5.9%

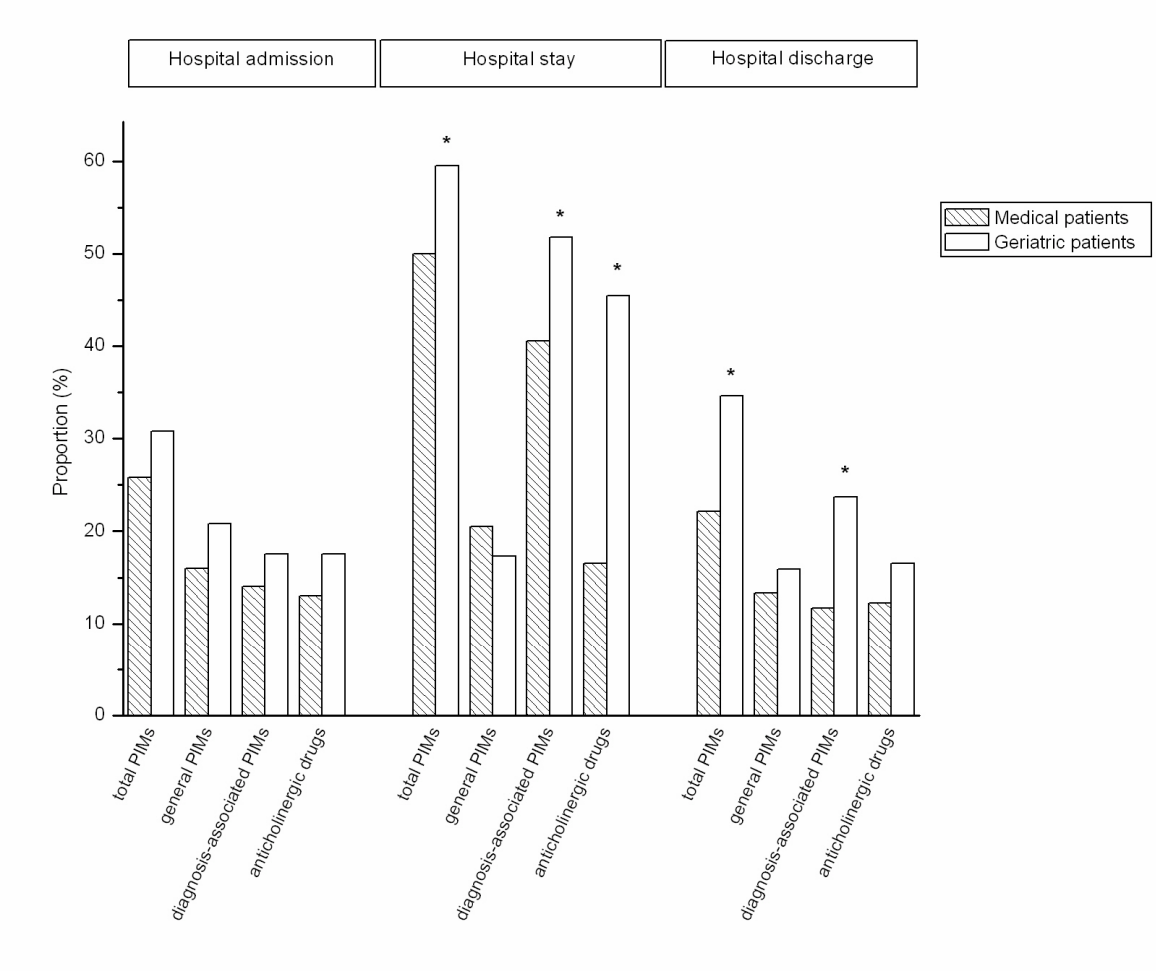

Figure 6. Changes in prevalence of use of potentially inappropriate medications (PIMs) and anticholinergic drugs in patients during hospital stays in general medical or geriatric wards. Total PIMs = general PIMs and/or diagnosis-associated PIMs. * indicates significant difference between medical and geriatric patients ($p < 0.05$).

higher than at hospital admission ($p < 0.05$). A reason for this finding was the higher number of benzodiazepines prescribed to patients with a history of falls/syncope or depression. Geriatric patients were not only more often hospitalized due to syncope or falls, they were also prescribed more benzodiazepines at discharge than were medical patients (111 versus 55 times, respectively), which may explain this result. Compared with admission, geriatric patients were also discharged more often with platelet aggregation inhibitors and LMWHs in prophylactic doses (see table 10).

At discharge, the prevalence of geriatric or medical patients treated with anticholinergic drugs was not significantly different (16.5% versus 12.2%, respectively; $p = 0.10$). There were no significant changes in prevalence of

anticholinergic drug use compared with use on hospital admission (figure 6). Conventional antipsychotic agents were identified as the anticholinergic drug class prescribed most often at discharge in both groups.

Table 11. Number of drugs or drug classes with anticholinergic properties identified in the study

	Number of anticholinergic drugs, n (%)					
	admission		**hospitalization**		**discharge**	
	MW	**GW**	**MW**	**GW**	**MW**	**GW**
	61	**81**	**80**	**207**	**53**	**65**
	(100.0)	**(100.0)**	**(100.0)**	**(100.0)**	**(100.0)**	**(100.0)**
Tricyclic antidepressants	23 (37.7)	19 (23.5)	23 (28.7)	16 (7.7)	16 (30.2)	12 (18.5)
Anticholinergic antispasmodics[a]	16 (26.2)	22 (27.2)	11 (13.8)	16 (7.7)	8 (15.1)	14 (21.5)
Conventional antipsychotics	16 (26.2)	32 (39.5)	38 (47.5)	171 (82.6)	26 (49.0)	36 (55.4)
First-generation histamine H1 receptor antagonists	4 (6.6)	4 (4.9)	4 (5.0)	2 (1.0)	2 (3.8)	1 (1.5)
Anticholinergic antiparkinson agents (biperiden and amantadine)	2 (3.3)	4 (4.9)	4 (5.0)	2 (1.0)	1 (1.9)	2 (3.1)

[a]tolterodine, trospium, oxybutynin, belladonna alkaloids, butylscopolamine.

GW = geriatric ward; MW = medical ward.

Discussion

The exposure prevalences of PIMs which should generally be avoided found in this study on both wards (13.3-20.5% on the medical ward and 15.9-20.8% on the geriatric ward) were in accordance with prevalences ranging from 5.8% to 25.7% found in other studies using the Beers criteria published in 2003.[122-124] However, comparisons with other studies must be interpreted carefully. Reasons for this include differences in patient settings, interpretation of the Beers criteria, and country-specific use of drugs. Inappropriate drugs often identified in other studies were nitrofurantoin, long-acting benzodiazepines, short- to intermediate-acting benzodiazepines at high doses, amitriptyline, doxazosin, amiodarone and estrogens.[122-124] These findings are quite similar to those of the present study, in which amiodarone, long-acting benzodiazepines, anticholinergic antispasmodics, paraffin and estrogens were the most prevalent inappropriate drugs.

