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Polypharmacy and Drug Interactions in Elderly In- and Outpatients

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Polypharmacy and drug interactions in elderly in- and outpatients

Introduction Polypharmacy is a major risk factor for functional decline and secondary morbidity in elderly patients. The purpose of this paper is to investigate polypharmacy, prescription routine and the potential for drug interactions in elderly patients attending the Department of Internal Medicine at the Medical University Graz. Apart from recent, local data on prevalence and importance of potential drug interactions, this paper provides detailed information about pharmacokinetics in elderly patients and mechanisms of drug interactions.

Methods Data were collected from patients older than 65 yrs attending the Emergency Clinic of the Department of Internal Medicine at the Medical University Graz for 2-months (n= 723). Collection of data focused on drug therapy at time of admission and at the end of ambulatory (n= 323, age 76.7±8.0 yr) or inpatient (n= 400, age 79.8±7.5 yr) treatment. Potential drug interactions were evaluated electronically with MEDIS©.

Results The mean number of drugs at admission was significantly higher in patients further treated on inpatient (IP) basis (7.64±3.61) compared to the outpatient (OP) group (6.50±4.17) ($p \leq 0.001$). At discharge overall change in mean number of drugs in IP group to 7.78±3.17 was not statistically significant. In OP group the mean number of drugs was significantly increased to 7.00±4.12 ($p \leq 0.001$). In IP group significant increase was found in the age group between 65-74 yrs ($p \leq 0.005$), while significant decrease was found in the oldest old above 85 yrs ($p \leq 0.05$). In OP group increase in absolute number of drugs was significant throughout all age groups. The mean number of potential drug interactions in IP group did not significantly change from 3.12±3.33 to 2.99±2.88 while increase from 2.53±3.61 to 2.81±3.85 in OP group was highly significant ($p \leq 0.001$). Changes in absolute numbers of potential drug interactions in IP group were not statistically significant in any age group. Increases of potential drug interactions in OP group were significant throughout all age groups.

Discussion Our data support the hypothesis that short term visits at emergency clinics not employing doctors trained in the special needs of elderly patients may contribute to polypharmacy. An increase of number of drugs prescribed per patient also raises the potential for drug interactions. Therefore particularly elderly patients require careful evaluation of drug regimen.

Polypharmazie und Arzneimittelinteraktionen bei älteren stationären und ambulanten Patienten

Einleitung Polypharmazie ist einer der wichtigsten Risikofaktoren für funktionellen Abbau und sekundäre Morbidität bei älteren Patienten. Diese Arbeit soll Polypharmazie, Verschreibungsverhalten und das Potential für Arzneimittelinteraktionen bei älteren Patienten an der Universitätsklinik für Innere Medizin Graz untersuchen. Neben diesen aktuellen Daten zur Prävalenz und Bedeutung von potentiellen Arzneimittelinteraktionen werden die Hintergründe zur Pharmakokinetik bei alten Patienten sowie zu den grundlegenden Mechanismen von Interaktionen beleuchtet.

Methoden Daten wurden von Patienten über 65 gesammelt, die innerhalb von 2 Monaten die zentrale Notaufnahme der Universitätsklinik für Innere Medizin (EBA) besuchten (n=723). Dabei wurden die Medikamente bei Aufnahme und bei Entlassung aus ambulanter (n= 323, Alter 76.7±8.0) oder stationärer Behandlung (n= 400, Alter 79.8±7.5) erfasst. Potentielle Arzneimittelinteraktion wurden mit MEDIS© ermittelt.

Ergebnisse Die mittlere Anzahl an Medikamenten bei Aufnahme war bei stationär behandelten Patienten (IP) (7.64±3.61) signifikant höher als bei ambulant behandelten (OP) (6.50±4.17) ($p \leq 0.001$). Bei Entlassung zeigte sich keine signifikante Veränderung bei der mittleren Anzahl der Medikamente in der IP Gruppe, während sie sich bei der OP Gruppe signifikant auf 7.00±4.12 erhöhte ($p \leq 0.001$). In der IP Gruppe wurden Medikamente bei Patienten zwischen 65 und 74 Jahren signifikant erhöht ($p \leq 0.005$) und bei Patienten über 85 Jahren signifikant reduziert ($p \leq 0.05$). In der OP Gruppe zeigte sich in jeder Altersgruppe ein signifikanter Anstieg ($p \leq 0.001$). Die mittlere Anzahl an potentiellen Arzneimittelinteraktionen änderte sich in der IP Gruppe nicht signifikant von 3.12±3.33 auf 2.99±2.88 während sie sich in der OP Gruppe hoch signifikant von 2.53±3.61 auf 2.81±3.85 erhöhte. Veränderungen der potentiellen Arzneimittelinteraktionen in den Altersuntergruppen waren in der IP Gruppe nicht signifikant. In der OP Gruppe erhöhten sich die potentiellen Arzneimittelinteraktionen in allen Altersgruppen signifikant.

Diskussion Unsere Ergebnisse unterstützen die Hypothese, dass kurzzeitige Aufenthalte an Ambulanzen ohne speziell geriatrisch geschulte Ärzte zu Polypharmazie beitragen können. Eine Erhöhung der Medikamente eines Patienten erhöht auch das Risiko für Arzneimittelinteraktionen. Deshalb benötigen gerade ältere Patienten eine umsichtige Beurteilung ihrer medikamentösen Therapie.

Polypharmacy and Drug Interactions in Elderly In- and Outpatients

David Baumgartner

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List of abbreviations

ABC	ATP-binding cassette
ABDA	Federal Union of German Associations of Pharmacists
ACE	Angiotensin converting enzyme
ADE	Adverse drug event
ADME	Absorption, distribution, metabolism, elimination
ADR	Adverse drug reaction
ASA	Acetylsalicylic acid
AT II	Angiotensin II
AUC	Area under the curve
cAMP	Cyclic adenosine monophosphate
CNS	Central nervous system
CYP	Cytochrome P450
DGG	German Society for Geriatrics
EC_{50}	Half maximal effective concentration
ESC	European Society of Cardiology
GERD	Gastroesophageal reflux disease
GFR	Glomerular filtration rate
INR	International normalized ratio
LMWH	Low molecular weight heparin
MAOI	Monoamine oxidase inhibitor
MDRD	Modification of Diet in Renal Disease
MRP2	Multi-drug-resistance-associated protein type 2
NSAID	Non- steroidal anti-inflamatory drug
OAT	Organic anion transporter
OATP	Organic anion- transporting peptides
OCT	Organic cation transporter
OTC	Over the counter
p- gp	P- glycoprotein
SLC	Solute carrier family
SSRI	Selective serotonin reuptake inhibitor
TCA	Tricyclic antidepressant
UEMS	European Union of Medical Specialists
V_D	Volume of distribution

A. Introduction

1. The Geriatric Patient and Polypharmacy

Definitions of 'the geriatric patient' have been changing in the past and they will still be modified in the future. According to the German Society for Geriatrics (DGG) geriatric patients are defined by typical geriatric multimorbidity and higher chronological age (70 years and older) or by age above 80 years and typical increased geriatric vulnerability ('frailty') (DGG 2008; Sieber 2007). However definitions are usually not rigidly adhered to and thus geriatric patients are often simply referred to as people aged above 65 years.

The proportion of people above 65 years has been increasing over the last decades and it will even more increase in the future as baby boomer generation reaches the higher age. Nowadays, on average 16.9 % of total EU27 population are aged above 65 and there will be an increase up to 28.26% in 2015 (EUROSTAT 2007).

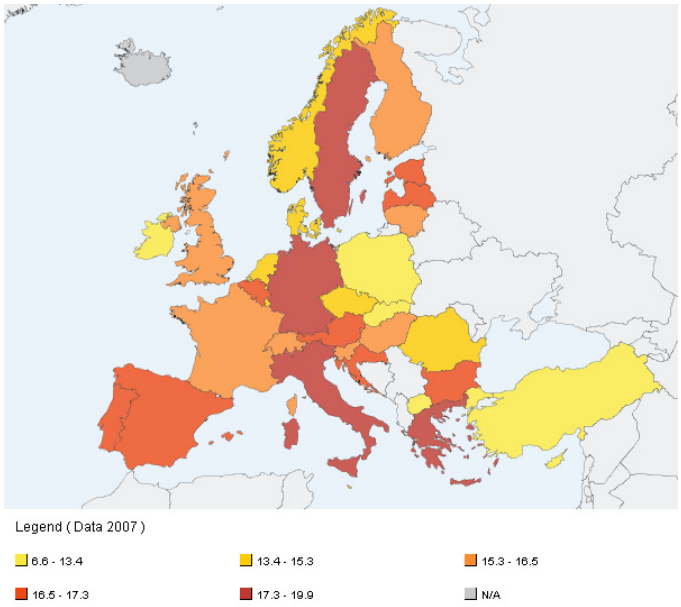


Figure 1 Proportion of population aged 65 and over in EU27 (% of total population)

'Normal aging' implicates a decline of functional reserves apart from concomitant disease. Additional diseases might therefore drastically limit functionality and autonomy of elderly people. In the most recent statement of geriatric medicine by the Geriatric Section of the European Union of Medical Specialists (UEMS) the optimization of the functional status of elderly and the improvement of quality of life and autonomy is the main goal (UEMS 2008).

Diagnostics and therapy of geriatric patients and especially of oldest old (> 80years) will become more important due to demographic change. The major

problems affecting elderly have often been referred to as the 'I's' or 'giants' of geriatrics.

Immobility
Instability
Intel Impairment
Incontinence
Isolation
Iatrogenic Complications

Table 1 The I's of Geriatrics

Iatrogenic complications have been added recently. Most of them may be attributed to polypharmacy.

The term 'polypharmacy' commonly describes the use of multiple medications albeit the number of drugs used varies from 2 up to 9. A second, probably more important definition emphasizes the administration of more medications than are clinically indicated, hence representing 'unnecessary drug use'. A large study evaluating drug therapy in elderly home care patients throughout Europe (N= 2707; mean age 82.2 years) found that 51% of patients took ≥ 6 medications per day and 22% of patients ≥ 9 drugs per day (Fialova et al. 2005).

The consequences of polypharmacy have also been examined in various studies (Hajjar, Cafiero, & Hanlon 2007). Even after controlling for multiple comorbidities, polypharmacy is associated with a decline in activities of daily living and increased risk of mortality. Patients taking multiple medications are more likely to receive inappropriate medication, to have adverse drug reactions (ADR), to develop poor adherence and to have potentially dangerous drug interactions (Hajjar, Cafiero, & Hanlon 2007). *(See Chapter 2, page 6)*

The role of polypharmacy and drug interactions in the elderly in daily clinical routine is the main focus of this paper. Screening for drug interactions by using computer based checks is a common and feasible method. However the reliability and relevance of those drug interaction programs is arguable and should also be discussed. Furthermore there are differences in prescription behavior between outpatient and inpatient treatment.

The knowledge of pharmacokinetics and especially of its age- related changes is crucial for understanding mechanisms of interactions. *Chapter 2, page 6 and chapter 5, page 24* provide a detailed overview.

2. Adverse Drug Events

Adverse drug events (ADEs) are defined as an injury resulting from the use of a drug. About 5% to 10% of hospital admissions are related to the management of elderly people suffering from drug- related toxicity. Furthermore adverse drug events have been estimated to be the fourth to sixth most frequent cause of death in geriatric patients (Lazarou, Pomeranz, & Corey 1998; Mannesse et al. 2000; Mjorndal et al. 2002).

ADEs can be triggered by various mechanisms. Drugs at usual doses can directly cause harm for instance by side effects. This type of ADE is commonly referred to as adverse drug reaction (ADR). Other mechanisms are drug-drug interactions and drug-disease interactions. Drug-drug interactions are described in detail in *Chapter 5, page 24*. Drug-disease interactions are caused by drugs that exacerbate preexisting diseases. For example NSAIDs or Aminoglycosides can cause acute renal failure in preexisting renal impairment.

Increased susceptibility of elderly people to ADEs results from altered pharmacokinetics and pharmacodynamics in older age. Some risk factors for ADEs have been recognized in older patients *(See Table 2)*.

Table 2 Risk factors for adverse drug reactions in elderly patients (Todd P.Semla & Paula A.Rochon 2006)

Age > 85
Low body weight or low body mass index
≥ 6 concurrent chronic diagnoses
An estimated GFR < 50ml per min
≥ 9 Medications
≥ 12 doses of medications per day
A prior adverse drug reaction

Lists of potentially inappropriate medications and drug-drug and drug-disease pairs have been published. The most common one was developed by the consensus of experts in geriatric medicine and pharmacology. It is well known as the ‘Beers list’ (Fick et al. 2003).

3. Principles of Pharmacokinetics in the Elderly

Pharmacokinetics describes the time course of a drug and its metabolites throughout the body (popularly known as ‘what the body does to the drug’). Traditionally pharmacokinetics is specified by four parameters: absorption, distribution, metabolism and elimination (‘ADME’). This chapter presents an overview of the effects of normal aging on each parameter and their clinical relevance. Beside polypharmacy and multimorbidity particularly elderly patients are prone to adverse drug reactions because of age related changes in pharmacokinetics.

3.1. Absorption

Absorption is the movement of a drug from the site of its administration into the central compartment, the blood.

The drug has to traverse the plasma membrane of many cells either by passive membrane transport or by carrier- mediated membrane transport.

Absorption of a drug on the one hand depends on the chemical properties of the drug, its chemical nature, its molecular weight and its solubility. On the other hand absorption is widely influenced by physiological variables which are determined by the route of administration.

The most common and preferred route of drug administration is orally or enteral as liquid, tablet or capsule. While drugs in liquid form are immediately available for absorption, tablets and capsules must first be disintegrated and dissolved in the stomach or in the gut fluids. The dissolved drug may then cross the intestinal mucosa in the stomach or the intestine, in the first instance consisting of an unstirred water layer, a mucus coat, the epithelial surface, the basement membrane and the interstitial space. After accessing the bloodstream through mesenteric capillaries and veins the drug reaches portal circulation. Following absorption some drugs undergo metabolism within the gut wall and the liver, the so called ‘first pass effect’ before entering the main blood stream.

Important physiologic variables affecting oral absorption are the local acid concentration or pH at the absorption site, gastric motility, the total area of

absorbing surface and its permeability, the mesenteric blood flow, presystemic elimination or first- pass effect and the way of ingestion (Clive Page et al. 2006). Most of these factors have been studied in geriatric patients.

