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Review

Geriatric drug therapy: Neglecting the inevitable majority

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ABSTRACT

Demographic evolution will considerably increase the number of people aged 65 years and beyond in the coming decades. The elderly not only represent the most heterogeneous population, but also are a major user group for prescribed medicines, a predominance that will continue to further increase. Medicines and medication management are much more complex and challenging in the elderly and can only be addressed through a multidisciplinary approach.

There is strong evidence that the elderly are able to properly manage their medication; however, their medications require different features than the standard medications used by adults. The elderly are exposed to several chronic disease conditions and their treatments, as well as experience age-related changes and limitations that need to be reflected in their medication management strategies.

Geriatric drug therapy remains a multidisciplinary task. The health care industry, physicians, pharmacists, nurses and care givers provide and guide the patient's therapy according to individual needs, while the health care system and regulatory authorities build the necessary framework of support and resources.Any realistic and significant enhancement to the elderly patients' medicines and medication management needs to be addressed by all disciplines and stakeholders involved since the absence of any of the stakeholders in the overall process negatively impacts the achievable enhancement in geriatric drug therapy.

1. Introduction

Traditionally, the pharmaceutical industry is focusing its research and development on the efficacy, safety and quality of a new drug therapy. With the increasing importance of the health care payers and patients this focus is going to enlarge. The medicinal products of the future will not only be judged on their efficacy to treat a disease conditions, but they will also be judged on their ability to manage the disease by reducing morbidity and mortality (eventually in combination with other drug products), improve the quality of life, safety, ease of use, level of patient compliance and finally reduce the overall caring costs [Jefferys et al., 2008; Palo and Murphy, 2009].

To achieve the aims of an effective drug therapy the drug product needs to be accurately tested, documented and designed as well as prescribed and used appropriately. We therefore use the term "geriatric drug therapy" as a term that includes the entire value chain starting from the product development through utilization of the product by the patient. The objective of this multidisciplinary review is not only to address the challenges of geriatric drug therapy in its various clinical and pharmaceutical aspects, but also from a patient aspect in order to stimulate an interdisciplinary discussion about future geriatric drug therapy.

2. The geriatric paradigm

The demographic trend in both developed and developing countries is moving towards a society with an increasing percentage of people above 65 years of age (Table 1) [www.earthtrends.wri.org].

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Table 1
Total demographic evolution across all ages and demographic evolution of people >65 years over the next 40 years in developed and developing countries [www.earthtrends.wri.org].

	2010	2020	2030	2040	2050
Developed countries [people in mio]					
Total population	1,365,899	1,397,353	1,411,479	1,412,224	1,402,753
Population ≥ 65 years	204,140	248,215	298,215	327,122	343,396
% of total population	14.9	17.8	21.1	23.2	24.5
Developing countries [people in mio]					
Total population	5,539,491	6,267,938	6,903,864	7,408,412	7,785,103
Population ≥ 65 years	323,716	467,255	671,557	919,185	1,122,963
% of total population	5.8	7.5	9.7	12.4	14.4

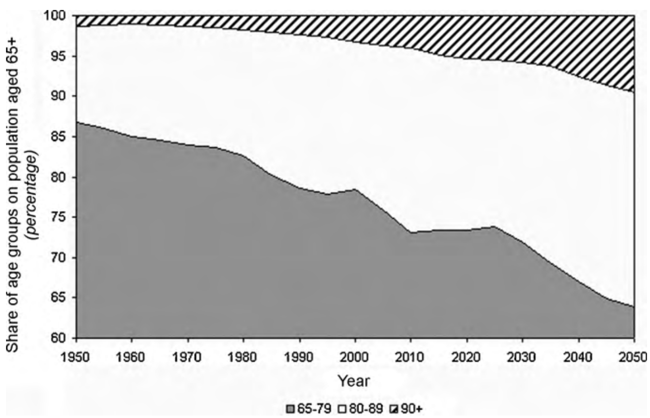

Fig. 1. Age composition of people aged 65 or over, by broad age group and development group (more developed countries) [www.un.org/ageing/challenges.html].

More significant will be the shift in composition of the elderly population over the next 4 decades towards more people above 80 years of age, resulting from increased life expectancy and the generation of the baby-boomers passing the age of 65 years (Fig. 1).

The number of people 90 years and older will increase from 8.1 to 37.7 million in the developed countries and from 12.9 to 123.5 million in the developing countries representing an increase of 463% and 954%, respectively (Table 2).