Only a few studies have assessed the use of inappropriate drugs related to underlying diseases. The reported prevalences found in an outpatient setting ranged between 3.1% and 5.1%,[122,171,172] which are lower than the prevalences found in this study (11.7-40.5% in medical and 17.5-51.8% in geriatric patients). These differences may be explained by inclusion of hospitalized patients in this study, in whom the combination of platelet aggregation inhibitors with unfractionated heparin or LMWHs, especially at prophylactic doses, is common, but which is considered as potentially inappropriate according to the Beers criteria published in 2003.[121] To our knowledge, only one study including ambulatory patients and analyzing inappropriate drug use in relation to comorbidities according to the 2003 Beers criteria has been published.[122] As observed in our study, use of short- to intermediate-acting benzodiazepines in patients with a history of falls or syncope was common, as was administration of NSAIDs to patients with a history of gastric or duodenal ulcer.

It was expected that geriatricians might be more aware of problematic drugs and PIMs for the treatment of elderly patients, which would lead to a significant reduction in use of those drugs during hospitalization. Indeed, the prevalence of use of PIMs generally to be avoided was 6.2% lower in patients discharged from the geriatric ward compared with admission, whereas there was no difference in exposure prevalence in comparison with patients discharged from the medical ward. Our finding supports the findings of Laroche et al.,[166] who reported that the prevalence of PIM use was reduced by about 24% during hospitalization on geriatric wards. However, another study comparing the prevalence of PIM use in elderly patients hospitalized either on a geriatric or medical ward failed to show a significant reduction in PIM use in geriatric patients at discharge.[167] This may be explained by the small sample size. Out of 127 patients hospitalized on the geriatric ward, 13 patients (10%) were admitted and five patients (4%) discharged with PIMs, whereas of 127 medical patients, 12 (9%) and seven patients (6%) had PIMs at admission and discharge, respectively. In our study, an additional 21 geriatric patients (5.9%) were discharged with PIMs according to underlying diseases compared with hospital admission. One reason for this finding was the frequent administration of benzodiazepines to patients with a history of falls or syncope, which is a risk factor for falls. Not only were geriatric patients more often hospitalized due to syncope or falls, they were also more often prescribed short- to intermediate-acting

benzodiazepines at discharge compared with medical patients, which may explain this finding. The indications for prescription of these benzodiazepines were not assessed.

Hospitalization may increase the frequency of starting benzodiazepine treatment.[173] One reason for this is that hospital admission may provoke anxiety and insomnia. Insomnia is a common problem in the elderly and all available hypnotics, not only benzodiazepines but also zolpidem, may increase the risk of falls and fractures.[49,118,119,174-176] Furthermore, short-acting benzodiazepines appear to be no safer in this respect than longer-acting agents;[119,176] and they should therefore be prescribed only very restrictively to elderly patients, especially at hospital discharge. Newer compounds such as zopiclone, zolpidem or zaleplon are considered to be safer, because of their short half-lives and more selective pharmacological activities at the benzodiazepine-1 receptor. However, definitive proof of their safety in relation to falls in the elderly is lacking so far. In the elderly, half of the recommended adult dose should be prescribed.[49,174] In addition, short-acting benzodiazepines should not be considered as first-line treatment in anxious depressed elderly patients, because of the additional risk of cognitive impairment.[51,177] Adequate treatment with antidepressants such as SSRIs represents a safer option in these patients.[51,177]

Use of drugs with anticholinergic effects in elderly patients has been associated with an increased risk of delirium and cognitive decline.[108,165,178] Additional factors contributing to delirium are dementia, severe comorbidities, metabolic disorders (hypoalbuminemia, dehydration), surgery, infections, environmental factors (unfamiliar environment, stress) and use of centrally active drugs such as benzodiazepines and opioids.[178-180] The prevalences of use of drugs with anticholinergic effects found in the present study (12.2-17.0% on medical wards and 16.5-45.0% on geriatric wards) were consistent with those reported in other studies, which ranged between 10% to 42%, depending on the population setting evaluated.[108,170] During hospital stay, 37.5% of geriatric patients were treated with haloperidol, a drug with anticholinergic properties. However, because of its high antipsychotic potency, the risk of anticholinergic effects with this drug is low. Haloperidol at low doses (0.25-0.5 mg/day) is recommended as prophylaxis for delirium in hospitalized, elderly patients, in whom this condition may occur in 10-38%

of patients.[178-180] In contrast to findings from the study by Saltvedt et al.,[167] no difference in the prevalence of anticholinergic drug use between admission and discharge was found in geriatric or medical patients in the current study.

Our study has several limitations. Direct comparison of the prevalence of use of PIMs between the two study populations may be limited by differences in age, proportion of female patients, reason for hospitalization, differences in underlying diseases, and length of hospital stay (table 8). It is known from other studies that the number of drugs per patient is a strong risk factor for the use of PIMs,[123,181,182] but this parameter was not different between geriatric and medical patients in our study. Age and sex were often not significant risk factors in multivariate analyses,[181,182] and higher age in one study was actually associated with reduced risk for PIMs.[123] Therefore, if the prevalence of PIM use had been influenced by the characteristics of the two populations studied, underlying diseases and reasons for hospitalization (e.g. frequent history of falls in geriatric patients) would have been the most likely factors.

Because of the retrospective study design, the clinical consequences of intake of PIMs or anticholinergic drugs are unknown. Some studies have investigated outcomes following administration of PIMs and found an association with poorer self-perceived health status, higher healthcare costs and a higher number of inpatient, outpatient or emergency room visits.[183-185] Other studies, however, failed to show any association between intake of PIMs and an increase in number of outpatient visits, increased healthcare utilization or decrease in quality of life.[186,187] Administration of inappropriate drugs according to the Beers criteria has not been associated with higher mortality,[85,185,188] except in two studies.[164,181] One of these two studies used a combined endpoint, however, consisting of hospitalization, emergency department visit and death.[181]

Because of the limitations of the Beers criteria, the results of this study have to be interpreted carefully. The Beers criteria are a useful tool for evaluating drug prescriptions in elderly patients with the intention to improve prescribing. However, the criteria are based on expert opinions and not on an evidence-based methodology.[189,190] Even if the drugs in the Beers list may be considered as inappropriate, they are not contraindicated per se, and their benefit-to-risk ratio must

be assessed in the context of the individual patient's clinical condition.[189,190] However, the Beers criteria do not propose an alternative therapy with a better tolerability and/or outcome than the drugs listed as inappropriate.[189]

In the Beers criteria, concomitant treatment with platelet aggregation inhibitors is defined as potentially inappropriate in patients receiving anticoagulant therapy, because of an increased risk of hemorrhage.[121] This risk has been demonstrated in a number of studies.[191-194] However, in patients with acute coronary syndrome, initial treatment with unfractionated heparin or LMWHs in combination with low-dose aspirin (acetylsalicylic acid) is associated with reductions in recurrent myocardial infarction and death.[193] In patients, assessment of the individual risks and benefits, taking into account the individual clinical situation is important. The dosages of the anticoagulant used should be adjusted according to renal and hepatic function, and effects monitored closely, as high doses are associated with increased risk of bleeding.[104,191,195-197] Most of the patients comedicated with platelet aggregation inhibitors and anticoagulants in our study were treated with LMWHs for thrombosis prophylaxis during hospitalization because most hospitalized elderly patients are at increased risk of venous thromboembolism.[104,198] If such patients are taking prophylactic rather than therapeutic dosages of LMWHs, they may be exposed to only to a slightly increased risk of bleeding, because of the dose dependency of this ADR.[199] However, the Beers criteria do not differentiate between prophylactic and therapeutic use of heparin or LMWHs in combination with platelet aggregation inhibitors.