The pH at the absorption site determines the fraction available in the non- ionized form that can easily diffuse across cell membranes. Early studies on changes in gastric pH in the elderly suggested a decline of gastric acid secretion in old age. More recent studies could demonstrate that aging effects on gastric acid secretion are likely to be confounded by long term infection of Helicobacter pylori, leading to gastric atrophy. Subsequently hypochlorhydria, which may be altered by the popular use of acid- suppressive drugs like proton pump inhibitors and H2-receptor antagonists may occur. There were no age- related changes in gastric acid secretary function found in older individuals without those confounders (Feldman 1997; Hurwitz et al. 1997; Katelaris et al. 1993). However as about 50% of elderly are infected with Helicobacter pylori with increasing prevalence with advanced age (Marshall 1994; Salles-Montaudon et al. 2002), changes in gastric physiology are still widespread among the elderly.

Gastric motility has been reported to slow down with age mainly due to region-specific loss of neurons (Evans et al. 1981; Hall 2002; Orr & Chen 2002). Regardless of the characteristics of a drug, the main site for drug absorption is the small intestine due to its extremely large surface. Thus any factor that delays gastric emptying will be likely to decrease the rate of drug absorption, while the amount of drug absorbed remains equal (Clive Page, Michael Curtis, Michael Walker, & Brian Hoffman 2006; Laurence L.Brunton, John S.Lazo, & Keith L.Parker 2006).

Even more important than physiological changes in aging on drug absorption is the impact of diet, age- related diseases and drugs on gastric motility. Impaired gastric emptying is caused by diseases such as diabetes mellitus, depression, hypothyroidism, chronic renal failure, anticholinergic drugs, especially antidepressants with anticholinergic effect, metoclopramid, opioid analgesics or calcium antagonists (O'Mahony, O'Leary, & Quigley 2002).

Studies of intestinal permeability in old age have been conducted with passively as well as actively transported substrates. Passive permeability measured by the lactulose/mannitol ratio absorption test seems to be unchanged in healthy subjects above 65 years (Saltzman et al. 1995). Some studies in aging rats with D-Xylose, urea and valproid acid also report unchanged passive permeability (Cato, III, Pollack, & Brouwer 1995; Yuasa et al. 1997) while others report increased permeability for macromolecules like polyethylenglycol (Hollander & Tarnawski 1985). Active transport of molecules like glucose (Yuasa, Soga, Kimura, & Watanabe 1997), calcium (Armbrecht, Boltz, & Kumar 1999) and vitamin B12 (Toyoshima, Inada, & Kameyama 1983) is impaired. Reduced glucose uptake and a decline of glucose transporters density per epithelial cell was found in elderly mice (Ferraris et al. 1993). Impaired vitamin D dependent active transport of calcium has been associated with decreased induction of intestinal plasma membrane calcium pump protein (Armbrecht, Boltz, & Kumar 1999). Vitamin B12 absorption is influenced by many factors, impaired active transport of cobalamin is mainly caused by deficiency of intestinal cobalamin transport proteins (Andres et al. 2004).

Many drugs like lisinopril, L- Dopa, pravastatin, cephalosporin or β- lactam antibiotics are substrates of different active uptake or efflux transporters (Tsuji & Tamai 1996). A key efflux transporter protein influencing the permeability of drugs is P- glycoprotein. It is expressed on the apical surface of normal intestinal mucosa and in contrast to absorptive transporters, P- glycoprotein returns parts of the drug entering the mucosa back into the intestinal lumen. Together with intestinal CYP3A4, P-glycoprotein widely determines intestinal first-pass metabolism (Doherty & Charman 2002; Doherty & Pang 1997; Lin & Yamazaki 2003). The effect of age on the activity of P-glycoprotein and intestinal CYP3A4 has not been reported exclusively but both act as an important site for drug- drug or drug- food interactions *(See chapter 5 Mechanisms of Interaction, page 24).*

While these mentioned factors are mainly affecting drugs with low permeability and low solubility, high permeability drugs are supposed to be of limited uptake by mesenteric and portal blood flow which are probably reduced in healthy aged patients (James 1983; Wynne et al. 1989; Zoli et al. 1989)

The effect of age on hepatic metabolism and first- pass effect will be described below *(See chapter 3.3 Metabolism, page 15)*.

Clinicians, however, are primarily concerned about the overall bioavailability rather than single aspects of absorption itself. The bioavailability reflects the fractional amount of a drug that reaches systemic circulation. The conclusions of studies on old age and the bioavailability of orally administered drugs are variable. While the bioavailability for lidocaine, verapamil, propanolol and levodopa has been found increased with age, no differences were found for amitryptiline, metoprolol and morphine (Wilkinson 1997). It is additionally difficult to differentiate the effects of altered absorption from altered first- pass metabolism on bioavailability.

In conclusion, despite all of the above age-related physiological changes in the enteral pathway of a drug, there is no sure evidence that absorption is severely altered by aging alone and thus considered as the less meaningful factor of the ADME scheme (Jerry Avorn, Jerry H.Gurwitz, & Paula Rochon 2003; Todd P.Semla & Paula A.Rochon 2006).

Transdermal drug administration has a number of advantages for the elderly. It avoids gastrointestinal absorption and hepatic first- pass metabolism, it minimizes adverse effects arising from peak plasma concentrations, there is no risk of infection and it improves patient compliance. Studies have shown that age-related changes in hydration and lipidic structure of the stratum corneum of the skin result in an increased barrier for hydrophilic coumpounds. In clinical practice however, no significant differences in absorption of drugs from transdermal delivery systems in the elderly have been demonstrated and therefore dose adaption due to impaired absorption is not necessary (Kaestli et al. 2008).

Data on the absorption of sublingual and transbronchial administered drugs in the elderly is too limited to allow conclusions regarding age-related changes, even though the elderly are among the most prominent user of such delivery systems.

3.2. Distribution

Following absorption or systemic administration drugs distribute into interstitial and intracellular fluids (Clive Page, Michael Curtis, Michael Walker, & Brian Hoffman 2006; Karen Birckelbaw Kopacek 2007; Laurence L.Brunton, John S.Lazo, & Keith L.Parker 2006). This process is influenced by a number of physiological factors and the particular chemical properties of the drug. The rate of delivery and the potential amount of drug distributed into a tissue is determined by cardiac output, regional blood flow, capillary permeability and tissue volume. Hence well perfused organs like liver, kidney or brain initially receive most of the drug whereas delivery to resting muscle, skin or fat is slower. Partitioning of the drug between blood and the particular tissue depends on lipid solubility of the drug and transmembrane pH gradients on the one hand and on the relative binding of drug to plasma proteins and tissue macromolecules on the other hand.

In blood drugs are transported partly in solution as free (unbound) drug and partly reversibly bound to blood components (plasma proteins and blood cells). Albumin is a major carrier for acidic drugs; α_1- acid glycoprotein binds basic drugs. Certain drugs may also bind to lipoprotein or specific hormone carrier proteins like sex-hormone binding globulin or thyroxin- binding globulin. Only unbound drug is available for passive diffusion to their site of action. Thus the unbound drug concentration in systemic circulation determines drug concentration at the site where the pharmacologic effects of the drug occur and therefore drug efficacy. Usually there is a chemical equilibrium between the bound and unbound drug fractions. The unbound part of a drug is determined by the affinity of the drug to proteins, the concentration of the specific binding protein and the concentration of drug compared to that of the binding protein. In most cases, drug concentrations at therapeutic doses are far below those of the binding protein and the fraction unbound is constant. As metabolism and excretion continuously only lower the free drug concentration, the equilibrium between bound and unbound drug is simultaneously reestablished by rapid dissociation of drug from the unbound fraction.

In addition to plasma protein binding, many drugs accumulate in tissue in higher concentrations than those in extracellular fluids and in blood. Tissue binding sites are usually cellular components like proteins, phospholipids or nuclear proteins. Like plasma protein binding, tissue binding is usually reversible. A large fraction of drug may be bound this way, serving as a reservoir that prolongs drug action or toxicity in that same tissue or systemically. Especially fat tissue is an important and rather stable reservoir for many lipid- soluble drugs.

A useful parameter for elucidation of drug disposition is the 'apparent volume of distribution (V or V_D)'. It is defined by the pharmacokinetic space a drug distributes into. The volume of distribution is thereby an abstract, estimated space and not an anatomical space. Its calculation is based upon the dose of drug administered and the resulting concentration in circulating plasma. For example, if 1000 mg of a drug is given and the subsequent plasma concentration is 10 mg/l, it may be estimated that 1000mg of drug seems to be distributed in 100 l of plasma volume (V = dose/ concentration; V=1000 mg / 10 mg/l = 100 l). Basic drugs which are highly tissue bound seem to have a very high volume of distribution since the plasma concentration is low. Acidic drugs that remain in the circulation tend to have a low volume of distribution. The apparent volume of distribution provides a reference for the plasma concentration expected for an administered dose but it provides little information about the specific pattern of distribution as each drug is uniquely distributed.

Another important parameter reflecting overall drug exposure is the 'area under the curve' of the unbound fraction (AUC). The AUC provides information about the drug concentration that reaches the blood stream over time. In clinical practice AUC measurements are commonly used in the monitoring of immunosuppressants like cyclosporine or tacrolimus.

Age related changes of protein binding and altered body composition as well as their consequences on drug distribution and above-mentioned pharmacokinetic parameters have been extensively studied.

There is evidence that normal aging results in a modest decline of serum albumin levels of about 0.1g/dl per decade and an overall decline of about 10% in the

oldest old (Campion, deLabry, & Glynn 1988; Gom et al. 2007; Greenblatt 1979; Salive et al. 1992). Hypoalbuminemia (serum albumin level < 3.5g/dl) is common in the elderly. A Japanese study of community- dwelling elderly observed that 2.4% of males and 1.5% of females had hypoalbuminemia (Gom, Fukushima, Shiraki, Miwa, Ando, Takai, & Moriwaki 2007). An evaluation of albumin serum levels in elderly nursing facility patients who were admitted to hospital reported hypoalbuminemia in 99% of patients (Ferguson et al. 1993). Low serum albumin in the elderly is a complex mix of pathophysiological processes. Protein uptake may be lowered due to inadequate nutrition and gastrointestinal malabsorption. Hepatic synthesis of albumin may be depressed due to liver dysfunction (e.g. cirrhosis, cancer, chronic illness). Stressors like infection, trauma or burns result in cytokine release which additionally reduce albumin synthesis and increase catabolism. Albumin losses may be increased due to renal damage, hemorrhage, open wounds or protein losing enteropathy (e.g. in celiac disease or Crohn's disease).

In contrast to serum albumin levels α1- acid protein levels are probably slightly increased in the elderly but since α1- acid protein is an acute phase protein, changes may be secondary to age- related inflammatory disease (Grandison & Boudinot 2000; Wallace & Verbeeck 1987).

Lower concentration of albumin is sometimes associated with an increase in the unbound fraction of drugs as there are less binding sites. On average the unbound fraction of drugs increases by approximately 10%, matching the age- related decrease in albumin, but those changes are predominately attributed to renal or hepatic dysfunctions (Grandison & Boudinot 2000). Examples are phenytoin (Patterson et al. 1982), diazepam (Davis et al. 1985), warfarin (Shepherd et al. 1977) and verapamil (Schwartz, Capili, & Daugherty 1994). Drugs like lidocaine which are particularly bound to α1- acid protein may have a decreased unbound fraction (Grandison & Boudinot 2000). Nevertheless age- related changes in protein binding have minimal clinical significance, as drug elimination enhances when the unbound fraction is increased (Benet & Hoener 2002; Grandison & Boudinot 2000; Turnheim 2003; Wallace & Verbeeck 1987). It also has been shown that protein binding does not influence the AUC of the unbound drug fraction of orally applied drugs (Benet & Hoener 2002). The only drugs whose

distribution may be bothered by altered protein binding are those highly extracted by the liver, extensively protein bound and administered intravenously. Examples are fentanyl, haloperidol, lidocaine, midazolam, propofol, propanolol and verapamil (Benet & Hoener 2002). As most of these drugs have a wide therapeutic index changes in unbound drug fraction that result from protein- binding changes will have negligible clinical effects. Lidocaine, which has a narrow therapeutic index and a rapid effect, might cause a clinically meaningful response during the time the body needs to re-equilibrate (Benet & Hoener 2002).

Most therapeutic drug monitoring techniques reflect total drug concentrations rather than unbound concentration shifts in bound/ unbound drug ratio. This fact has to be taken into account especially when prescribing drugs to elderly patients with malnutrition or chronic illness.

As the volume of distribution is influenced by relation of lean body mass, fat and water, age related changes in body- composition can markedly influence drug distribution. Lean body mass, especially the skeletal muscle mass declines in the elderly. Body fat increases with age by 20 to 40% while body water decreases by 10 to 15% until the age of 80 (Beaufrere & Morio 2000). Gender specific differences have to be taken into account as relative increase of total body fat is higher in old men (total body fat increase in aging men from 18% to 36%; in aging women from 33% to 45%) (Thurmann & Hompesch 1998; Vestal 1997). Lipid-soluble drugs as benzodiazepines or verapamil will thus have a greater volume of distribution in an older patient and water soluble- drugs like lithium or digoxin will have a smaller volume of distribution.

Very old, frail individuals lose weight, the proportion of fat decreases accordingly leading to a lower volume of distribution for lipophilic drugs. Body weight below 50 kg in addition to advanced age is therefore a major risk factor for overmedication (Campion et al. 1987).

These alterations in body composition can have important implications for both half- life and steady- state concentration of many medications, especially when changes in renal clearance occur *(see chapter 3.4 Elimination, page 18)*. A higher volume of distribution contributes to an increase in half- life and an increase in the

time necessary to reach steady- state serum concentration during repeated drug administration. Hence drug effects may be delayed in those circumstances but also prolonged.

3.3. Metabolism

Metabolism of drugs is essential for their elimination from the body, as well as for termination of biological and pharmaceutical activity. The lipophilic characteristics of drugs promote their passage through biological membranes and access to their site of action and prevent them from excretion. Biotransformation reactions generate more polar and usually inactive metabolites that can easily be excreted. In some cases metabolites with potent biological activity or toxicity are formed by biotransformation.

Drug metabolism reactions are classified into phase I and phase II reactions. Phase I processes are oxidation, reduction, hydrolysis reactions that provide a chemical group to the drug, which increases polarity (hence usually water solubility) and generally inactivates the drug. Phase II processes involve conjugation or synthetic reactions attaching a large chemical group like glucuronic acid, sulfate, glutathione amino acids or acetate. The conjugate- complexes are generally highly water soluble and may be excreted via urine and feces.

Enzymes involved in biotransformation of drugs are primarily localized in the liver. Additive organs with a certain metabolic capacity are GI tract, kidneys and the lungs. Drug metabolizing enzymes generally occur in various isoforms. Interindiviual differences in their genetic expression may contribute to interindividual differences in drug metabolism. Furthermore some enzymes are expressed constitutively with permanent activity, while others are only expressed when triggered by the presence of an exogenous chemical. Additionally, the activity of some enzymes may sometimes be increased (induced) or inhibited by diet or drugs.