3. The impact of the demographic change

This shift in demographic composition is expected to raise the costs of long-term care services in the USA from 195 bio USD in 2000 to 540 bio USD in 2040 [Eskildsen and Price, 2009]. Unfortunately there are very few reports recognizing the valuable contributions the elderly provide to our society (e.g. care giving and charity functions) but these underline the importance of drawing special attention to this generation in terms of their specific health and medication needs [Hoyer, 2008]. The elderly must be seen as a valuable contributor to any flourishing society adding experience, knowledge, diversity and balance that will pay off in various ways to all of our benefit when we are able to maintain their health at an acceptable level.

The use of medicinal drug products is the main intervention when treating and managing medical conditions of people in our society. Safe and effective medicinal drug products have contributed significantly to the increasing health and longevity of mankind. Advances in drug research have led to several new treatment options that have steadily increased the prescription drug spending in all age groups. However, while the prescription drug spending increased from 113 USD to 347 USD between 1987 and 2000 in the under 65 years age group, the spending raised from 482 USD to 1249 USD at the same time for the patients of 65 years and older [Meara et al., 2004].

While a medicinal drug product has a precise definition, as dosage form and dose strength, the patient population represents a vast heterogeneity. With our increasing knowledge on the heterogeneity of disease conditions and patients, the therapeutic approaches that are developed tend to become more specific for patient populations and thus more individualized in terms of drug selection, dose strength, dosage form convenience, drug combinations as well dosing regimen. Consequently, drug product development will have to change its paradigm by including the geriatric patients and heading towards an approach of integrating new medicinal products into a disease management concept.

4. Aging

Aging is a gradual change of various physiological, biological, physical and social functions of the human being. Age-related changes are not necessarily of issue unless they are becoming critical for the individual and he/she is no longer able to manage her/his own daily life.

Aging has been considered as the differential process that begins after maturation and becomes prominent in the post reproductive stage [Smith and Gerstorf, 2004; Turnheim, 2005]. The aging process and the consequently occurring functional changes can differ widely between individuals and are not a matter of numerical age. Frailty might develop in the elderly following an incident of acute illness or hospitalization leading to a stepwise decline in various

Table 2
Age composition of people aged 65 or over, by broad age group [people in mio] [www.un.org/ageing/challenges.html] and the total increase [in %] corrected by demographic evolution of people aged > 65 years [www.earthtrends.wri.org].

	2010		2050		% increase
Developed countries	204,140		343,396		
90 + years	4%	8.166	11%	37.774	463
80–89 years	23%	46.952	25%	85.849	183
65–79 years	73%	149.022	64%	219.773	147
Developing countries	323,716		1,122,963		
90 + years	4%	12.949	11%	123.526	954
80–89 years	23%	74.455	25%	280.741	377
65–79 years	73%	236.312	64%	718.696	304

organ functions with incremental declines due to additional acute events [Ahmed et al., 2007]. The elderly thus present a heterogeneous patient group that requires special attention in medicinal therapy.

Although aging is a continuous process it was suggested to differentiate within the elderly patient population between the “early-old” ranging from 65 to 74 years, the “middle-old” ranging from 75 to 84 years and the “late-old” starting from 85 years of age [Swanlund, 2010]. Other authors looking to the elderly from a physiological point of view tend to classify the elderly as “fit elderly” and “frail elderly”. This classification is independent from the numerical age and regards the elderly from the physiological functions that can be maintained over a long age period or decline very rapidly with an acute disease or hospitalization [Ahmed et al., 2007]. There is evidence that in the middle-old, and especially in the late-old, age-related limitations become inevitably visible and require individual assessment and support strategies [Lindenberger and Ghisletta, 2009].

Additional complexity has been observed once elderly patients are discharged from the hospital after admission to an internal medicine department. The high readmission rate within 3 months after discharge was due to higher complexity in terms of socio-demographic data, medical history, functional and cognitive status, severity of illness and co-morbidities [Nardi et al., 2007].

When the elderly are losing their independence due to health issues they will have to receive expensive personal home care or hospital care [Nöthen and Böhm, 2009]. With the increasing life expectancy of the population in the developed and developing countries, the population of senior citizens will grow continuously and become an increasing challenge for society, and it is expected that this increase will go along with an increase in the need for personal home care and hospitalization [Comas-Herrera et al., 2003].

5. Age and medication use

Along with age-related gradual changes, the incidence for chronic diseases and co-morbidity increases are followed by chronic drug therapy. However, drug therapy in the elderly is much more challenging and complex than in younger adults especially due to this co-morbidity and the increasing number of drugs for the treatment of different conditions (polypharmacy). Increasing age is also associated with impaired adaptive and hemeostatic mechanisms making older people more sensitive to environmental and internal stress. When Adverse Drug Reactions (ADRs) occur they can have a serious impact on the elderly and cause significant medical costs that are preventable.