Another example of a drug commonly identified as potentially inappropriate in the current study according to the Beers criteria is amiodarone, because of its potential to prolong the QT interval and induce torsade de pointes. These two ADRs are considered to be dose dependent. However, there is no evidence that age is associated with a significant alteration in the pharmacokinetics of amiodarone or that the risk of cardiac adverse events is increased in the elderly.[200] Prolongation of the QT interval and torsade de pointes occur in <1% of the patients treated with amiodarone.[201,202] In comparison, studies have shown beneficial effects of amiodarone in the treatment of sustained ventricular tachyarrhythmias and/or atrial fibrillation in patients after myocardial infarction, especially in patients with left

ventricular dysfunction.[201,203] In the presence of ventricular tachyarrhythmias, elderly or critically ill patients may profit from treatment with amiodarone, when the implantation of a cardioverter defibrillator is not possible.[201,203]

Conclusion

The results of this study show that the use of inappropriate drugs according to the Beers criteria is common on both medical and geriatric wards. Compared with internists, geriatricians have a better understanding for PIMs that should generally be avoided. On the other hand, similar to internists, geriatricians did not reduce the prevalence of PIM use associated with a specific diagnosis or use of anticholinergic drugs.

Many of the drugs identified as inappropriate according to the Beers list in this study may be considered to be appropriate, when taking into account the patient's clinical condition. Examples of such drugs include amiodarone or the combination of anticoagulants or LMWHs with platelet aggregation inhibitors. The Beers criteria are a useful tool for identifying potential pharmacological problems in the elderly, but their use in clinical practice is limited because age per se is not a good indicator of the individual's health status and the elderly are not a homogeneous population. It is essential to determine the benefit-to-risk ratio of a drug therapy individually for each patient, taking into account the clinical condition of the patient, the degree of impairment of hepatic and/or renal function, and the potential for interactions with existing drug therapies. In addition, elderly patients, especially those taking PIMs, should be monitored closely for potential ADRs.

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Appendix

Drugs listed in the Beers criteria published in 2003,[121] but not marketed in Switzerland are: carisoprodol, chlorpheniramine, chlorzoxazone, cyclobenzaprine, cyproheptadine, desiccated thyroid, dicyclomine, disopyramide, ethacrynic acid, guanadrel, guanethidine, halazepam, hyoscyamine, isoxsurpine, mesoridazine, metaxalone, methamphetamine, methocarbamol, methyltestosterone, orphenadrine, oxaprozin, pemolin, perphenazine-amitriptyline, prazosin, propantheline, propoxyphene, pseudoephedrine, quazepam, tacrine, thiothixene, ticlopidine, trimethobenzamide and tripelennamine.

CASE REPORT

LITHIUM INTOXICATION AS A RESULT OF AN INTERACTION WITH ROFECOXIB

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Abstract

Objective: To report the occurrence of lithium intoxication in a patient with bipolar disorder after adding rofecoxib to the medication regimen.

Case summary: A 68-year-old woman with bipolar disorder under long-term treatment with lithium, carbamazepine, pipamperone, and mirtazapine was prescribed rofecoxib 25 mg twice daily for the treatment of leg pain. Within one week, she showed progressive hypokinesia and tremor, which was treated with propranolol. Subsequently, she developed bradycardia, necessitating treatment with isoproterenol. Her lithium serum concentration had doubled compared with those before rofecoxib, and her renal function had deteriorated. After stopping lithium and rofecoxib, her laboratory values and neurologic signs improved or normalized within 2 days. An objective causality assessment revealed a probable relationship between concomitant use of the drugs and the resulting symptoms.

Discussion: As of May 24, 2004, only 3 cases of reversible lithium intoxication as a result of a possible interaction with rofecoxib or celecoxib have been previously reported. The mechanism of the interaction between lithium and cyclooxygenase (COX) 2 selective inhibitors is most probably related to inhibition of renal synthesis of prostaglandins, which are important for the maintenance of renal perfusion and tubular function. Impairment of renal blood flow, leading to a decrease in the glomerular filtration rate, and increased proximal tubular absorption are the most likely mechanisms by which COX-2 selective inhibitors reduce lithium clearance.

Conclusions: Coadministration of rofecoxib and lithium may result in life-threatening lithium intoxication, especially in patients with a preexisting decrease in renal function and/or decreased intravascular volume.

Introduction

Selective COX-2 inhibitors are frequently used to treat acute and chronic inflammatory diseases and pain because they appear to have a lower risk for gastrointestinal toxicity compared with conventional NSAIDs.[204] However, the expectation that COX-2 selective inhibitors could also reduce untoward renal effects compared with conventional NSAIDs could not be met.[205] Considering reviews about the effects of selective COX-2 inhibitors on the kidneys, it appears that their nephrotoxicity is similar to that of nonselective COX-2 inhibitors.[205,206] COX-2, initially thought to be expressed primarily in inflamed tissues, has been shown to also play a role in physiologic processes, including maintenance of renal function. This is particularly the case in conditions involving increased renal prostaglandin dependence such as decreased sodium intake, volume depletion, renal artery stenosis, liver cirrhosis, and heart failure.[205,207] Renal expression of COX-2 is increased in the conditions mentioned above to maintain renal blood flow and GFR, as well as tubular functions involved in sodium, potassium, and water homeostasis. Acute renal failure associated with COX-2 selective inhibitors has been reported in patients with the same risk factors as reported for conventional NSAID-associated renal adverse effects.[205,207]

Lithium is an established treatment for patients with bipolar disorders. Due to its toxicity, the lithium serum concentration must be maintained within a narrow range. Neurologic manifestations of toxicity are dose dependent and may begin with nausea/vomiting, drowsiness, lethargy, coarse hand tremor, and muscular weakness, followed by nystagmus, ataxia, confusion, dysarthria, and myoclonic twitches, finally resulting in impaired consciousness, seizures, coma, and death. Electrocardiographic changes (flat or inverted T waves) may also be observed.[208]

The pharmacokinetic properties of lithium and its DDIs have been reviewed.[208] Lithium is absorbed rapidly and completely from the upper gastrointestinal tract, is not bound to plasma proteins, is distributed evenly in the body water (showing a volume of distribution of 0.7 L/kg), and is eliminated almost entirely by the kidneys. Lithium is filtered by the glomerulus, and approximately 75% of the amount filtered is reabsorbed in parallel to sodium, mostly in the proximal tubule.[209] Several drug

classes, including diuretics (particularly thiazides), ACE inhibitors, and NSAIDs have been shown to decrease renal lithium clearance and increase lithium serum concentrations.[210]

Since selective COX-2 inhibitors show effects on the kidney similar to those of conventional NSAIDs,[205,207] COX-2 inhibitors could also decrease renal lithium clearance. However, to the best of our knowledge, only a few cases of possible interactions of lithium with celecoxib[211,212] or rofecoxib[213] have so far been reported in the literature. Most recently, Phelan et al.[214] described 18 patients with increased serum lithium concentrations associated with the addition of a COX-2 inhibitor to their medication regimen; these cases had been reported to the Food and Drug Administration.