The liver has an important gatekeeper role and protects systemic organs from toxic xenobiotics. Therefore changes in hepatic function and first- pass effect will

influence susceptibility to toxins and adverse drug reactions (Birnbaum 1991; Wilkinson 1997).

The effects of aging on hepatic drug metabolism clearance continue to be a controversial issue though they have been reviewed widely. Liver size reduces in old age by 20% to 35%, the endoplasmatic reticulum is diminished and hepatic intracellular space increases. Hepatic blood flow declines by about 40%, bile flow and the rate of synthesis of proteins, lipids and glucose are also reduced (Durnas, Loi, & Cusack 1990; Le Couteur & McLean 1998; McLean & Le Couteur 2004; Schmucker 2001).

P-450 cytochromes (CYP) are members of the heme protein enzyme isoforms that catalyze oxidative metabolism of many drugs and different exogenous chemicals. Three families of CYPs are important in metabolizing drugs (CYP1, CYP2, and CYP3). However there are hundreds of isoforms and subfamilies prsent in humans (CYP1A2, CYP2D6, CYP3A4, etc.).

In vitro studies found no relationship between age and activity of phase I metabolism including hepatic microsomal protein content or activity of various hepatic enzymes including CYP isoforms (Schmucker et al. 1990). Examinations of human liver samples reported a decline of CYP3A and 2E1, but not CYP1A2 or 2C although there were confounding factors like disease, drugs and smoking (George, Byth, & Farrell 1995). In vitro studies on phase II enzymes found no reduction of enzyme activity in older age (Le Couteur & McLean 1998).

In vivo studies of aging and drug metabolism usually report pharmacokinetics of a single drug. Though many studies reflect confounding factors like frailty, comorbidity, polypharmacy, smoking, alcohol intake or altered nutrition it is possible to determine the effects of age- related changes in blood flow, enzyme activity and liver size (Le Couteur & McLean 1998). The metabolic clearance of drugs in age has been attributed to the extraction ratio by the liver. Metabolism of drugs, that are highly extracted by the liver, is referred to as ‘blood- flow limited’ metabolism. As liver perfusion declines in the elderly metabolic clearance of those drugs is decreased by about 30% to 40%, correlating well with the age related reduction in blood flow. Examples for flow- limited drugs are morphine, propanolol,

amitryptiline and verapamil. On the other hand metabolic clearance of drugs with low hepatic extraction depends on total tissue content of metabolizing enzymes, the so called ‘intrinsic clearance’. This type is termed ‘capacity- limited’ metabolism (Le Couteur & McLean 1998). Though age is associated with a reduction in liver size there is no obvious association between age and the clearance of capacity limited drugs. Capacity- limited drugs are for example diazepam, digitoxin, salicylic acid and warfarin (Le Couteur & McLean 1998).

Even though in vitro activity of phase I enzymes does not change with age, most drugs metabolized via phase I pathways showed reduced clearance in elderly patients (McLean & Le Couteur 2004; Tanaka 1998). These included flow- limited as well as capacity- limited drugs. Age related decreases were found in most CYP enzymes (CYP1A, CYP2C9, CYP2C19, CYP2D6, CYPA3/4, CYP2E1) (Tanaka 1998). Clearance of drugs undergoing phase II metabolism seems to be unaffected by age in vivo (McLean & Le Couteur 2004).

There is currently no satisfactory explanation for impaired activity of phase I enzymes in the elderly. McLean and Le Couteur (Le Couteur & McLean 1998; McLean & Le Couteur 2004) suppose that there might be a decline in oxygen supply of enzymes due to thickening and defenestration of the sinusoidal endothelium. Especially phase I metabolism is directly dependent on oxygen as a substrate in contrast to phase II enzymes which require oxygen indirectly.

In general however the interindividual variations in metabolic drug clearance by phase I reactions exceed the age- related decline (Turnheim 2003).

The nutritional status of a patient has to be taken into account as drug metabolism is diminished frail elderly compared to geriatric patients with normal age (Vestal 1997; Walter-Sack & Klotz 1996).

In summary genetic, environmental and other patient- specific parameters have a greater clinical importance concerning hepatic metabolism than the aging process itself. Therapeutics interventions should therefore be based on individual patient characteristics as well as expected physiologic changes due to aging.

3.4. Elimination

Drugs are excreted from the body by several routes including the kidneys via urine, the intestinal tract via bile and feces, the lungs via exhaled air, sweat and others. Excretion in urine and feces represents the most important ways of drug and drug metabolite elimination.

Excretion of drugs depends on their polarity and solubility characteristics. Polar compounds are eliminated more efficiently than substances with high lipid solubility. Lipophilic drugs are not eliminated until they are metabolized into more polar substances. Furthermore the extent of plasma binding determines the rate of elimination as only unbound fraction of drug is excreted.

Renal excretion of drugs and their metabolites includes three distinct processes: glomerular filtration, active tubular secretion and passive tubular reabsorption. Changes in overall renal function usually affect all three processes to a similar extent.

The amount of drug entering the tubular lumen by filtration depends on the glomerular filtration rate (GFR) and the extent of plasma protein binding. In proximal renal tubule active carrier- mediated secretion may also excrete drug to the tubular fluid. Those transporters like p- glycoprotein (p-gp), multi-drug-resistance-associated protein type 2 (MRP2) or ATP- binding cassette (ABC) are localized primarily in the proximal tubular membrane. Drugs may further be actively reabsorbed by various transmembrane transporters located in the distale tubule. In both parts, proximal and distal tubule, drugs are further passively reabsorbed by diffusion into tubular cells and into blood vessels. Passive reabsorption widely depends on pH of the tubular fluid. When tubular urine is more alkaline weak acidic drugs are largely ionized. Thus they are more water soluble and therefore they are excreted more rapidly and to a larger amount. Acidic tubular fluid will reduce the fraction of ionized drugs and excretion is likelywise reduced. Therefore alkalinization and acidification of urine surely have the opposite effect on weak bases.

The effect of age on renal function is one of the most important and also a controversial discussion in geriatrics.

In most studies a substantial reduction in kidney volume has been reported with aging, ranging up to 40% in the very elderly (Tauchi, Tsuboi, & Okutomi 1971). However, elderly patients included in those studies showed high prevalence of comorbidity. Recent studies of healthy elderly found no significant reduction (Kasiske & Umen 1986) or a moderate reduction by 20% to 25% (Beck 1998). Especially after the age of 75 sonographic studies reported a considerable decline in kidney size and parenchyma diameter (Emamian et al. 1993). According to some studies the number of sclerotic glomeruli and interstitial fibrosis increases with old age leading to a loss of about 20% to 30% of glomeruli compared to younger adults (Neugarten et al. 1999). Evaluation of healthy elderly who died by trauma showed only minimal glomerulosclerosis (Kasiske & Umen 1986).

From the clinical perspective the glomerular filtration rate (GFR) is the most sensitive index to measure renal function and determine renal disease in the elderly. The knowledge of a patient's GFR is obligate in the use of renally eliminated drugs especially if they have a narrow therapeutic index like gentamicin, digoxin or lithium. The glomerular filtration rate (GFR) is defined as the volume of plasma filtered by all the glomeruli in a given period of time (Ginsburg JM & Borke JL 2008).

According to studies on kidney size, the decrease of GFR with age was assumed as 'inevitable' until recently. Newer studies revealed important and very common confounding factors that may critically accelerate decrease of GFR with age: atherosclerosis, hypertension and left ventricular dysfunction, glucose intolerance and diabetes mellitus, obesity, heart failure, undetected renal disease, smoking and disabling diseases (Obermayr et al. 2008; Yamagata et al. 2007; Zhang & Rothenbacher 2008). Without those confounding factors there was less decrease in GFR with normal aging. Renal blood flow however is impaired in elderly patients

Figure 2 Studies on glomerular filtration rate in old age (McLean & Le Couteur 2004)

Date of Study	Age Range	No.	Subjects	Renal Clearance				Reference
				Substance	Youngest or 20 years	Oldest or >80 years	Decrease in clearance in old age	
1950	25–89	70	Vascular disease in older subjects	Inulin	123 ml/min/1.73 m^2	65 ml/min/1.73 m^2	46%	Davies and Shock, 1950
1976	18–92	249		Creatinine	114.9 ml/min	37.4	68%	Cockcroft and Gault, 1976
1985	30–90	254	Baltimore Study, included hypertension	Creatinine	156 ml/min	94	40%	Lindeman et al., 1985
1989	19–93	30	Ambulatory volunteers	Creatinine	117 ml/min	53	55%	Friedman et al., 1989
1994	40–95	279	Healthy females	Creatinine	94 ml/min/1.73 m^2	66	30%	Sokoll et al., 1994
1997	26 ± 3 vs 68 ± 7	53	Healthy nonhypertensive volunteers	Inulin	121 ml/min/1.73 m^2	103	15%	Fliser et al., 1997a
1999	18–86	1629	Kuna Indians and Bostonians	*p*-Aminohippurate, inulin	Bostonians, 129 ml/min Kuna, 143 ml/min	107, 86	17%, 40%	Hollenberg et al., 1999
2000	1–80	143	Outpatients	EDTA	78 ml/min/1.73 m^2	67	14%	Peters et al., 2000
2001	25–78	43	Healthy volunteers	Creatinine	~145 ml/min/1.73 m^2	~100	30%	Adachi et al., 2001
2001	19–76	21	Potential kidney donors	Inulin	127 ml/min/1.73 m^2	76 ml/min/1.73 m^2	40%	Fuiano et al., 2001
2001	25–67	53	Healthy young, hypertensive old	Inulin	119 ml/min/1.73 m^2	104 ml/min/1.73 m^2	13%	Fliser and Ritz, 2001

as renovascular resistance increases and renovascular vasodilatation is limited compared to younger adults. Those changes result in a higher sensitivity of the older kidney towards decreased perfusion (i.e. exsiccosis, volume deficit caused by vomiting or diarrhea, decrease of blood pressure) (Fliser 2008b).

As renal function is variable with age due to high prevalence of comorbidity it has to be assessed individually. There are various markers, assessments and estimation methods used to determine the GFR and renal function. The most common and convenient endogenous markers are serum creatinine and serum cystatin C.

The level of serum creatinine mainly results from the balance between muscle catabolism and renal excretion. The amount of creatinine produced is thought to be relative stable; hence the serum level is determined by the rate of excretion. Serum creatinine however has important limitations, especially the so-called 'creatinine- blind area'. When serum creatinine increases above normal range, the GFR has already decreased by at least 40% in a younger person, and even more in the elderly (Fliser 2008b). Moreover normal ranges of serum creatinine used for younger adults may be inappropriately high for the elderly as creatinine production is decreased in old age due to decrease of muscle mass (i.e. lean body mass). As a consequence, serum creatinine in the upper range might already indicate severe impairment of renal function in old patients (Swedko et al. 2003). In a study correlating serum creatinine measurement with the gold standard of GFR measurement, the inulin clearance, 40% of individuals with decreased GFR had normal serum creatinine levels (Levey et al. 1999).

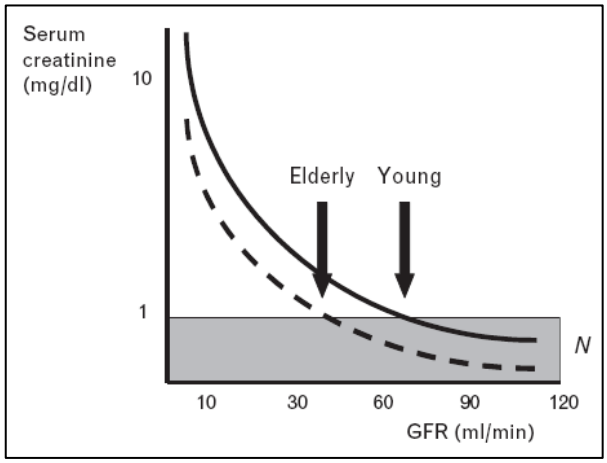


Figure 3 Relationship between glomerular filtration rate and serum creatinine (Fliser 2008b)

The curve drifts to the left with increasing age. As a consequence, in elderly people, an increase in serum creatinine out of the normal range (N) happens later than in younger individuals, and thus signals a more pronounced reduction of glomerular filtration rate.

An alternative endogenous marker developed to estimate GFR is serum cystatin C, a protein that is expressed in all nucleated cells. Studies have shown that cystatin is an accurate marker of subtle changes in GFR in elderly people and diagnostically superior to serum creatinine with better correlation with GFR (Fliser & Ritz 2001). This study found an increase of cystatin c in the elderly hypertensive patient group compared to young normotensive subjects while plasma creatinine was still within normal range. As cystatin c measurement is still much more expensive than that with creatinine, it should be applied when more precise assessment of renal function is necessary (Fliser 2008b).

The most precise assessments of glomerular filtration rate are accurate measurements of excreted markers. The optimal substrate should be non-protein bound, not reabsorbed in distal tubule, strictly renally excreted and if an endogenous substance is used, steadily produced (McLean & Le Couteur 2004). The most reliable but costly and cumbersome markers are specific markers like inulin, Cr- EDTA or Tc^{99m} DTPA. As mentioned before those methods are referred to as gold standard. Creatinine clearance is assessed by collecting urine and measuring creatinine excretion over time, usually 24h. However this test is prone to errors in urine collection as it is technically difficult, especially for elderly impaired. Additionally it may overestimate GFR because creatinine is also secreted in advanced renal insufficiency (Fliser 2008b).

Estimation equations for creatinine clearance and glomerular filtration rate are very common in daily clinical routine. There are several prediction formulas estimating GFR by serum creatinine concentration in combination with other factors as age, sex and weight. The best validated, particularly in elderly people, are the Cockcroft- Gault equation and the so- called Modification of Diet in Renal Disease (MDRD) formulas. Comparisons of the Cockcroft- Gault equation with direct measurement of GFR in a variety of clinical setting have uniformly revealed that this formula underestimates GFR in patients with normal and moderately reduced levels of renal function (Fliser et al. 1997; Marx et al. 2004). Additionally the formula is not considered to be reliable for obese or edematous patients (Fliser 2008a; Verhave et al. 2005). Several studies report an underestimation of GFR in elderly people, especially in the oldest old (Froissart et al. 2005; Garg et al. 2004;

Verhave, Fesler, Ribstein, du, & Mimran 2005). Cockcroft- Gault equation provides superior information about renal function compared to serum creatinine concentration alone but it is a limited screening method for chronic kidney disease in the elderly (Swedko, Clark, Paramsothy, & Akbari 2003). The MDRD formulas are mathematically complex, using different numbers of variables. The most precise of these are on the basis of six different variables (MDRD6) including a patient's sex, age, race, serum albumin and creatinine and blood urea nitrogen. Various studies suggest a slightly better performance of the MDRD in elderly populations above 65 years (Froissart, Rossert, Jacquot, Paillard, & Houillier 2005; Garg, Papaioannou, Ferko, Campbell, Clarke, & Ray 2004; Verhave, Fesler, Ribstein, du, & Mimran 2005). Nevertheless both formulas lack precision as staging of chronic kidney disease for both of them leads to misclassification in approximately 30% of subjects (Froissart, Rossert, Jacquot, Paillard, & Houillier 2005).