Case report

A 68-year-old woman with a bipolar disorder, who had been on a stable treatment regimen with lithium 200 mg twice daily for 12 years (serum concentrations 0.74 - 0.94 mEq/L), was hospitalized due to pain in the left leg after an accidental fall 3 months earlier. Additionally, she had been prescribed carbamazepine 400 mg twice daily (for 12 years), pipamperone 60 mg daily and zopiclone for sleeping (for 6 years), and mirtazapine 30 mg daily (for 3 months). There was no history of previous use of NSAIDs or aspirin. X-ray investigations revealed osteochondrosis at L5-S1, but no direct cause for the pain in the left leg. Physical examination revealed kyphosis of the thoracic vertebral column and hyperlordosis. Since the woman had pain upon compression of the lumbar and pelvic musculature, a diagnosis of lumbospondylogenic syndrome was made. Additional diagnoses were chronic pancytopenia of unknown origin and impaired renal function (reason not known, first diagnosis 3 years before presentation), with calculated creatinine clearance approximately 40 mL/min. On the day of hospitalization, her serum creatinine concentration was 1.25 mg/dL, heart rate 68 beats/min, and blood pressure 90/60 mm Hg, a normal value for her. To treat the pain, administration of rofecoxib

25 mg twice daily was started. On the second day of hospitalization, the patient's serum lithium concentration was just above the upper therapeutic range (0.81 mEq/L, range 0.5-0.8). On day 3, she started to develop hand tremor. She was examined by a neurologist, who diagnosed an extrapyramidal syndrome consisting of tremor, rigor, and hypokinesia, possibly associated with neuroleptic treatment. On day 8 at 11:00, the patient was treated with a single dose of propranolol 40 mg because the tremor had worsened. In the late afternoon, approximately 6 hours after administration of propranolol, the patient reported headache, nausea, and vomiting. An electrocardiogram showed sinus bradycardia and intermittent complete atrioventricular block with sinus arrests up to 4 seconds, but no signs of heart failure. She was transferred to the intensive care unit (ICU) for supervision.

Table 12. Clinical signs and laboratory values in a patient treated with lithium and rofecoxib

	Day							
Parameter	**1**[a]	**2**	**7**	**8**[b]	**9 (01:45)**	**9 (12:51)**	**10 (06:45)**	**10 (13:30)**
Lithium concentration (therapeutic range: 0.5-0.8 mEq/L)		0.81		1.67		1.32	0.92	
Carbamazepine concentration (therapeutic range: 4-10 mg/L)						12.7		
SCr concentration (reference range: 0.5-1.0 mg/dL)		1.25		1.77	1.58	1.59	1.33	1.24
Calculated Cl_{cr} (mL/min)		41		28		28	38	41
Potassium level (reference range: 3.5-5.0 mEq/L)		4.3		5.4	5.3	4.3	4.5	4.3
Blood pressure (mm Hg)	90/60	120/60	120/68	90/40	102/68	112/90	118/48	104/54

[a]Rofecoxib started.

[b]Single oral dose of propranolol was administered; rofecoxib and lithium were stopped.

Cl_{cr} = creatinine clearance; Scr = serum creatinine.

Upon admission to the ICU, her heart rate was 40 beats/min, and blood pressure was 90/40 mm Hg (table 12); no atrioventricular block or signs of heart failure were noted.

She was alert, her speech was slurred, she exhibited tremor of her hands at rest, and intermittent periods of drowsiness occurred. Neither nystagmus nor asterixis was present. Intravenous isoproterenol was administered, resolving bradycardia and increasing blood pressure. During the whole episode, the patient's urine output had been >70 mL/h, indicating that renal perfusion had been maintained. In comparison with the value obtained 6 days earlier, the lithium serum concentration had doubled (1.67 mEq/L), reaching the toxic range. As shown in figure 7, this increase could partially be explained by a drop in the clearance of lithium since the calculated creatinine clearance was 27 mL/min at this time. An electrocardiogram revealed inversion of the T wave, compatible with increased lithium serum concentration. Rofecoxib and lithium were stopped on day 8, and carbamazepine was stopped on day 9. After rofecoxib was stopped, the creatinine clearance reached the prehospitalization level over 2 days, with a parallel fall in the serum lithium concentration to 0.92 mEq/L over that same period (figure 7).

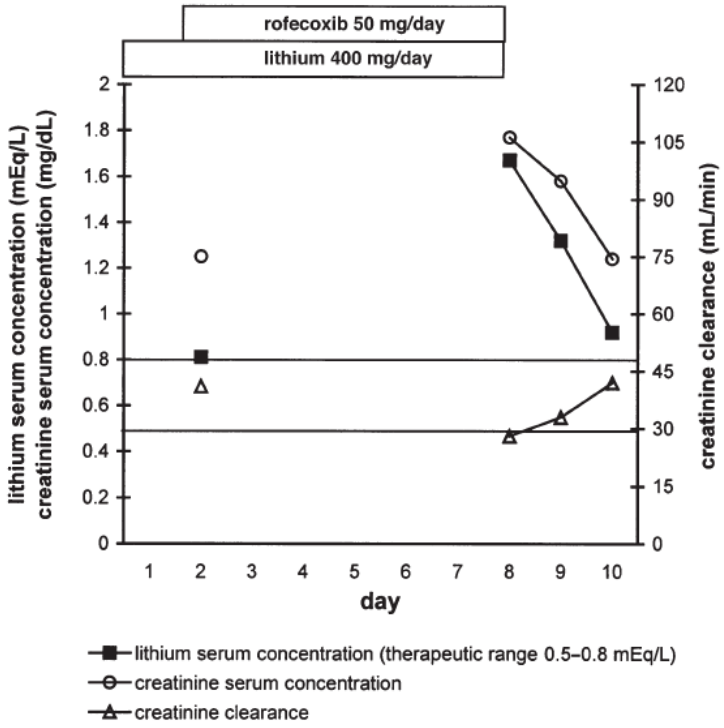

Figure 7. Lithium and creatinine serum concentrations and creatinine clearance during concomitant rofecoxib therapy.