In conclusion (Fliser 2008a) measurement of serum creatinine is notoriously unreliable, hence GFR estimates as timed creatinine clearance, GFR estimation formula or serum cystatin c should be used. MDRD formula should be used instead of Cockcroft- Gault equation in most elderly patients. If there is concern about reliability of estimated GFR, cystatin c or even an isotope clearance method may be helpful, for example in dosing of nephrotoxic drugs.

Gastrointestinal excretion of drugs is another important way of drug elimination. Some drugs and their metabolites are excreted into bile by transporters similar to those in the kidney (p- gp, MRP2). Those transporters are located on the canalicular membrane of hepatocytes. During digestive process the bile containing drugs and metabolites is released into the gastrointestinal tract. Direct secretion of drugs may also occur from enterocytes into the intestinal lumen by specific transporters. Some metabolites are recycled by the intestinal microflora to the original drug substance. Hence part of drugs may also be reabsorbed back into systemic circulation. This process is called enterohepatic circulation.

Currently there are no data available on effects of aging on gastrointestinal excretion of drugs.

4. Principles of Pharmacodynamics in the Elderly

Pharmacodynamics describes the pharmacologic effects of a drug, both volitional as well unintended ones. Hence age- related changes in pharmacodynamics can result in greater therapeutic effect as well as an increased potential for toxicity. As every drug has its own special pharmacodynamics, its changes with aging are more difficult to define than pharmacokinetic changes.

Most organs and bodily systems show clinically significant age related change. Examples include changes in cardiovascular control systems, alterations in hormone homeostasis, thymic involution or loss of trophic factors and matrix formation in the skeleton. Effects of old age on the activity and the expression of many receptors have also been reported but the consequences on pharmacodynamics are unclear.

The study of pharmacodynamics is complicated by the fact that the effects of many drugs are already confounded by altered pharmacokinetics in the elderly. Moreover physiologic changes in functionality are often misinterpreted as impairment caused by drugs when compared to younger subjects.

Certain drugs have been studied for altered pharmacodynamics in the elderly. However most important drugs affected are benzodiazepines. Increases in medication sensitivity have also been suggested for calcium channel blockers, beta-mimetics and beta-blockers, warfarin or opioids.

- *Benzodiazepines*

Age- related changes in the pharmacodynamics of benzodiazepines are particularly important from the clinical perspective. An association between benzodiazepines, falls and hip fractures in older people has been demonstrated (Cumming & Le Couteur 2003). In the absence of major pharmacokinetic changes some benzodiazepines demonstrated greater effect in elderly people than in younger subjects. The EC_{50}, the concentration of a drug where half of its maximal effect is observed, for sedation is reduced by 50% in older people after admission of midazolam (Albrecht et al. 1999). Therefore greater sensitivity of the central nervous system to some benzodiazepines is suggested.

- *Beta-mimetics and beta-blockers*

Aging is associated with changes in the β- adrenergic system as β- adrenergic receptors are downregulated, plasma levels of noradrenaline are elevated and cAMP response to β- adrenergic stimulation is reduced (Scarpace 1988). As a consequence reduced bronchodilatory effect of beta-mimetics has been reported in elderly (Connolly et al. 1995). As cardiac β-1 receptors are also down- regulated in older people, beta-blockers may be less effective than other antihypertensive agents (Grossman & Messerli 2002).

- *Warfarin*

There is an increased sensitivity of elderly patients taking warfarin. A dose reduction of about 11% per decade of age has been proposed. Pharmacokinetic age- related changes in warfarin metabolism are regarded as negligible. The pharmacodynamic changes have not been well characterized. Alterations in drug receptor affinity and number, signal transduction, cellular responses and homeostatic regulation are under current investigation.

5. Mechanisms of Interaction

An interaction is suspected when the effects of one drug seem to be changed by the presence of another drug, herbal medicine, food, drink or any other environmental chemical agent (Baxter Karen 2007a). The outcome of an interaction can be harmful for instance if drug toxicity is increased or drug plasma concentrations are altered. However some drug interactions are beneficial and valuable: i.e. the prescription of various different antihypertensive drugs to achieve better effects.

Some drugs interact together in totally unique ways but there are certain mechanisms of interaction that are very common. Basically mechanisms of interaction are subdivided into pharmacokinetic and pharmacodynamic interactions.

Due to altered pharmacokinetics and polypharmacy especially elderly patients are prone to drug interactions.

5.1. Pharmacokinetic Interactions

As referred to in *chapter Principles of Pharmacokinetics in the Elderly, page 7* pharmacokinetic interactions affect absorption, distribution, metabolism and elimination of a drug. Basic understanding of pharmacokinetics and especially age related changes can also be found in *chapter Principles of Pharmacokinetics in the Elderly, page 7.*

5.1.1. **Drug absorption interactions**

The majority of interactions that happen within the gut result in reduced rather than in increased absorption. Interaction mechanisms that cause altered absorption are:

- *Changes in gastrointestinal pH*

Absorption depends upon the extent of the non- ionized lipid- soluble form of the drug which is widely governed by its pKa and the gastric pH. The pKa is an acid dissociation constant that measures the strength of an acid in solution and gives information about the extent of dissociation at certain pH levels. As every drug substance has its defined pKa value, optimal pH for absorption can be estimated. Drugs like proton pump inhibitors or H_2- receptor antagonists increase gastric pH. In practice the outcome and effect of this interaction is often uncertain as it may be accompanied by other interaction types. However significant reduction in absorption of azole antifungals like ketokonazol and itrakonazole has been reported (caused by rises in pH due to acid- suppressive drugs). If an antisecretory agent is necessary those antifungal drugs can be swallowed together with acidic fluids like Coca-Cola (Hansten & Horn 2008).

- *Adsorption, chelation and other complexing mechanisms*

Activated charcoal is a popular example for an adsorbing agent. It is used in the treatment of drug overdose and to remove other toxic materials but it can therefore also affect absorption of drugs given in therapeutic doses. Antacids can also

adsorb a large number of drugs. Quinolone and tetracycline antibiotics can chelate with a number of divalent and trivalent metallic ions like calcium, aluminum, zinc or iron in order to form complexes that cannot be absorbed. Therefore intake or ingestion of substances including those ions should be separated by several hours (Hansten & Horn 2008). Cholestyramine also binds to various drugs including furosemid and thiazide- diuretics, leading to reduced absorption.

- *Changes in gastrointestinal motility*

Drugs with antimuscarinic effects like tricyclic antidepressants decrease the motility of the gut, altering the exposure time of drugs to gastric or intestinal mucosa. This increases the absorption of some drugs while that of other drugs is decreased. Absorption of levodopa i.e. may be reduced if motility is decreased. Metoclopramid has the opposite effect as it increases gut motility.

- *Induction or inhibition of drug transporter proteins*

The oral bioavailability is influenced by the action of drug transporters, which eject drugs that have diffused across the gut wall back into the intestinal lumen. As drug transporter proteins are widespread throughout the body this mechanism of interaction will be explained in *5.1.5 Drug transporter proteins, page 32.*

- *Malabsorption*

Neomycin causes a malabsorption syndrome, reducing absorption of various drugs including digoxin and methotrexate.

5.1.2. **Drug distribution interactions**

- *Protein- binding interactions*

Depending on concentration and affinities for certain binding sites on plasma proteins, drugs may compete and displace each other from those sites. Apart from drugs competing for binding sites, displacement reactions may also be caused by endogenous substances in patients with uremia. The amount of displaced drug turns active and the concentration of unbound drug rises. For example if plasma protein binding of a drug is reduced from 99% to 95%, the concentration of the unbound active drug increases fivefold from 1% to 5%. Free and active drug

plasma concentration will only be raised if the majority of the drug is within the plasma rather than tissues, thus only drugs with a low apparent volume of distribution will be affected. Another important factor is clearance of drug. If only a small portion of the drug is eliminated during a single- passage through the eliminating organ (low- extraction ratio drugs), protein binding reactions will be unlikely as any increase in free fraction will be cleared effectively. Most highly protein bound drugs that are subject to displacement reactions have low-extraction ratios (e.g. warfarin, sulphonylureas, methotrexate, phenytoin and valproate).

In general many common drugs are capable of being displaced in vitro but in vivo effects seem almost always to be balanced effectively. As mentioned before in *chapter 3.2 Distribution* this interaction mechanism is likely to be important for drugs given intravenously that have a high- extraction ratio, a short pharmacokinetic and –dynamic half- life and a narrow therapeutic index (Baxter Karen 2007a; Benet & Hoener 2002). Lidocaine for instance is a drug fitting those criteria. Many drug interactions that had been assumed due to changes in protein binding have also been shown to have other interaction mechanisms.

However, knowledge of altered protein binding is important for therapeutic drug monitoring. Especially geriatric patients who may have disease- related altered protein binding should be evaluated for active amount of a certain drug rather than total amount of drug.

- *Induction or inhibition of drug transport proteins*

Drug transporters are not only important for absorption of drugs. The distribution of drugs into tissues and organs is also limited by drug transporters like P-glycoprotein. Drugs inducing or inhibiting those proteins may therefore alter drug uptake into organs. The detailed mechanism of interaction will be explained in *5.1.5 Drug transporter proteins, page 32.*

5.1.3. **Drug metabolism interactions**

- *Changes in first- pass metabolism*

Some drugs can have a marked effect on the extent of first pass metabolism by altering hepatic blood flow and inhibiting or inducing metabolizing enzymes in the gut wall. There are few clinically important examples of drugs that interact with others only by changing hepatic blood flow. A common example of enzyme inhibition in the gut wall is grapefruit juice, which inhibits CYP3A4 causing reduced metabolism of oral calcium channel blockers.

- *Enzyme induction*

Enzyme induction caused by a drug means that the activity of metabolizing enzymes increases in the course of time. If another drug that is metabolized by the same enzymes is also present, its enzymatic metabolism is similarly increased and larger doses are needed to maintain the same therapeutic effect. However not all enzyme- inducing drugs induce their own metabolism. Some drugs affect more than one enzyme.

The most commonly induced metabolic pathway is phase I oxidation, represented by the cytochromes P450 isoenzymes. Examples for enzyme inducers are barbiturates and phenytoin (CYP1A2) or rifampicin (CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP3A4). Enzyme induction is not confined to drugs and is therefore also triggered by tobacco smoke (CYP1A2), St. John's wort (CYP2C19, CYP3A4) or some insecticides (Baxter Karen 2007a; Hansten & Horn 2008). The extent of induction depends on the drug and its dosage. Induction interactions are usually delayed by 2 to 3 weeks in onset and similarly slow to resolve when the inducer is stopped. A selection of various CYP inducers can be seen in *Figure 5, page 1*.

- *Enzyme inhibition*

More common than enzyme induction is the inhibition of enzymes. This results in reduced metabolism of an affected drug. Consequently drug concentration rises and it may accumulate in the body. The extent of inhibition tends to be dose related and it additionally depends on the inhibiting drug.

Unlike enzyme induction, enzyme inhibition can occur within 2 to 3 days, causing rapid development of toxicity. The metabolic pathway that is most commonly inhibited is phase I oxidation by the CYPs. There is an endless number of enzyme inhibiting drugs affecting the CYP 1, 2 and 3 families (*Figure 6, page 1*). The clinical relevance of many inhibition interactions depends on the extent of consecutive serum levels of drugs.

- *Genetic factors in drug metabolism*

Cytochrome P450 isoenzymes are subject to genetic polymorphism which means that some of the population have variants with different (usually poor) activity. A variant with low activity of CYP2D6 for instance is found in 5% to 10% in Caucasians and 0% to 2% in Asians and black people (Baxter Karen 2007a). This group is usually referred to as slow metabolisers. Other isoforms showing polymorphisms are CYP2C9 and CYP 2C19.

- *Cytochrome P450 isoenzymes and predicting drug interactions*

Most CYP interactions are based on in vitro studies. Sometimes however metabolism of drugs is not fully understood, hence not all in vitro interactions may be clinically relevant. As some drugs may be inducers, inhibitors and substrates of more than one enzyme, overlooking all metabolism interactions might be impossible. *Figure 4, page 1; Figure 5, page 1 and Figure 6, page 1* show common substrates that are very likely to be affected by inducers and inhibitors listed.

Figure 4 Clinically relevant substrates of common CYPs (Flockhart 2008)

SUBSTRATES							
1A2	2B6	2C8	2C19	2C9	2D6	2E1	3A4,5,7
clozapine cyclobenzaprine imipramine mexiletine naproxen riluzole tacrine theophylline	bupropion cyclophosphamide efavirenz ifosfamide *methadone*		Proton Pump Inhibitors: omeprazole lansoprazole pantoprazole rabeprazole Anti-epileptics: diazepam phenytoin phenobarbitone amitriptyline clomipramine clopidogrel cyclophosphamide progesterone	NSAIDs: diclofenac ibuprofen piroxicam Oral Hypoglycemic Agents: tolbutamide glipizide Angiotensin II Blockers: NOT candesartan irbesartan losartan NOT valsartan celecoxib fluvastatin naproxen phenytoin sulfamethoxazole tamoxifen tolbutamide torsemide warfarin	Beta Blockers: S-metoprolol propafenone timolol Antidepressants: amitriptyline clomipramine desipramine imipramine paroxetine Antipsychotics: haloperidol risperidone thioridazine aripiprazole codeine dextromethorphan duloxetine flecainide mexiletine ondansetron tamoxifen tramadol venlafaxine	acetaminophen chlorzoxazone ethanol	Macrolide antibiotics: clarithromycin erythromycin NOT azithromycin telithromycin Anti-arrhythmics: quinidine Benzodiazepines: alprazolam diazepam midazolam triazolam Immune Modulators: cyclosporine tacrolimus (FK506) HIV Protease Inhibitors: indinavir ritonavir saquinavir Prokinetic: cisapride Antihistamines: astemizole chlorpheniramine Calcium Channel Blockers: amlodipine diltiazem felodipine nifedipine nisoldipine nitrendipine verapamil HMG CoA Reductase Inhibitors: atorvastatin cerivastatin lovastatin NOT pravastatin simvastatin aripiprazole buspirone gleevec haloperidol (in part) methadone pimozide quinine NOT rosuvastatin sildenafil tamoxifen trazodone vincristine

Figure 5 Clinically relevant inducers of common CYPs (Flockhart 2008)

INDUCERS							
1A2	2B6	2C8	2C19	2C9	2D6	2E1	3A4,5,7
tobacco	phenobarbital phenytoin rifampin		N/A	rifampin secobarbital	N/A	ethanol isoniazid	carbamazepine phenobarbital phenytoin rifabutin rifampin St. John's wort troglitazone

Figure 6 Clinically relevant inhibitors of common CYPs (Flockhart 2008)

INHIBITORS							
1A2	2B6	2C8	2C19	2C9	2D6	2E1	3A4,5,7
cimetidine fluoroquinolones fluvoxamine ticlopidine	thiotepa ticlopidine	gemfibrozil montelukast	fluoxetine fluvoxamine ketoconazole lansoprazole omeprazole ticlopidine	amiodarone fluconazole isoniazid	amiodarone buproprion chlorpheniramine cimetidine clomipramine duloxetine fluoxetine haloperidol methadone mibefradil paroxetine quinidine ritonavir	disulfiram	HIV Protease Inhibitors: indinavir nelfinavir ritonavir amiodarone NOT azithromycin cimetidine clarithromycin diltiazem erythromycin fluvoxamine grapefruit juice itraconazole ketoconazole mibefradil nefazodone troleandomycin verapamil

5.1.4. **Drug elimination interactions**

Drug elimination interactions affect excretion via the urine or the bile.