The patient was discharged from the ICU on the tenth day of hospitalization (3 d after entering the ICU) with a normal heart rate, normal electrocardiogram, and clearly improved tremor. After the reintroduction of lithium and carbamazepine at the same dosage as before and initiation of paracetamol as analgesic, the patient had no further complications. Using the Naranjo probability scale, a probable relationship was found for lithium intoxication and an interaction between lithium and rofecoxib.[215]

Discussion

Three cases of an interaction between COX-2 inhibitors (celecoxib or rofecoxib) with lithium, resulting in increased serum lithium concentrations and lithium toxicity, have been reported in detail.[211-213] All of these cases are comparable with the one we describe here. All patients were elderly, had been treated with lithium and other drugs for many years, and had maintained serum lithium concentrations within the therapeutic range. All patients developed signs of lithium intoxication (confusion, tremor, gait disturbance) leading to hospitalization a few days up to 3 months after beginning treatment with a COX-2 inhibitor. In all patients, toxic serum lithium concentrations (>1.2 mEq/L) and elevated serum creatinine values were measured. After withdrawal of lithium and the COX-2 inhibitor, all patients recovered within one week, and the lithium and creatinine serum concentrations returned to the values prior to administration of the COX-2 inhibitor. Our patient was also treated with carbamazepine, which has been reported to have a pharmacodynamic interaction with lithium.[208] Such an interaction may therefore have contributed to the neurologic symptoms experienced by our patient.

A case series published in abstract form included 10 patients on lithium therapy who were treated with rofecoxib 50 mg for 5 days due to various pain states.[216] In 9 of these patients, the serum lithium concentrations increased, and one of these patients developed signs of mild lithium toxicity. After stopping treatment with rofecoxib, the lithium concentrations of all patients returned to near baseline.

Of 20 cases of lithium intoxication reported spontaneously to the Swiss Agency for Therapeutic Products between 1996 and 2003, 2 patients (including ours) were treated with rofecoxib (10% of the reported cases) and 6 patients received conventional NSAIDs (ibuprofen, diclofenac, mefenaminic acid, aspirin; 30% of the reported cases). Most patients were on stable, long-term therapy with lithium, and signs and symptoms of lithium intoxication occurred a few days after introduction of the NSAID or COX-2 inhibitor. Three patients (including ours) had relevant comorbidities, such as preexisting renal failure and/or dehydration.

Most recently, Phelan et al.[214] found 18 possible cases of lithium interacting with COX-2 inhibitors: 13 with rofecoxib and 5 with celecoxib. The increase of the serum lithium concentration after the addition of celecoxib ranged from 56% to 99% and, after rofecoxib was introduced, from 58% to 448%. The adverse effects were consistent with the symptoms of lithium intoxication. Most patients recovered after discontinuation of the COX-2 inhibitor and/or reduction of the lithium dosage. Unfortunately, the case series lacks information about preexisting renal disorders, concomitant drug use, and medical history of the patients.

As mentioned above, approximately 75% of the filtered lithium ion is reabsorbed by the renal tubules and collecting ducts. The major part of this reabsorption occurs in the proximal tubule (up to 70% of the lithium filtered),[209,217] and minor amounts are reabsorbed in the loop of Henle and the collecting ducts.[218,219] Although the mechanism of proximal tubular reabsorption of lithium is debated,[220,221] it competes with the reabsorption of sodium and may be driven by the sodium-hydrogen exchanger[209]. This is compatible with the observation that administration of sodium to patients with lithium intoxication is associated with increased lithium clearance. Reabsorption of lithium in the loop of Henle is bumetanide sensitive and proposed to be accomplished by the sodium-potassium-chloride cotransporter[219] and, in the collecting ducts, by the sodium channel.[209] Dehydration is associated with reduced clearance of lithium primarily due to impaired renal perfusion resulting in reduced lithium filtration, but also due to increased reabsorption of lithium.[209,210,222] It has been shown that age-related changes in the glomerular filtration rate may explain the prolonged plasma half-life of lithium in the elderly.[223]

The interaction between NSAIDs and lithium is well established and, apparently, the effect on lithium clearance differs among the individual NSAIDs (e.g., the effect of aspirin and sulindac is less pronounced than with other NSAIDs).[210,224] However, the mechanism of the interaction between NSAIDs and lithium leading to increased lithium serum concentrations is not fully understood.[136] COX-2 is constitutively expressed in the thick ascending limb of the kidney, in interstitial cells of the papilla, and in cells of the macula densa.[205,207] Although the role of COX-2 in the kidney is not completely clear, it seems to be important for the regulation of the renal function, more so than COX-1.[225] Vasodilating prostaglandins, predominantly prostaglandin E2 (PGE_2), play an important role in the maintenance of renal blood flow, particularly in patients with decreased sodium intake, volume depletion, renal artery stenosis, or heart failure.[205,207] Administration of an NSAID or COX-2 inhibitor to such patients may therefore cause a sharp decrease in renal blood flow, possibly leading to acute renal failure.[206,207,210] In addition, PGE_2 may play also a role in controlling renal salt and water reabsorption, and reduced renal PGE_2 levels may be associated with increased reabsorption of sodium and lithium in patients treated with NSAIDs.[206,210,224]

Summary

Similar to nonselective COX inhibitors, the administration of COX-2 selective inhibitors to patients treated with lithium may result in increased lithium serum concentrations and lithium intoxication. The lithium serum concentration may increase rapidly (within days) after introduction of the COX-2 selective inhibitors. Patients at risk are those with conditions of increased prostaglandin dependence of renal perfusion, such as those with reduced sodium intake, volume depletion, impaired renal function, liver cirrhosis, or heart failure.

In patients treated with lithium, NSAIDs or COX-2 inhibitors should therefore be avoided, particularly in the presence of risk factors. If anti-inflammatory treatment with COX-2 inhibitors or NSAIDs is considered to be necessary in such patients,

lithium concentrations should be monitored closely and lithium doses should be adjusted to lower levels accordingly. If anti-inflammatory treatment is stopped, the reverse reaction will occur, and lithium doses should be increased to prevent exacerbation of bipolar disorder.

DISCUSSION, CONCLUSION, OUTLOOK

Discussion

Because of demographic aging medical care of elderly patients is an important issue. One aspect of special concern is the higher risk for ADRs associated with medical treatment. This increased risk may not only be ascribed to age-related physiological changes, but is also directly associated with specific drug classes prescribed to the elderly.[226]

In the first study age-related differences in the prevalence of pDDIs were analyzed in a high risk population for polymorbidity and polypharmacy, in dyslipidemic patients treated with a statin. As expected, patients aged ≥75 years had a significantly higher prevalence of pDDIs compared to patients aged ≤54 years. Factors mainly responsible for this finding were the higher prevalence of underlying diseases leading to a higher number of pharmacologically active substances prescribed as well as a higher number of substances per diagnosis prescribed. This result confirms that polypharmacy in comorbid patients is an important risk factor for pDDIs that may lead to ADRs.[89,129] It is therefore advised to reduce the number of drugs prescribed, whenever possible. Arrhythmia and heart failure have been identified as risk factors for pDDIs in patients aged ≥75 years. These diagnoses are surrogate parameters for the drugs used in the treatment of heart failure and arrhythmias that were involved in statin and non statin pDDIs such as amiodarone, digoxin, ACE inhibitors, oral anticoagulants, diltiazem and verapamil. The risk for ADRs resulting from the pDDIs identified could in most cases be lowered by dose adjustment, close monitoring or selection of an alternative drug. As an example, pDDIs involving atorvastatin or simvastatin could often be avoided when pravastatin that is not significantly metabolized by CYP isozymes in the liver is given instead. On the other hand, it has to be considered that atorvastatin and simvastatin are more potent at moderate doses than pravastatin and produce a greater reduction in low-density lipoprotein cholesterol concentrations.[227,228] Although myopathy in patients who receive statin therapy is estimated to occur only in 0.1-0.5% of the patients and rhabdomyolysis in 0.04-0.2% of the patients, DDIs have been suspected to be the cause in 55-58% of the cases of rhabdomyolysis.[155,229,230] DDIs with statins, especially with simvastatin and atorvastatin, known to increase the risk for rhabdomyolysis should therefore be

avoided. The relevance of the results of the first study may be limited, because only pDDIs were evaluated and not ADRs resulting from these pDDIs. On the other hand, the pDDIs identified in our study have to be considered by physicians when prescribing drugs to elderly patients, because they are associated with a potentially serious outcome, because in the elderly other predisposing factors may further enhance the risk for ADRs, and lastly because pDDIs are a preventable risk.

Certain drugs or drug classes are directly associated with a higher risk for ADRs, especially in the elderly.[226] This was investigated in the second study, where the prevalence of PIM and anticholinergic drug use was assessed in elderly patients hospitalized either on a medical or geriatric ward. Compared to medical patients, patients discharged from the geriatric ward were significantly less PIMs prescribed than at admission. Similarly, also Laroche et al.[166] could show a significant decrease in the prevalence of PIM use in patients after hospitalization to an acute medical geriatric unit. These results show that patients may profit being treated by geriatricians with special knowledge of problems in the medical care of elderly patients. However, this possible benefit has yet to be confirmed in other studies. It has also been shown that clinical pharmacists may have an impact on appropriate prescribing and reduction of polypharmacy.[231,232] The strength of our second project was that also PIMs considering underlying diagnoses were evaluated, because most other studies did not include this aspect of the Beers criteria. The study revealed that geriatric patients were significantly more often prescribed PIMs considering underlying diseases at discharge than at admission. This was related to the frequent prescription of short-acting benzodiazepines to geriatric patients with a history of falls or syncope. Falls are a serious problem in the elderly and associated with increasing morbidity and mortality.[120] It is hypothesized that the newer compounds such as zopiclone, zolpidem or zaleplon may be safer for the elderly in half of the recommended adult dosage, because of their short half-lives and more selective pharmacological activities at the benzodiazepine-1 receptor.[174] However, their safety concerning the risk of falls has not been proven yet.[174] Elderly patients are also more vulnerable to anticholinergic effects.[233] Nevertheless, the overall prevalence of drugs with strong anticholinergic effects has neither been reduced in geriatric nor medical patients throughout hospital stay. However, especially the combination of

anticholinergic drugs, or the administration of anticholinergic drugs to patients with dementia should be avoided because of a higher risk for delirium.[77,112,165]

The Beers criteria have been shown to be a valuable tool to identify potential problems concerning the selection of drugs in the elderly, but they have also several limitations. In our study, one of the most common drugs identified as potentially inappropriate in both patient groups was amiodarone. But reviewing the literature it is not clear, why amiodarone has been listed as potentially inappropriate.[201,203] Also the classification of amitriptyline as potentially inappropriate without any limitation is questionable as amitriptyline has shown to be effective in the treatment of pain syndromes at low doses.[201,203,234] Lower doses may also be associated with a lower risk for anticholinergic effects.[235] Nevertheless, the list may help physicians to be aware of drugs associated with a higher risk for ADRs, but the decision to prescribe a certain drug must be made based on the patient's individual clinical situation. Other criteria published in the literature for the evaluation of appropriate prescribing such as the criteria published by Zhan et al.[236] or McLeod et al.[237] are equally based on the Beers criteria. Although similar, the three criteria do not completely agree on the drugs that should always be avoided. This demonstrates the problems of defining appropriateness of drugs that depends on several factors such as dosage, therapy duration, indication, and in particular the individual patient's clinical condition, because physiological functions, e.g. renal function, may markedly vary between individual patients in this age group. As the criteria published by Zhan et al. in 2001[236] or McLeod et al. in 1997[237] have not been updated since their publication, they are not considered superior to the latest Beers criteria published in 2003.

In the case report a clinically relevant DDI between a selective COX-2 inhibitor, rofecoxib, and lithium has been described. In the meantime, rofecoxib, valdecoxib and parecoxib, a prodrug of valdecoxib, have been withdrawn from the market in 2005, because of an increased risk for cardiovascular events including myocardial infarction, stroke, peripheral thrombosis and pulmonary embolism and in case of valdecoxib and parecoxib also because of severe cutaneous reactions (Stevens-Johnson syndrome, toxic epidermal necrolysis, erythema multiforme).[238-240] Celecoxib is the only selective COX-2 inhibitor left on the market at the moment. The introduction of selective COX-2 inhibitors raised hope that this class would cause

less adverse renal effects compared to conventional NSAIDs. However, COX-2 has been shown to also play an important role in maintaining renal function such as regulation of renal perfusion, salt and water handling and renin release.[205] COX-2 expression is higher in elderly patients and variably induced in conditions such as hypertension, congestive heart failure, and diabetic nephropathy.[241,242] This might explain the increased susceptibility of the kidney to COX-2 inhibitors in patients whose renal function is prostaglandin-dependent.[205,242] The patient described had a chronic renal impairment with a calculated creatinine clearance of 40 mL/min, raising the question, if treatment with a selective COX-2 inhibitor was appropriate in this case. Initiation of rofecoxib led to an immediate deterioration of renal function and accumulation of lithium that is mainly cleared through the kidney. It has been described that elderly patients are more vulnerable for neurotoxic effects even at serum lithium concentrations, which are considered therapeutic in general adult populations (0.4-1.2 mmol/L).[223] Summarized, several risk factors predisposed the patient for an ADR such as higher age, renal insufficiency, and treatment with lithium, a drug with a narrow therapeutic range and exclusively cleared through the kidney. Lithium intoxication could have been avoided by selecting paracetamol as analgetic treatment, by close therapeutic drug monitoring of lithium concentrations and dose adjustment of lithium.