- *Changes in urinary pH*

Like gastric pH the urinary pH determines the solubility of a drug dependent on the drugs pKa values. Ionized water- soluble drugs remain in the tubular fluid and are excreted via urine while non- ionized lipid- soluble drugs diffuse back into tubular cells. Thus changes in urinary pH alter the amount of excreted and resorbed drug. Though, the clinical significance of this interaction is small as almost all weak acid or basic drugs are metabolized by the liver into inactive compounds. In practice only a small number of drugs seem to be affected by changes in urinary pH. For example methotrexate clearance is lowered by inhibitors of anionic tubular secretion like NSAIDs, ciprofloxacin or omeprazole (Hansten & Horn 2008).

- *Changes in active renal tubular excretion*

Drugs that use similar active transport systems in the renal tubules can compete with another for excretion. Probenecid inhibits the renal excretion of penicillin, methotrexate, cephalosporins, quinolones and others by organic anion transporters and renal ABC transporters like P- glycoprotein (*5.1.5 Drug transporter proteins, page 32)*.

- *Changes in renal blood flow*

Renal blood flow is controlled by the production of renal vasodilatory prostaglandins and the renin- angiotensin- aldosterone system. This interaction mechanism has been suggested for lithium as toxicity has been reported when using NSAID's or ACE inhibitor and angiotensin receptor blockers (Hansten & Horn 2008).

- *Biliary excretion and the enterohepatic shunt*

Enterohepatic recirculation necessarily requires gut flora, as bacteria metabolizes conjugated drugs back into lipid- soluble, reabsorbable compounds. If gut flora is diminished by antibacterial therapy some drugs are not recycled and lost more quickly. Famous example is the rare failure of oral contraceptives when using antibiotics, especially amoxicillin, ampicillin or tetracyclines.

Hepatic and biliary drug transporter proteins are involved in secretion of drugs and might also be affected by interactions *(See below).*

5.1.5. **Drug transporter proteins**

Drugs and endogenous substance do not only cross biological membranes by passive diffusion, they are often transported by carrier- mediated processes. Those transporters are one of the most important objects to current pharmacokinetic research. The best known among them is P- glycoprotein (P-gp), which is a product of the MDR1 gene (ABCB1 gene) and a member of the ATP-binding cassette (ABC) family of efflux transporters.

It is found in membranes of certain cells, evolving an impact on the extent of drug absorption (decreasing absorption via the intestine), drug distribution (decreasing distribution to brain, testis or placenta) and drug elimination (increasing excretion into the urine and bile). The main purpose of P- glycoprotein is to push metabolites and drugs out of cells; therefore it is acting as a barrier to absorption and distribution plus it forces drug excretion.

There is recent evidence about the important role of P- glycoprotein in drug interactions. Similarly to the CYPs induction and inhibition of P-glycoprotein can have a significant impact on pharmacokinetics. For example inhibition of P-gp by

verapamil, clarithromycin or cyclosporine may increase plasma concentration of digoxin two to four- fold (Hansten & Horn 2008). Effects on drug distribution (e.g. into the brain) might even be greater than on drug absorption (e.g. plasma levels) (Baxter Karen 2007a).

Other transporters that are involved in some drug interactions are the organic anion transporter (OATs), organic anion- transporting peptides (OATPs) and organic cation transporters (OCTs), which are members of the solute carrier superfamily (SLC) of transporters.

5.2. Pharmacodynamic Interactions

Pharmacodynamic interactions are those where the effects of one drug are changed by the presence of another drug at its site of action. Drugs can compete directly for particular receptors or an indirect reaction leads to interactions with physiological mechanisms. As this kind of interactions is a very heterogeneous group, superordinate classification is difficult.

5.2.1. **Additive or synergistic interactions**

If two drugs with the similar pharmacological effect are applied simultaneously the effects can be additive. Synergistic effects may occur with both, therapeutic as well as adverse effects. Many additive interactions are used deliberately in clinical routine in order to increase effects of several substances. A common example is antihypertensive therapy where several drug groups have one synergistic effect. Some additive effects however are solely toxic.

Examples for additive interactions are listed in *Table 3* below.

Table 3 Additive, synergistic or summation reactions (Baxter Karen 2007a)

DRUGS	RESULT OF INTERACTION
Antipsychotics + Antimuscarinics	Increased antimuscarinic effects; heat stroke in hot and humid conditions, adynamic ileus, toxic psychosis
Antihypertensives + Drugs that cause hypotension (e.g. Phenothiazines, Sildenafil etc.)	Increased antihypertensive effects; orthostasis
Beta- agonist bronchodilators + Potassium- depleting drugs	Hypokalaemia
CNS depressants in combination *Alcohol + Antihistamines* *Benzodiazepines + Anesthetics* *Opioids + Benzodiazepines*	Impaired psychomotor skills, reduced alertness, drowsiness, stupor, respiratory depression, coma, death
Drugs that prolong the QT interval in combination (e.g. Antiarrhytmics, Antipsychotics, TCAs, several antibiotics, etc.)	Additive prolongation of QT interval, increased risk of torsade de pointes
Nephrotoxic drugs in combination (e.g. Aminoglycosides, Cyclosporine, Cisplatin, Vancomycin etc.)	Increased nephrotoxicity
Potassium supplements + potassium- sparing drugs (e.g. ACE inhibitors, AT II receptor antagonists, Potassium- sparing diuretics, etc.)	Hyperkalaemia
Serotonergic drugs in combination (e.g. MAOI, TCAS, SSRIs, etc.)	Serotonine syndrome; altered mental status, autonomic dysfunction, neuromuscular abnormities
Drugs that affect hemostasis in combination (e.g. ASA, Clopidogrel, oral anticoagulation, heparins, SSRI, etc.)	Increased risk of bleeding

5.2.2. **Antagonistic or opposing interactions**

In contrast to additive drug interactions, also contrary effects of certain drug pairs may be observed. This usually results in reduced efficacy of the affected drug. Examples for antagonistic interactions are listed in *Table 4* below.

Table 4 Opposing or antagonistic interactions (Baxter Karen 2007a)

DRUG AFFECTED	INTERACTING DRUG	RESULT OF INTERACTION
ACE inhibitors or Loop diuretics	NSAIDs	Antihypertensive effects opposed
Anticoagulants	Vitamin K	Anticoagulant effects opposed
Antidiabetics	Glucocorticoids	Blood- glucose lowering effects opposed
Levodopa	Antipsychotics with dopamine antagonist effects	Antiparkinsonian effects opposed

5.3. Drug- Herb Interactions

There are relatively few clinical reports of drug interactions involving herbal medications. Some herbal drug interactions however are well documented. The prevention of adverse drug herbal interactions is difficult as those substances can be bought without prescription (‘over the counter’, OTC) and therefore escape medical advisory by a doctor. Moreover most herbal products lack standardization procedures and are adulterated with other substances.

The best known example for herbal drug interactions is St. John’s wort. Evidence has shown that it can induce the CYP3A4 and p-glycoprotein. Hence levels of cyclosporine, simvastatin or digoxin are decreased by St. John’s wort. As St. John’s wort has also serotonergic effects cases of serotonine syndrome have been reported when used together with SSRIs (Baxter Karen 2007a).

Other herbal products with interaction potential that have less evidence are ginkgo biloba, ginseng, valerian, kava or danshen and dong quai (Hansten & Horn 2008).

5.4. Drug- Food Interactions

Food interacts with drugs in a lot of different ways. Effects on drug absorption by calcium, aluminium and iron, or acidic or basic fluids can be seen in *chapter Principles of Pharmacokinetics in the Elderly, page 7.*

Drug absorption interactions, *page 25*. Food can also alter drug metabolism, currently grapefruit juice causes the most clinically relevant of these interactions.

- *Grapefruit juice*

Grapefruit juice mainly inhibits intestinal CYP3A4 and only slightly affects hepatic CYP3A4. Intravenous products are therefore not much affected by grapefruit juice while oral preparations are. The results are increased drug levels of orally admitted drugs metabolized mainly by CYP3A4. Besides grapefruit juice possibly inhibits some drug transporters, OATP's and P- glycoprotein. The active constituent of grapefruit juice is uncertain (Baxter Karen 2007a).

- *Cruciferous vegetables and charcoal- broiled meats*

Cruciferous vegetables like brussels sprouts, cabbage and broccoli contain substances that are inducers of the CYP1A2. Chemicals formed by 'burning' meats also have these properties. Those foods may not interact solely with drugs but they may complicate CYP1A2 drug to drug interactions (Baxter Karen 2007a).

- *Other food- drug interactions*

Tyramine (for example in some cheese) may reach toxic concentrations in patients taking MAOIs. Garlic, cranberry juice and ginger might increase the risk of bleeding under warfarin therapy (Hansten & Horn 2008).

- *Parenteral and enteral nutrition*

Interactions between drugs and parenteral or enteral nutrients occur often and they can have a harmful impact on patient outcome. As nutrients are complex mixtures there are many mechanisms they can interact with drugs (Sacks GS 2004).

When nutrients and drugs are mixed outside the body (for instance in y-site connectors) there may be chemical or physical reactions. Parenteral formulations which include lipid emulsion (milky- white appearance) may be destabilized by acidic drugs or electrolyte salts. In this case the small emulsified droplets begin to aggregate into larger fat globules that may cause pulmonary embolsim. For example haloperidol, heparin, midazolam or excess amounts of calcium should not be mixed directly with intravenous lipid emulsions. Enteral nutrients may also be

physically altered by drugs. Acidic preparations may cause clumping of the enteral nutrient formula and enteral tube obstruction.

Some drug- nutrient interactions affect absorption of drugs. Tablets need to be crushed when given via an enteral feeding tube. Especially pharmacokinetics of extended- release tablets and encapsulated products changes when those tablets are crushed or capsules are opened. Complexation of medications with components of enteral formulations may reduce absorption. Fluoroquinolone antibiotics like ciprofloxacin and levofloxacin have shown decreased bioavailability when administered in combination with enteral feedings, as those antibiotics bind with divalent cations *(See also 5.1.1 Drug absorption interactions, page 25).*

Other drug- nutrient interactions include pharmacodynamic mechanisms. For example intravenous lipid emulsions are an additional source of vitamin K which may cause anticoagulant resistance.

As nutrients and drugs occasionally share metabolic pathways changes in dietary composition can influence hepatic metabolism and renal clearance. High protein nutrients may accelerate the clearance of certain hepatic- cleared agents like propanolol. A protein restricted diet may decrease renal tubular clearance and renal blood flow. The metabolite of allopurinol for example has been shown to accumulate during a low- protein diet.

There are numerous issues that have to be taken into account to ensure safe and effective drug delivery in patients receiving parenteral or enteral nutrients. Hence consultation of an experienced clinical pharmacist may be necessary.

B. Methods

1. Main Objectives

The main objective was to evaluate polypharmacy and especially to determine the prevalence and incidence of drug interactions in elderly patients attending the Emergency Clinic of the Department of Internal Medicine at the Medical University of Graz. Another important issue was to compare prescription behavior between inpatient and outpatient, ambulatory setting. Furthermore the performance of computer based interaction checks was evaluated.

Before data collection several considerations were made how to illustrate those main objectives. Most frequent drug interaction types found by the interaction program should be checked for their relevance with acknowledged interaction literature. Potentially dangerous and relevant interactions should be extracted. Analyzing the number of drugs and drug interactions per patient before admission and at the end of out- or inpatient treatment should provide an overview about the prescription behavior. Most common interacting drugs should be found.

2. Data Collection

Data was collected retrospectively from patients attending the Emergency Clinic of the Department of Internal Medicine at the Medical University of Graz in a two-months period between August 13th, 2008 and October 13th, 2008.

Criterion for inclusion was age above 65 years. Criteria for exclusion were incomplete patient documentation, unreadable patient admission forms and death before hospital discharge.

Collection of patient data focused on: name, age, sex, in- or outpatient treatment, overall number and trade names of drugs at the time of admission and at the end of in- or outpatient treatment. Those data were collected from patient admission forms and from discharge letters of Emergency Clinic (outpatient) or the particular ward (inpatient). Only drugs that were admitted orally, intravenously, inhalatory or as eye drops were noted, topical admitted drugs were excluded.

A total of 922 patients that fulfilled inclusion criteria were collected within those two months. 358 were treated outpatient, 564 were admitted to responsible wards and were treated inpatient. 35 patients of the outpatient group were excluded due to unreadable patient admission forms, as those forms are only available handwritten. 35 patients of the inpatient group died in hospital, 129 patients had incomplete data and were consequently excluded. Eventually 723 patients (434 female and 298 male) were included into study. 400 patients were treated inpatient, 323 were treated outpatient.

Patient data was entered into a Microsoft Office Access© 2003 database.

After collecting basic patient data, admission and discharge medical therapy were checked for drug interactions by so called MEDIS© program (pr data 2008). MEDIS© is the common drug information program used in Styrian and other Austrian hospitals, which also offers drug interaction check functionality. The MEDIS© interaction analysis is based on interaction databases produced by the Federal Union of German Associations of Pharmacists (ABDA 2008). The ABDA-databases derive from summary of product characteristics and published literature (ABDATA 2008). Drug interactions found with MEDIS© were entered into database with following information: drug trade name and substance group interacting, severity and theoretical effect of drug interaction.

3. Statistical Analysis

Statistical analysis was carried out with SPSS 17© (SPSS Inc. 2008). Kolmogorov-Smirnov- Test with Lilliefors adaption was used to determine distribution. Paired normally distributed variables in two related samples were compared with dependent Student's t- test for paired samples. Two independent samples were compared using the independent two-sample Student's t- test. Correlation of variables and groups were checked with Pearson correlation coefficients for normally distributed variables. Statistical significance was defined by p- value ≤ 0.05 (Bühl A. 2008).

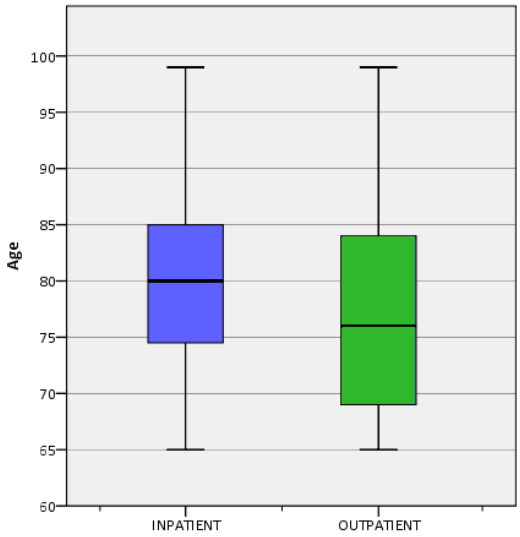
C. Results

Comparison of age in INPATIENT and OUTPATIENT group showed that there was statistically significant difference in distribution of age in both groups ($p \leq 0.001$). On average INPATIENT group is 3.09 older than OUTPATIENT group. Most patients in the INPATIENT group are between 75 and 84 years old (44.8%) while most patients in the OUTPATIENT group are aged between 65 and 74 (43.1%). Oldest old patient above 85 years are more frequent in the INPATIENT group (30.2%) *(See Table 5, Figure 7).*

Table 5 Age distribution

TREATMENT	Age	N	Percent
INPATIENT	**65 – 74**	100	25.0
	75 – 84	179	44.8
	85 and older	121	30.2
	Total	400	100
	Mean Age	79.78 ± 7.5	
OUTPATIENT	**65 – 74**	139	43.1
	75 – 84	118	36.5
	85 and older	66	20.4
	Total	323	100
	Mean Age	76.69 ± 8	

Figure 7 Age in both groups



The mean number of drugs differs in both groups. The OUTPATIENT group tends to have fewer drugs than the INPATIENT group. The OUTPATIENT group has a mean value of 6.50 ± 4.2 drugs on hospital admission while the INPATIENT group has 7.64 ± 3.6. More than half of the patients in the INPATIENT group receive between 5 and 9 drugs (51% at admission). Most OUTPATIENT treated patients take 0 to 4 or 5 to 9 medications (38.1%) at admission. The mean number of drugs at discharge increased in both groups *(See Table 6)*. The increase in the overall INPATIENT group is not statistically significant. The mean increase of number of drugs by 0.50 in the OUTPATIENT group is highly significant ($p \leq 0.001$). Significant increase in medication in INPATIENT group can be seen in people

aged between 65 and 74 years ($p \leq 0.005$). Significant decrease was found in the INPATIENT group at ages above 85 years.

Table 6 Patients per number of drugs

		Admission		Discharge	
TREATMENT	**Drugs**	**Frequency**	**Percent**	**Frequency**	**Percent**
INPATIENT	0-4	75	18.8	56	14.0
	5-9	204	51.0	233	58.3
	10-14	104	26.0	105	26.2
	≥ 15	17	4.2	6	1.5
Mean		7.64 ± 3.6		7.78 ± 3.2	
OUTPATIENT	0-4	123	38.1	100	31.0
	5-9	123	38.1	139	43.0
	10-14	66	20.4	71	22.0
	≥ 15	11	3.4	13	4.0
Mean		6.50 ± 4.2		7 ± 4.1	

Most people at discharge have 5 to 9 drugs (INPATIENT 58.3%, OUTPATIENT 43%). Mean number of medication is 7.78 ± 3.2 (INPATIENT) and 7 ± 4.1(OUTPATIENT).

Figure 8 Number of drugs at admission and discharge in INPATIENT group

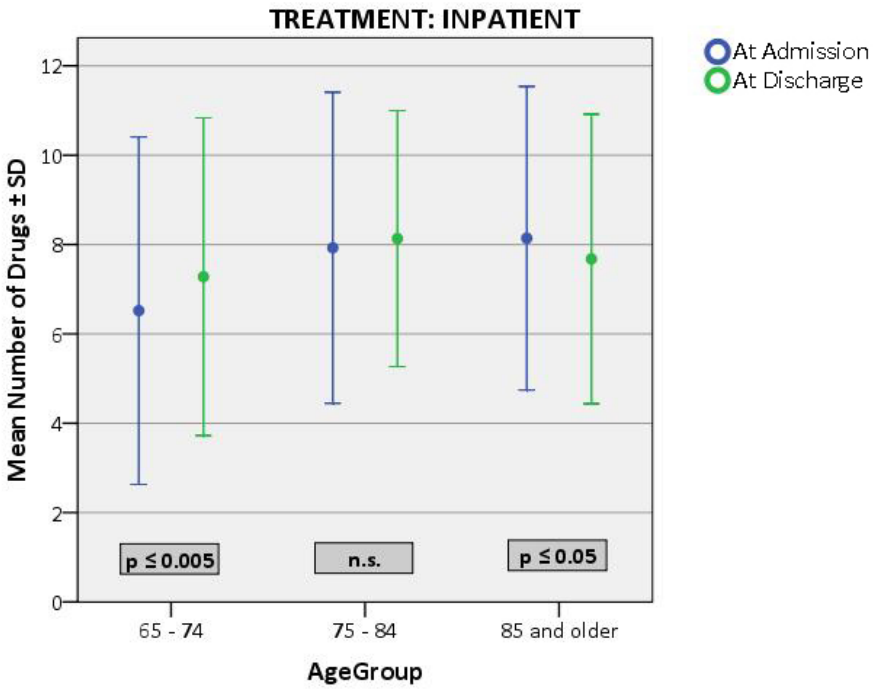


Figure 9 Number of drugs at admission and discharge in OUTPATIENT group

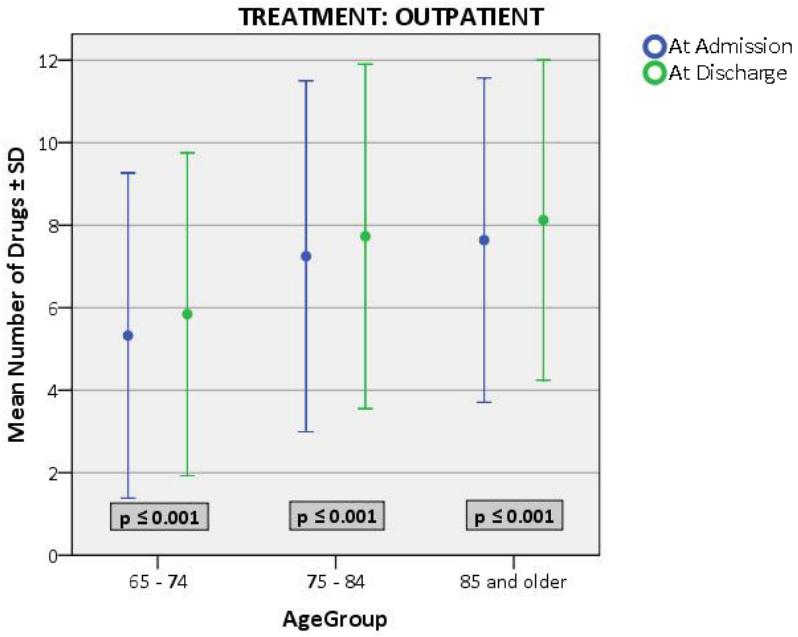
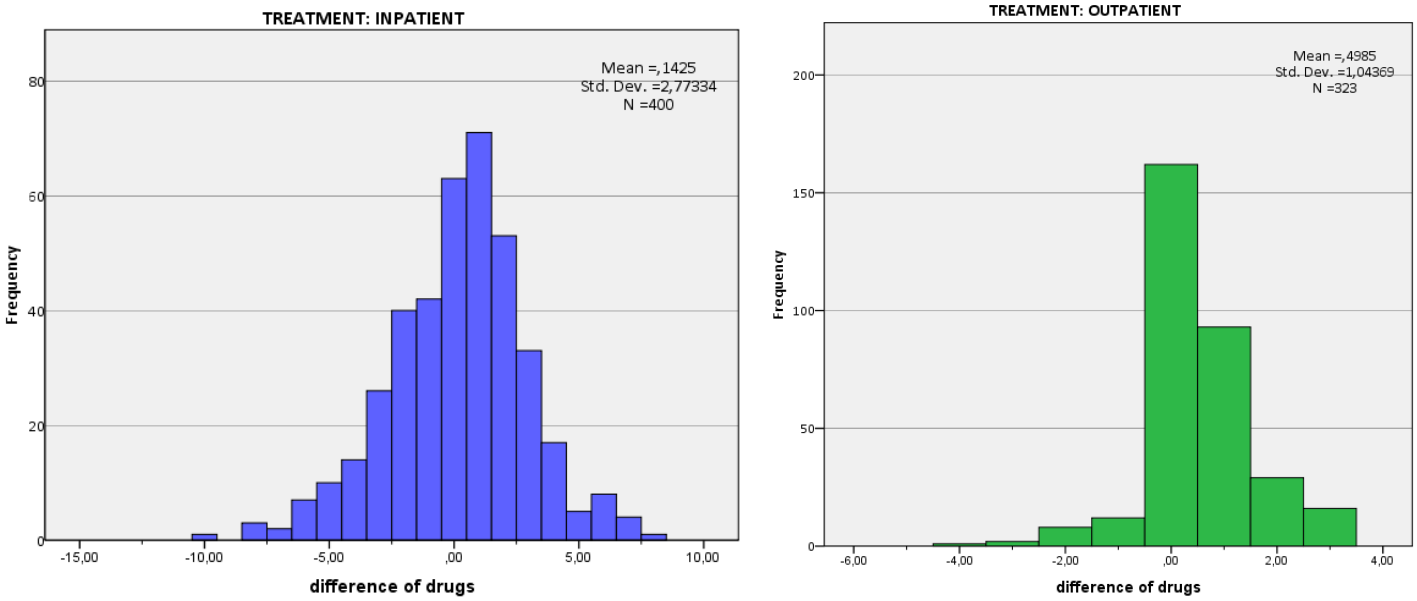


Table 7 Mean changes of drugs and statistical significance

TREATMENT	Age		N	Mean	p- value
INPATIENT	65 - 74	Admission	100	6.52 ± 3.9	
		Discharge	100	7.28 ± 3.6	p ≤ 0.005
	75 - 84	Admission	179	7.93 ± 3.5	
		Discharge	179	8.13 ± 2.9	n. s.
	85 and older	Admission	121	8.14 ± 3.4	
		Discharge	121	7.68 ± 3.2	p ≤ 0.05
OUTPATIENT	65 - 74	Admission	139	5,32 ± 3.9	
		Discharge	139	5.84 ± 3.9	p ≤ 0.001
	75 - 84	Admission	118	7.25 ±4.3	
		Discharge	118	7.73 ± 4.2	p ≤ 0.001
	85 and older	Admission	66	7.64 ± 3.9	
		Discharge	66	8.12 ± 3.9	p ≤ 0.001

Figure 8, Figure 9, Figure 10 and Table 7 summarize changes in drug quantity. Drug prescription routine can be seen in *Figure 10*. Prescription of new medications and discontinuation are quite balanced in the INPATIENT group while prescription of new drugs is dominant in the OUTPATIENT group.

Figure 10 Absolute change in number of drugs (drugs at discharge - drugs at admission): overall change IP +57 drugs (400 patients); OP +161 drugs (323 patients)



Drugs most frequently prescribed in both groups are acid- suppressive drugs like proton pump inhibitors (PPI) or H_2- receptor antagonists and beta blockers. Drugs that were reduced significantly during INPATIENT treatment were benzodiazepines and atypical antihypertensives like rilmenidin (Iterium©), moxonidin or urapidil (Ebrantil©). There was no drug class that was significantly reduced during OUTPATIENT treatment *(See Table 8 and Table 9).*

Table 8 Medications that changed significantly during INPATIENT treatment

INCREASE			
Drugs	**Admission (n)**	**Discharge (n)**	**p- value**
Acid- suppressive drugs	223	268	≤ 0.001
Beta-blockers	172	193	≤ 0.01
Antibiotics	36	123	≤ 0.001
Plavix (clopidogrel)	48	64	≤ 0.01
Inhal. Anticholinergics, Parasympatholytics	59	75	≤ 0.05
Inhal. β-2 mimetics	52	65	≤ 0.05
Spironolactone	34	52	≤ 0.01
LMWH	27	49	≤ 0.01
Corticoids	14	21	≤ 0.05

DECREASE

Drugs	Admission (n)	Discharge (n)	p- value
Benzodiazepines	94	73	≤ 0.05
Atypical Antihypertensives	38	20	≤ 0.001
NSAIDs	39	17	≤ 0.001
Metformin	23	15	≤ 0.05
TZA	13	9	≤ 0.05
Paracetamol/ Acetaminophen	7	1	≤ 0.05

Table 9 Medications that changed significantly during OUTPATIENT treatment

INCREASE

Drugs	Admission (n)	Discharge (n)	p- value
Acid- suppressive drugs	144	170	≤ 0.001
Beta-blockers	133	144	≤ 0.005
ASS	120	128	≤ 0.05
ACE inhibitors	111	125	≤ 0.001
Thiazide diuretics	93	100	≤ 0.05
Coronary therapeutics	82	91	≤ 0.05
NSAIDs	49	69	≤ 0.001
Ca Antagonists	56	69	≤ 0.01
Antibiotics	14	37	≤ 0.001
Inhal. Anticholinergics/ Parasympatholytics	29	35	≤ 0.05
Metamizol	12	16	≤ 0.05

All in all there were 2761 drug- drug interactions found by MEDIS in drug therapies at admission and 2819 at discharge. Some interactions were excluded from statistical calculations as those drug interactions referred to drugs in higher dosage than actually admitted (e.g. Acetylsalicylic acid (ASA) 100mg was found as interacting drug although drug interaction type only became important in higher analgesic dosages above 1000mg). Finally a total of 2065 interactions at admission and 2104 at discharge were used for statistical analysis.

At admission 76.5% of INPATIENT and 64.1% of OUTPATIENT group showed at least one potential drug to drug interaction. At discharge the number of INPATIENTS patients having drug interaction increased not significantly to 78.3%.

OUTPATIENT group increased significantly to 69% (p ≤ 0.001) *(See Table 10)*.