Based on the potential risk factors for ADRs identified in the review performed at the beginning of this thesis and the results of the two projects carried out, as well as considering the evidence-based quality indicators developed for the appropriate medication use in the Assessing Care of Vulnerable Elders (ACOVE) project, [243,244] the medication appropriateness index published by Hanlon et al.[245] and recommendations made in other published articles,[5,27,246] the following recommendations for a safer drug treatment can be made. A new drug should only be prescribed if there is a clear indication. Medical treatment with proven effect and established in geriatric medicine should be preferred. However, evidence base for prescribing to older people is small, because elderly patients are often excluded from clinical trials.[14] This makes selecting the right medication and dose for the individual older patient often difficult.[247] The Beers criteria[121] may help to avoid drugs with a negative risk-benefit-ratio. It is advised to start with 30-50% of the recommended adult dose and to uptitrate the dosage slowly, until the desired clinical effect is

reached or until ADRs occur.[5,15] Dose adjustment should particularly be considered for drugs with a high hepatic extraction due to a lower first liver pass effect than expected (table 1, page 19) and for renally excreted drugs (table 2, page 22). It has to be considered, however, that also accumulation of active metabolites with high renal clearance may occur during long-term treatment (e.g. morphine-6-glucuronide). Before a new drug is added to an existing drug therapy it should be checked for pDDIs (see also table 3, page 26) and drug-disease interactions. Results from the first study of this thesis showed that especially drugs used in the treatment of arrhythmia and heart failure are often involved in clinically relevant pDDIs. As already mentioned, these pDDIs could often be prevented by dose adjustment and/or close monitoring. The most common clinically relevant pDDI observed in the study was concomitant treatment of ACE inhibitors with potassium sparing diuretics or potassium supplements increasing the risk for hyperkalemia. Close monitoring of serum creatinine and potassium levels, especially in patients with renal impairment, could prevent hyperkalemia.[93] For digoxin, as well as for some antiepileptic drugs, blood drug concentration measurements are available.[27] Amiodarone is mainly involved in pharmacokinetic pDDIs and may lead to dose-dependent ADRs by inhibiting metabolism of other substances such as oral anticoagulants, atorvastatin or simvastatin. Dose reduction and regular monitoring of the international normalized ratio (INR) when adding amiodarone to a treatment with oral anticoagulants may reduce bleeding risk. In case of a potential drug-disease interaction often alternative drugs with a more appropriate drug profile exist. In patients with orthostatic hypotension, tricyclic antidepressants may be replaced by SSRIs and, in case of antipsychotic treatment, an agent with a low affinity to α1-receptors (e.g. olanzapine, quetiapine) may be selected. Long-term use of full-dosage NSAIDs such as naproxen, piroxicam or ketoprofen without prophylactic treatment with a proton pump inhibitor should be avoided, especially in patients with history of ulcer.[40,41] COX-2 inhibitors are associated with fewer gastrointestinal adverse effects,[248] but, as seen in the case report, they are no safer than conventional NSAIDs regarding renal safety in patients with impaired renal function. Whenever possible, treatment with paracetamol should be preferred.[40] The combination of drugs with anticholinergic and/or sedative properties may increase the risk for cognitive impairment or falls, especially in patients with dementia or a history of falls and syncope, and should

therefore be replaced by safer alternatives. Clinical benefit has to be assessed within 6 month after beginning treatment and the drug withdrawn, if the effect is considered insufficient despite adequate dosage over an appropriate time period. The possibility of an ADR, also resulting from DDIs, has always to be considered, if nonspecific complaints such as confusion, lethargy, weakness, orthostatic hypotension, dizziness, incontinence, depression, parkinsonian signs and/or falls occur, which may be mistaken for 'geriatric symptoms'.[5,89,246] If physicians do not recognize the event as drug-induced another drug may be prescribed enhancing the risk for polypharmacy, pDDIs and consequently ADRs. It is advised to reevaluate indication of a medical treatment from time to time and to review the drug regimen. This may reduce the administration of unnecessary drugs and reduce the risk for pDDIs. The medication list should always be updated at each visit and also include OTC drugs. However, patients should be discouraged to take self-administered drugs.

Problems of adherence should be addressed in the elderly and drug regimen has to be adapted to the patient's physical and cognitive abilities. Drugs with a simple administration schedule are preferred. Generally, once or twice daily drug regimens are acceptable. The number of drugs should be kept to a minimum, as poor adherence increase with the number of drugs used.[21] Although polypharmacy should generally be avoided and efforts should constantly be undertaken to reduce the number of drugs, one should also be aware of the possible risk to withhold beneficial treatments in the elderly.[5,162,246] Drugs sometimes not prescribed, but shown to have some benefit, include therapy with beta-adrenoceptor antagonist after myocardial infarction, antihyperlipidemic drugs, adequate treatment of hypertension, ACE inhibitors for heart failure and anticoagulants for nonvalvular atrial fibrillation.[5] It is further important to check if the drug regimen is practical and if the patients did understand the directions given. A pill box may help to improve adherence in case of polypharmacy and complex medication regimens. Relatives or caregivers of the patients should be involved in the management of pharmacotherapy if the patient is seriously ill and/or if cognitive function is impaired.

Conclusion

In this thesis some specific aspects in the medical treatment of elderly patients were evaluated increasing the risk for ADRs. In the first study the prevalence of clinically relevant pDDIs in dyslipidemic patients treated with a statin and potential risk factors were investigated. The prevalence of clinically relevant pDDIs was higher in patients aged ≥75 years than in younger patients. Risk factors identified for statin and non statin pDDIs in the elderly were polypharmacy, as well as the prescription of drugs used in the treatment of arrhythmia and heart failure such as digoxin or amiodarone. Because the study was not designed to record ADRs as a result of the pDDIs identified, the clinical relevance of the results remains to be elucidated.

In a second study the prevalence of drugs defined as potentially inappropriate and of drugs with anticholinergic properties was assessed in elderly patients hospitalized to a medical and geriatric ward. The prevalence of PIMs could be reduced in geriatric patients. On the other hand, more benzodiazepines were prescribed to geriatric patients with a history of falls or syncope. In addition, drugs with anticholinergic properties were often prescribed to medical and geriatric patients.

The case of lithium intoxication as a result of an interaction with rofecoxib illustrated the clinical relevance to assess potential risk factors for ADRs before a new drug treatment is initiated, the importance for careful selection of an appropriate treatment and of close monitoring, especially when drugs with a narrow therapeutic range are given.

Numerous risk factors may predispose elderly patients to an increased risk for ADRs. However, depending on the underlying disease, medical treatment with drugs associated with a high potential for pDDIs and/or ADRs may not always be avoided. It is therefore important to know pharmacokinetic and pharmacodynamic characteristics of the drugs prescribed, including the risk for pDDIs in combination with other drugs, to examine the patient’s clinical condition, especially renal function and cognitive status, and to prescribe drugs only for confirmed diagnoses in order to avoid the prescription of unnecessary drugs. Close monitoring may help to detect ADRs early. It has to be considered that they may also manifest as unspecific complaints that may be misdiagnosed as ‘geriatric symptoms’.

Outlook

In this thesis only potential risk factors were evaluated, but ADRs following the exposure to these risk factors were not investigated. In a next step it would be interesting to assess the number of ADRs resulting from pDDIs in elderly compared to younger patients. However, depending on the specific ADR evaluated e.g. rhabdomyolysis resulting from the combination of simvastatin or atorvastatin with CYP inhibitors a high number of exposed patients have to be included in the study because rhabdomyolysis is estimated to occur only in 0.04-0.2% of the patients.