Table 10 Numbers and percentages of patients who had at least 1 drug interaction

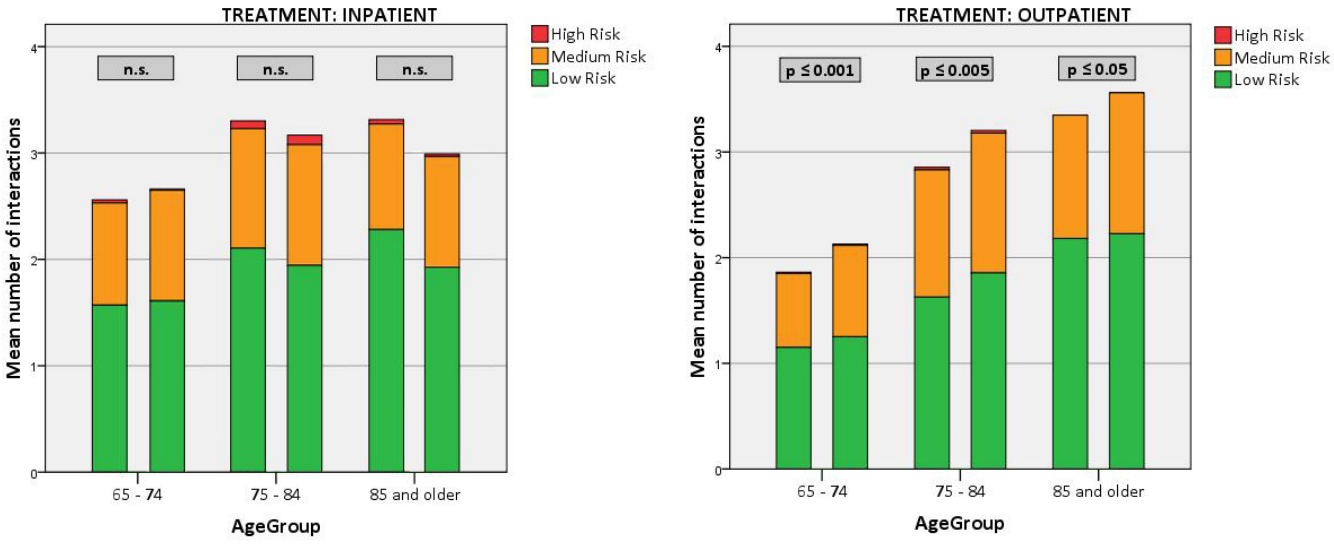
	Admission	Discharge	p- value
INPATIENT	306 (76.5%)	313 (78.3%)	n.s.
OUTPATIENT	207 (64.1%)	223 (69%)	p ≤ 0.001

The mean number of drug interactions at admission is 3.12 in INPATIENT group and 2.53 in OUTPATIENT group. Interactions classified as 'low risk' are most frequent (65% / 62% INPATIENT, 61% / 59% OUTPATIENT). 'Severe' classified interactions make up less than 2% in both groups *(See Table 11)*.

Table 11 Mean number of interactions per patient and significance of change in total number of interactions (classified by risk: low, medium, severe)

		Interactions at Admission				Interactions at Discharge				p
TREATMENT		*Total*	Low	Medium	Severe	*Total*	Low	Medium	Severe	
INPATIENT	Mean	**3.12**	2.03	1.04	0.05	**2.99**	1.86	1.08	0.05	n.s.
OUTPATIENT	Mean	**2.53**	1.53	0.98	0.02	**2.81**	1.67	1.13	0.01	p≤0.001

Figure 11 Changes in mean number of drug interactions ordered by age groups

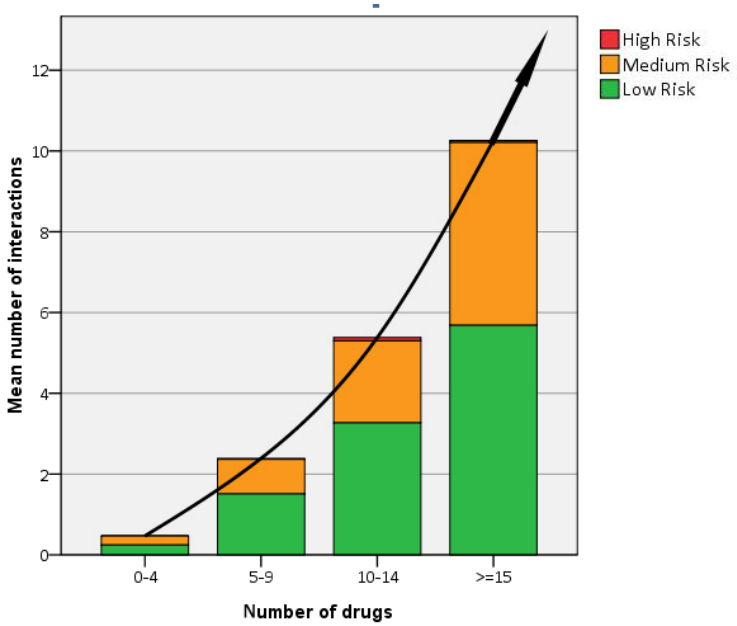


Changes in mean number of interactions in INPATIENT group are not statistically significant. The increase in total number of interactions and number of 'low' and 'medium risk' classified interactions in OUTPATIENT group is highly significant ($p \leq 0.001$) (*See Table 11*).

Changes in mean number of interactions in age subgroups are not significant in INPATIENT group. Increase of mean number of interactions in OUTPATIENT group is highly significant in age groups between 65 and 74 as well as between 75 and 84 ($p \leq 0.001$). Changes in >85 years subgroup are significant ($p \leq 0.05$) *(See Figure 11)*.

The number of interactions significantly correlates with the number of drugs applied (Correlation Coefficient 0.67; $p \leq 0.001$). The number of interaction almost exponentially increases with the number of drugs taken by a patient.

Figure 12 Changes in mean number of interactions per drugs admitted (classified by risk: low, medium, severe) (based on number of drugs and interactions at discharge)



The most frequent drug – drug interaction pairs can be seen in *Table 12.* Seven out of top ten interactions are classified as 'easy'. Interactions 'PPI with benzodiazepines', 'ACE inhibitors with allopurinol' and 'ASA with other antithrombotics' are classified as 'medium'. The three most frequent interacting

drug groups are antihypertensive medications (beta- blockers, ACE inhibitors and potassium depleting diuretics) *(See Figure 13)*.

Table 12 The 10 most frequent drug- drug interaction pairs (based on interactions at discharge)

	Interaction pair	%	N
1	ACE-inhibitors *with* Diuretics, potassium-depleting	6.7%	140
2	Benzodiazepines *with* Proton pump inhibitors	4.6%	97
3	Diuretics, potassium-depleting *with* Cardiac glycosides	4.3%	90
4	Beta-blockers *with* Nifedipine and derivates	3.3%	69
5	SSRI *with* Beta-blockers	2.9%	61
6	Cardiac glycosides *with* Beta-blockers	2.8%	60
7	ACE-inhibitors *with* Allopurinol	2.6%	54
8	Proton pump inhibitors *with* Anticoagulation, oral	2.6%	54
9	ASA *with* Antiplatelet agents	2.5%	53
10	NSAID *with* Diuretics, potassium-depleting	2.3%	49
11	Others	65.4%	1377
	Total number of interactions at discharge		**2104**

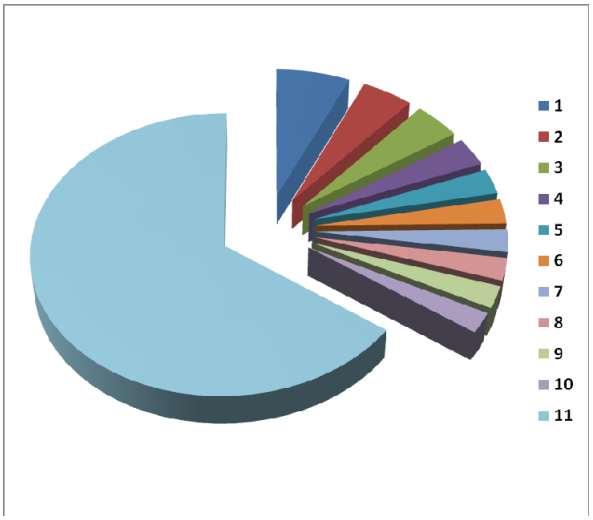
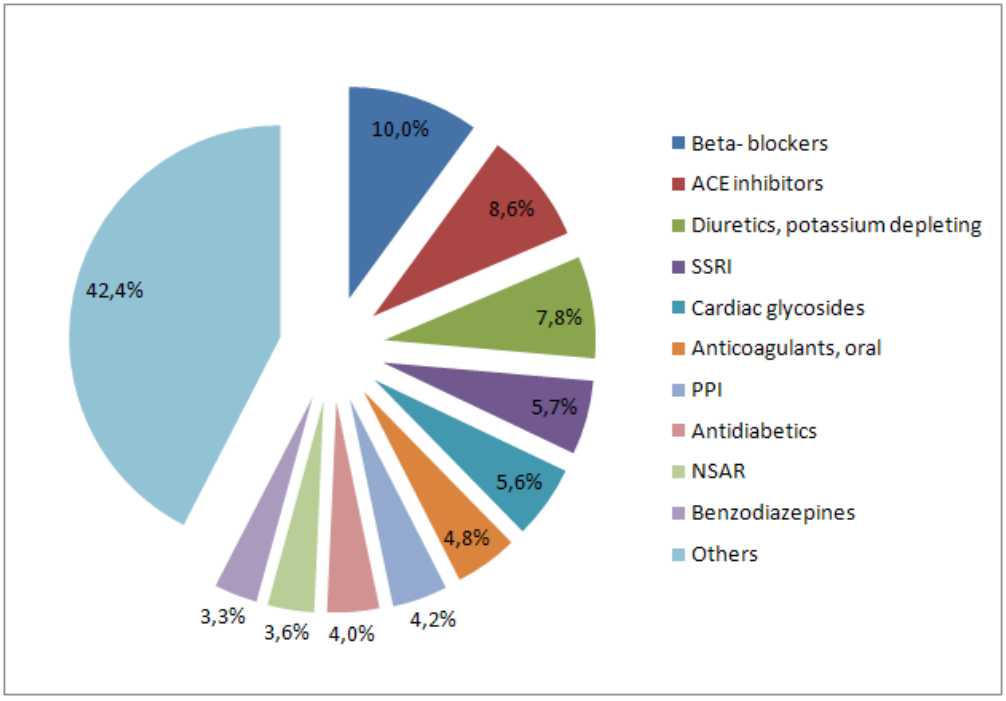


Figure 13 The 10 most interacting drug groups (based on interactions at discharge)



MEDIS© reported 26 ‘severe risk’ interactions at admission and 24 at discharge from hospital. Most ‘severe risk’ drug- drug interactions affected serum potassium level or bronchodilatory effects of beta mimetics and theophylline.

Table 13 Overall severe interaction pairs

Severe interaction pairs	N at admission	N at discharge
Potassium *with* Diuretics, potassium-sparing	7	4
Non-cardioselective Beta-blockers *with* Theophylline	6	6
Non-cardioselective Beta-blockers *with* Inhal. beta- mimetics	4	9
Benzodiazepines *with* Buprenorphin	5	1
Inhibitors of cholesterol- synthesis *with* Macrolide antibiotics	1	3
Neuroleptics *with* Amiodaron	1	1
H1- bocker, 2_{nd} generation *with* Macrolids	1	-
Amiodaron *with* Indapamid	1	-
Total number of severe interactions	**26**	**24**

D. Discussion

- **Patient group characteristics- Age and number of drugs**

Natural distribution of age above 65 years and number of drugs is not expected to be equally distributed either as number of people decreases with age and number of drugs usually rather increases with age. The study population is not representative for elderly people living in Austria as it is a selection of patients with diseases requiring treatment by specialists in internal medicine. The INPATIENT group is in mean more than 3 years older than OUTPATIENT group. This difference might be explained by higher morbidity of the oldest old, which require inpatient treatment. OUTPATIENT group shows greater variety in age distribution, the majority of patients are aged between 65 and 74 (43.1%), the number of patients is declining with age. This group suggests being more close to natural distribution of age. Ambulatory treated patients are supposed to be healthier than inpatient treated ones. The lower mean number of drugs in OUTPATIENT group confirms this fact. As patients were only selected by age some of them might not be identified as 'geriatric patient' when introductory definition is used *(See chapter 0, page 1).*

The mean number of drugs is 6.50 in OUPATIENT and 7.64 in INPATIENT group. Studies evaluating polypharmacy in geriatric patients in outpatient treatment or in nursing homes found that elderly patients use on average about 7 drugs (Avorn & Gurwitz 1995; Bjorkman et al. 2002). Community studies across Europe about drug use in people older than 65 years found an average of 2 to 3 daily prescribed drugs (Kennerfalk et al. 2002; Stuck et al. 2007). According to the recent World Health Organization (WHO) definition, the use of more than 5 drugs means polypharmacy. More than 81% of the INPATIENT group and about 62% of the OUPATIENT group took more than 5 medications per day on hospital admission. The number of drugs continuously increases with age additionally. The majority of geriatric patients in this study population are therefore at high risk of adverse drug reactions and polypharmacy primarily in the oldest old.

- **Prescription behavior – inpatient versus outpatient treatment**

One of the main findings of this evaluation is the remarkable difference in prescription behavior between outpatient and inpatient treatment.

Patients throughout all age groups treated on an outpatient setting had a significant increase of number of drugs prescribed while on an inpatient setting an increase of number of drugs prescribed was only found in younger patients (between 65 and 74 years). Furthermore there was a significant reduction in amount of drugs in oldest old above 85 in the inpatient setting.

A detailed look on the overall prescription behavior *(See Figure 10, page 1)* reveals that almost half of patients treated on an ambulatory basis had no changes in absolute number of drugs, a large number of patients had an increase and only in a few patients the number of drugs was reduced. There might be several reasons for those findings. Some patients who had no change in absolute number of drugs might have undergone diagnostics without a therapeutic consequence. Another important fact may be lack of documentation. As ambulatory treatment is documented on handwritten forms changes in medication strategies might not have been documented properly.

The small number of drug reductions and the high number of prescription increase throughout all ages might be due to the fact that there is only short time for patient visits and medication supervision. Hence ambulatory consultations are more restricted to treatment of signs and symptoms as well as risk factors rather than optimization of drug therapy. Apart from restrictions due to lack of time another influencing factor may be lack of training in geriatric medicine as most patients are treated by assistant doctors (interns). Sticking to guidelines in therapy of for instance vascular diseases is more conventional than reflecting matters of polypharmacy and drug interactions.

In contrast inpatient treatment provides enough resources and enough time to receive a holistic impression of patients, which facilitates optimization of drug therapy. Nevertheless inpatient treatment has several severe disadvantages for geriatric patients like restriction of mobility and autonomy with resulting risk of

losing functionality or risk of additional nosocomial infections. Inpatient treatment is usually supervised by well experienced physicians who are more familiar with adverse drug effects and more alert to risk of polypharmacy in the elderly. Nevertheless there was an increase in number of drugs in younger patients in inpatient group. Like in ambulatory group treatment of risk factors, signs and symptoms might be in foreground in those younger, commonly healthier patients. Furthermore, geriatric patients are currently distributed to the highly specialized divisions of the department of internal medicine as there is no division of geriatric medicine. This fact might enhance the problem of polypharmacy as each division emphasizes on its domain.

The reduction of the absolute number of drugs in the oldest old above 85 treated on an inpatient setting shows that there is awareness for polypharmacy. As those patients are supposed to suffer from a higher number of diseases, reduction of drugs may be taken into account automatically. Additionally due to reasons of compliance complicated medication might not contribute to raise patients' adherence.

The overall absolute change in number of drugs shows that reduction and increase of drugs are almost evenly distributed in INPATIENT group.

- **Medications that were increased or decreased significantly**

In both groups acid- suppressive drugs like proton pump inhibitors or H_2- receptor antagonists were prescribed to more than half of patients at discharge. The use of acid suppressive drugs is highly controversial in geriatric medicine. On the one hand the elderly are prone to peptic ulcer disease and gastro- esophageal reflux disease (GERD) due to altered physiology and high prevalence of ulcer promoting drugs. On the other hand those drugs have been associated with adverse drugs effects like vitamin B12 deficiency, pneumonia or Clostridium difficile infection (Aseeri et al. 2008; Kirn T. 2007; Valuck & Ruscin 2004). As acid- suppressive drugs are one of the most common contributors to polypharmacy indications should be checked individually. The use of new generation proton pump inhibitors may be beneficial in the elderly as they are minimally metabolized by CYP-

mediated reactions and therefore evade CYP2C19 polymorphisms and CYP2C19 drug interactions (Pilotto, Franceschi, & Paris 2005; Thjodleifsson 2002). But they do not differently influence the higher risk of vitamin B12 deficiency and infection.

Drugs used for treatment of cardiovascular diseases or risk factors have increased significantly in both groups *(See Table 8, page 43 and Table 9, page 44).* 6 out 10 drugs that were significantly increased in outpatient group and 3 out of 9 in inpatient group are used in the treatment of hypertension, coronary heart disease or peripheral vascular disease. Increase of those medications is a sign of the high prevalence of cardiovascular disease with increasing age.

Other drugs that were also increased during hospital treatment in both groups are antibiotics and inhalative antiobstructive therapy.

Significant decrease of certain drugs has only been found in inpatient group. Benzodiazepines, tricyclic antidepressants and chronic use of NSAIDs have been reduced according with the Beers list (Fick, Cooper, Wade, Waller, Maclean, & Beers 2003). Atypical antihypertensives might have been decreased in change for guideline oriented antihypertensives like beta-blockers, which have significantly increased in this group.

Interestingly NSAIDs have been significantly increased in outpatient treatment and significantly decreased in inpatient treatment. Pain is a common symptom in outpatient setting with lots of implications like isolation, depression or decreased functional status. (Merck Manual of Geriatrics 2005). In addition the elderly are at high risk of adverse reactions in the use of analgesics. Especially NSAIDs have the potential to produce GI bleeding, renal failure, high blood pressure, and heart failure (Fick, Cooper, Wade, Waller, Maclean, & Beers 2003). Hence treatment of pain is a complex thing in the elderly that is unlikely to be handled optimally in a short time ambulatory visit.

- **Drug- drug interactions – overall findings**

There was an extraordinary high number of theoretical drug- drug interactions in this study. Medis© reported interactions for the vast majority of patients in both groups *(See Table 10, page 45).* At admission 76.5% of inpatients (mean number

3.12 interactions per patient) and 64.1% (mean number 2.53 interactions per patient) of outpatients showed up with at least one drug to drug interaction. There is a great variety in studies evaluating interactions with different computerized detection programs. A study evaluating drug interactions in an elderly outpatient group across Europe found that 46% had at least one potential drug interaction, with an average of 0.83 potential interactions per patient, and of these interactions 10% were regarded as severe (Bjorkman, Fastbom, Schmidt, & Bernsten 2002). In contrast another study carried out in a geriatric ward in Brazil found in mean more than 4.5 interactions per patient (Locatelli J 2007). A study carried out in a psychiatric ward found that 25% of the elderly patients were prescribed a clinically relevant potential drug interaction involving CYP 2D6 and 11% involving CYP 3A4 (Davies et al. 2004).

Studies looking at potential interactions should be separated from those assessing actual interactions (i.e., with an adverse patient outcome as a result from the drug interaction) (Mallet, Spinewine, & Huang 2007). First, there are different definitions of drug interactions, their clinical importance and the sources used to detect them. Second, many potential drug interactions never lead to an actual clinical effect. Moreover drug interaction databases are not geriatric- specific.

Studies that focus on drug interactions leading to adverse patient outcomes (i.e. actual drug interactions) provide a better view of the clinical relevance of this topic. A study comparing adverse drug- related events with potential interactions in elderly patients presenting to an emergency department found that although 31% of the study population had a potential high risk drug interaction, not even one single adverse drug event was caused by a drug- drug interaction (Hohl et al. 2001). A French study showed that more than half of patients admitted had at least one potential drug interaction but this interaction only led to an adverse effect in less than a fifth of patients (Doucet et al. 1996). Another study evaluating inappropriate medication use among frail elderly inpatients found that 6% of these patients had a drug interaction with a detectable adverse outcome (Hanlon et al. 2004).

Apart from the clinical relevance of drug to drug interactions found in our study there is a consequential correlation between number of drugs and number of drug

interactions *(See Figure 12, page 1)*. The risk of drug interactions rises almost exponentially with number of drugs prescribed as there are more pairs of drugs to interact. Generally the prevalence of clinically relevant drug interactions is about 6% in patients taking two to four medications, 50% in those taking five and almost 100% in those taking 10 medications (Johnson, Seidemann, & Day 1994; Lin P. 2003).

Like changes in absolute numbers of drugs, mean number of interactions at discharge increased significantly in OUTPATIENT group throughout all age groups while there was no significant change in inpatient group *(See Table 11, page 45)*. Despite significant reduction of drugs in age group above 85 years the mean number of drug interactions did not decrease to a significant degree.

Nine out of the ten most frequent drug interaction pairs include drugs prescribed for cardiovascular diseases *(See Table 12, page 47)*. Especially those ten most frequent interaction pairs have very doubtful clinical relevance, although each of them has explicit evidence. Some of them are very common or even deliberate in clinical daily routine. Five of the top ten interaction pairs are pharmacodynamic interactions, four are pharmacokinetic interactions and one interaction is based on unclear immunological mechanisms.

The combination of ACE- inhibitors with potassium depleting diuretics is recommended in the treatment of hypertension by several guidelines including the European Society of Cardiology guidelines (ESC 2007). Medis however reports a possible adverse effect of this combination. In some cases it may cause severe hypotension, drowsiness, vertigo or even acute renal failure at first use. This so called first dose effect primarily emerges in patients with hyponatremia and hypovolemia (Baxter Karen 2007b). As this is common in geriatric patients they might be prone to adverse effects of this combination. This type of interaction has also been found to be most frequent in a Hungarian study evaluating 1.2 million prescriptions (Nyaka B. et al. 2008).

Other commonly used pairs of drugs among the top ten interactions are beta-blockers with nifedipine and derivates (may cause hypotension and heart failure), cardiac glycosides with beta- blockers (may cause bradycardia or AV conduction

disturbances) and acetylsalicylic acid with anti- platelet agents like clopidogrel (may cause intestinal bleedings) (Baxter Karen 2007b). Though relevance of these interactions may be arguable, elderly patients are more likely to develop those adverse effects due to altered pharmacodynamics, pharmacokinetics and altered mechanisms of compensation concerning regulation of blood pressure and bleeding risk.

The second most frequent interaction is a CYP2C19 and CYP3A4 dependent pharmacokinetic interaction between some proton pump inhibitors and benzodiazepines, which results in increased benzodiazepine effects including drowsiness, dizziness and ataxia (Baxter Karen 2007b). Increased effects of benzodiazepines should therefore be monitored closely in the elderly as their single use is increasing the risk for falls anyway (Fick, Cooper, Wade, Waller, Maclean, & Beers 2003). New generation proton pump inhibitors do not affect the metabolism of benzodiazepines to a significant degree (Pilotto, Franceschi, & Paris 2005; Thjodleifsson 2002).

The remaining most frequent drug interactions may cause increased cardiac glycoside toxicity (in combination with potassium depleting diuretics), increased effect of some beta blockers (in combination with SSRI), allergic reactions in simultaneous use of ACE- inhibitors and allopurinol, increased effect of oral anticoagulation (in combination with some proton pump inhibitors) and decreased antihypertensive effect of diuretics (in combination with NSAID) (Baxter Karen 2007b).

Ten drug groups are responsible for 57.6% of all the interactions found by Medis©. Drugs prescribed in hypertension therapy are involved in more than one quarter of the interactions *(See Figure 13, page 1).*

In both groups the number of severe interactions did not change significantly *(See Table 13, page 48)*. Interactions classified as ‘severe’ by Medis© are most likely to be clinically relevant as they may produce serious life- threatening events. Potassium in combination with potassium- sparing diuretics may cause hyperkalemia; non-cardioselective betablockers may cause serious bronchial spasm as they reduce effect of theophylline and inhalative beta mimetics.

Benzodiazepines combined with buprenorphin may result in respiratory depression and inhibitors of cholesterol synthesis like statins in combination with macrolide antibiotics may cause rhabdomyolysis. Interactions prolonging QT time and therefore increasing the risk of torsade de pointes were neuroleptics with amiodaron, H1- blockers of second generation with macrolids and amiodaron with indapamid (Baxter Karen 2007b; Hansten & Horn 2008). Those combinations should be clearly avoided if possible unless the benefit is judged to outweigh the increased risk.

- **Performance of drug interaction software**

The performance of computerized drug interaction screening has been widely evaluated with different methods. Several studies testing the performance of drug interaction software found that those systems were mostly operating at low levels of sensitivity and specificity (Abarca et al. 2006; Dallenbach, Bovier, & Desmeules 2007; Hazlet et al. 2001; Perkins et al. 2006). There is a great variety in performance of different computer programs but more recent studies indicate that sensitivity and specificity have improved (Abarca, Colon, Wang, Malone, Murphy, & Armstrong 2006). In a study testing performance by virtual patients with predetermined drug interactions the median sensitivity was 0.88 and median specificity 0.91 in community pharmacies. For hospital pharmacies the median sensitivity and the median specificity were 0.38 and 0.95 (Abarca, Colon, Wang, Malone, Murphy, & Armstrong 2006). A study comparing software findings to clinical pharmacologist opinion/ drug interaction compendia found a sensitivity of 0.81 and a specificity of 0.88 (Dallenbach, Bovier, & Desmeules 2007). At this level of sensitivity approximately one out of five drug-drug interactions would be missed.

A problem which was encountered throughout most studies was the high number of clinically unimportant interactions reported by the software. Efforts should therefore focus on flagging drug interactions with a high probability of true- positive adverse clinical effects and ignoring or putting behind interactions that have a high

probability of having no clinical adverse effect (Abarca, Colon, Wang, Malone, Murphy, & Armstrong 2006).

- **Managing drug interactions in the elderly**

The most recent paper offering strategies to detect, manage and prevent drug interactions in the elderly has been published in The Lancet (Mallet, Spinewine, & Huang 2007). The main proposes will be summarized in this section.

The understanding and management of drug interactions in the elderly can be very challenging as there are myriads of pharmaceutical molecules and elderly people often take many drugs to treat several diseases. Drug interactions can be categorized in three groups. The first category includes drug interactions that are common. Especially drugs with narrow therapeutic index such as digoxin, phenytoin or warfarin are likely to develop drug interaction with an adverse effect. As those drug interactions are well documented they are usually detected by commercial software systems. Furthermore CYP450 based interactions are also commonly involved in drug- drug interactions and can also be detected by accurate software.

The second category is complex interactions in patients with nine of more drugs and five or more comorbidities. The total combination of drugs and diseases could result in unwanted results. The third category is cascade interactions. The prescribing cascade begins when an adverse drug reaction is misinterpreted as a new medical disorder. Another drug is then prescribed and the patient is at risk of developing new additional adverse drug effects. A study for instance found that patients with dementia who were dispensed cholinesterase inhibitors had an increased risk of subsequently receiving an anticholinergic drug to manage new urinary incontinence (Gill et al. 2005).

Computer- assisted drug interaction software can serve as a reference source as it can decrease the risk of drug errors. Software however has to be up-to-date and provide a clear and precise overview. However there are no commercial systems designed for specific use in elderly patients.

The optimum drug management in the elderly requires a holistic, geriatric multiprofessional approach including a physician (geriatrician), a nurse and a pharmacist.

In order to detect drug interactions there are several helpful suggestions:

- *Identification of the nature of the interaction* – Is there a potential interaction between a drug and another drug, disease, food, nutrition or a combination of any of these factors
- *Understanding the mode of action of the interaction* – Is the interaction pharmacokinetic or pharmacodynamic? What is the time course of the interaction? Is the interaction documented in published work?
- *Identification of potential or real outcomes for the patient* – What are short or long-term outcomes for the patient? Is the patient having new problems (e.g. falls, bleeding, confusion, blood pressure changes)? Does the patient have risk factors that might trigger an adverse outcome (e.g. comorbidities, other drugs, pharmacogenetics)?
- *Monitoring and follow up for potential drug interactions* – Is there an appropriate monitoring plan (e.g. INR, electrolytes, blood pressure, glucose concentration)? Has the drug been documented in the patient's medical record?

There are different strategies how to manage drug interactions with adverse effect:

1. If possible drugs causing the interaction or drugs affected by the interaction should be discontinued. Alternatives might be to decrease dose or change the time of administration.
2. All drugs taken by a patient should be reviewed for appropriate indications. A lowest effective dose should be targeted. 'Start low – go slow'
3. Substitution of suspected drug with another drug of similar efficacy but lower interaction potential should be considered.
4. Drug concentrations should be monitored if possible.
5. Drugs should be rather discontinued than added.

6. Drugs should be prescribed on a regular basis with hold parameters instead of as needed
7. Optimum drug profile should be observed long enough.
8. Documentation of the drug interaction and communication to other health professionals increases security in drug therapy.

As the above strategies are implemented, appropriate pharmacotherapy in elderly people could result in better health and well being for the patient and decreased health care costs.

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