It would also be necessary to evaluate, how many patients develop ADRs due to the treatment with PIMs as listed in the Beers criteria. This would help to quantify the risk associated with each specific drug listed. It is suggested that in this case also minor ADRs should be assessed, because elderly patients are often predisposed to multiple risk factors for ADRs, and an additional minor causative factor can already lead to the clinical manifestation of an adverse event e.g. delirium or falls. Because studies are lacking so far, it would also be interesting to compare the risk of falls associated with the use of short-acting benzodiazepines with those of the newer compounds such as zolpidem, zopiclone or zaleplon in elderly patients. This would provide useful information if these newer compounds are safer than benzodiazepines and should therefore be preferred in the treatment of insomnia.

It would also be interesting to check in an elderly population, if every drug prescribed is also indicated based on the diagnoses listed in the medical record. It is suggested that the number of drugs could be reduced in many patients, because drugs without clear indication are prescribed. In practice, especially at hospital admission the medical record could be thoroughly reviewed and unnecessary drugs withdrawn, because the patients could be closely monitored for adverse effects resulting from withdrawal of these drugs. A clinical pharmacist could assist in the review of the drug regimen. Equally, it could also be assessed if a potentially beneficial treatment is not given, as undertreatment has also been discussed to occur in the elderly.

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CURRICULUM VITAE

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Education

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2002	**Swiss Federal Diploma in Pharmacy**, University of Basel, Basel, Switzerland Diploma thesis at the Clinical Pharmacology & Toxicology, University Hospital of Basel, Basel, Switzerland, entitled: *'Potential drug-drug interactions in the medication of medical patients at hospital discharge'.* Directed by Dr. Raymond Schlienger.
1997 - 2002	Study of pharmacy, University of Basel, Basel, Switzerland
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Professional Development

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Supervision of diploma theses of pharmacy students entitled:

- *'Prevalence of potentially inappropriate medication use in elderly hospitalized patients'*

- *'Adverse drug reactions of antimycotics used for the treatment of aspergillosis in hospitalized patients after stem cell transplantation'*

Practical Work Experience

08/2003	- 01/2007	Regular replacements as pharmacist at Apotheke Aarberg, Aarberg, Switzerland (Owner of the pharmacy Dr. Christine Bourquin)
01/2003	- 07/2003	Replacements as pharmacist at Apotheke Aarberg, Aarberg, and Geno Apotheke, Biel/Bienne, Switzerland
09/1999	- 08/2000	Practical year at Apotheke Aarberg, Aarberg, Switzerland. Therefrom 3 months at the hospital pharmacy of the Spitalzentrum Biel, Biel/Bienne, Switzerland

Lectures & Symposia

- **Public Health/Epidemiologie** (C. Desax, CR. Meier, R. Schlienger), University of Basel, Basel, Switzerland
- **Molekulare Mechanismen der Toxikologie** (J. Drewe, S. Krähenbühl, G. Weitz-Schmid), University of Basel, Basel, Switzerland
- **Biostatistics** (P. Vounatsou), University of Basel, Basel, Switzerland
- **Pharmathemen**: *Adipositas* (09/2003), *Herzinsuffizienz* (04/2004), *Analgetika und Antirheumatika* (10/2004), *Therapieoptionen bei Kachexie* (03/2005), *Dermatologie* (09/2005), *Reisemedizin* (03/2006), *Arzneimittelinteraktionen in der Apotheke* (09/2006) organized by the Clinical Pharmacology & Toxicology, University Hospital of Basel, Basel, Switzerland
- **Therapie im Alter: Wenn Medikamente mehr schaden als nützen** (04-12/2006) organized by the Bürgerspital Basel, Basel, Switzerland
- **SGIM Congress** (Schweizerische Gesellschaft für Innere Medizin): Interactive poster presentation to SKPT entitled *Potential drug-drug interactions in the medication of medical patients at hospital discharge* (05/2003) in Basel, Switzerland

Publications

1. **Egger SS**, Bachmann A, Hubmann N, Schlienger RG, Krahenbuhl S. Prevalence of Potentially Inappropriate Medication Use in Elderly Patients: Comparison between General Medical and Geriatric Wards. Drugs Aging 2006; 23(10): 823-37.
2. Bodmer M, **Egger SS**, Hohenstein E, Beltraminelli H, Krahenbuhl S. Lichenoid eruption associated with the use of nebivolol. Ann Pharmacother 2006; 40 (9): 1688-90.
3. **Egger SS**, Studer IG, Bravo AE, Krahenbuhl, S. Minocyclin-induzierter Lupus erythematodes. Fallbericht und UAW-Meldungen bei Swissmedic und WHO. Schweiz Rundsch Med Prax 2006; 95(35): 1297-303.
4. **Egger SS**, Ratz Bravo AE, Hess L, Schlienger RG, Krahenbuhl S. Age-related differences in the prevalence of potential drug-drug interactions in ambulatory dyslipidaemic patients treated with a statin. Drugs Aging 2006; accepted.
5. Burri E, Rüegg S, Rutishauser J, **Egger SS**, Lampert ML. Subtherapeutische Phenytoinspiegel infolge eines Medikationsfehlers. Schweiz Rundsch Med Prax 2006; accepted.
6. **Egger SS**, Sawatzki MG, Drewe J, Krahenbuhl S. Life-threatening hemorrhage after dalteparin therapy in a patient with impaired renal function. Pharmacotherapy 2005; 25 (6): 881-5.
7. **Egger S**, Drewe J. Interaktionen kardialer und antiretroviraler Medikation. Herz 2005; 30 (6): 493-503.
8. **Egger SS**, Schlienger RG, Krähenbühl S, Stoller R, Fattinger K. Unerwünschte Wirkungen von Arzneimitteln. In: Schweizerische Gesellschaft für Klinische Pharmakologie und Toxikologie (Herausgeber). Grundlagen der Arzneimitteltherapie. 16. Auflage. Basel: Documed AG; 2005. s. 54-148.
9. **Egger SS**, Krahenbuhl S, Schlienger RG. Umgang mit unerwünschten Arzneimittelwirkungen in der zahnärztlichen Praxis. Schweiz Monatsschr Zahnmed 2005; 115(12): 1209-13.
10. **Egger SS**, Schlienger RG, Krähenbühl S. Vorgehen bei unerwünschten Arzneimittelwirkungen. Schweiz Med Forum 2005; 5(11): 292-6.
11. Ratz Bravo AE, **Egger SS**, Crespo S, Probst WL, Krahenbuhl S. Lithium intoxication as a result of an interaction with rofecoxib. Ann Pharmacother 2004; 38 (7-8): 1189-93.
12. **Egger SS**, Drewe J, Schlienger RG. Potential drug-drug interactions in the medication of medical patients at hospital discharge. Eur J Clin Pharmacol 2003; 58 (11): 773-8.