The number of chronic disease conditions increase with age. Naughton et al. found that 86% of the Irish population $\geq$70 years have at least one chronic condition, mainly cardiovascular, CNS, musculo-skeletal and gastrointestinal disease conditions. Co-morbidity of at least two conditions was found in 27%, three conditions in 19% and four or more conditions in 24% of the elderly [Naughton et al., 2006]. Yamanaka found that people in Japan aged 72–95 years have between 1 and 11 (average 5) symptoms of which the most common ones are lumbar and back pain, cognitive disorders, hearing losses, visual impairment, sleep disorders and gait disorders [Yamanake et al., 2007].

As a result geriatric patients use 30–50% of all the prescription drugs [Swanlund, 2010] and in the majority of cases they receive polypharmacy. From a Medline survey it was found that the average number of prescribed medications in people > 65 years of age is 2–9, with reports showing that 57% of woman 65 years and older take $\geq$5 prescribed drugs and 12% take $\geq$10 prescribed drugs. Moreover the results suggested that the number of prescribed medicines is increasing with age [Hajjar et al., 2007]. These data are inline with other studies reporting that the elderly take an average of 2–6 prescription drugs and 1–3 nonprescription drugs routinely. Moreover it was found that 51% of patients were taking drugs that were not reported in the physicians report, 29% were not taking the medicines that were reported in the physicians report and in 20% of the cases the dose strength was modified by the patient [Delafuente, 2003].

5.1. Compliance and adherence of geriatric patients

Once the appropriate medications have been prescribed, compliance and adherence to the prescription remains the most critical aspect in reaching the expected therapeutic outcomes. The focus and goal of geriatric drug therapy must be on understanding and enhancing adherence and compliance as an integral part of the therapy.

Poor adherence has been identified by the World Health Organization (WHO) as a growing global problem which is more pronounced in the developing countries than in the developed countries and which is an area where improvements can have greater impact on the health improvement than better medical treatments [Sabaté, 2003].

Potential issues with adherence start with the first prescription of a medicinal product and are not the only problem with elderly patients. Due to the increasing prevalence of chronic diseases with age, adults above 50 years of age often face several chronic diseases and receive a series of different drug products making adherence problems more likely [Murray et al., 2004].

The rate of compliance/adherence is estimated to be around 50% in the elderly [Swanlund, 2010; Park et al., 1992; Murray et al., 2004] and a potential further decrease with the number of drugs and the complexity of the treatment [Miller, 2008]. In a meta-analysis of published adherence data, the adherence rate ranged from 4.6 to 100% (average 75.2%) depending on the methodology to measure adherence [George et al., 2008]. The main two critical issues with regard to understanding the true adherence issue, are the absence of reliable and accurate adherence measurement methods [George et al., 2008; Murray et al., 2004; Vik et al., 2004] as well as the ‘voluntariness’ of the patients investigated in the studies which most likely exclude the less motivated, poorly compliant patients [George et al., 2008].

Several studies have investigated the reasons for non-adherence and identified a series of potential factors that might lead to a voluntary or involuntary deviation from the prescription schedule by the patient [Balkrishnan, 1998; Vik et al., 2004; Murray et al., 2004]. The various potential factors that might correlate with adherence are patient-related factors like morbidity/co-morbidity, physiological capabilities, cognitive abilities, health beliefs, race/gender, socioeconomic status, drug related factors like understanding of the therapy, administration schedule and number of drugs, packaging, perceived effects/ADRs and environmental factors like the physician/pharmacist relationship/communication and community support. For example, Vik et al. (2006) found that that in older home care patients non-adherence has a significant association with vision problems, a history of smoking, depressive symptoms and a high medication regimen complexity. Based on these potential factors, several interventions to improve the adherence have been proposed and reviewed by several authors [George et al., 2008; Hughes, 2004; Murray et al., 2007; Gleeson et al., 2009; Bassill and Grossberg, 2009; Park et al., 1992; Morrow et al., 2005; Conn et al., 2009]. Consistently, interventions in the form of improved communication/education, individualized medication plans and medication provision, regimen simplification and the use of medication organizers demonstrate some positive effects on adherence. The overall conclusion however, suggests that a patient-centered, multidimensional approach is needed to significantly and persistently improve adherence [George et al., 2008; Murray et al., 2004; Hughes, 2004; Sabaté, 2003; Tam-McDervitt, 2008].

Besides the scientific research done on adherence, we would like to emphasize that the patient remains a human being that might perceive and react in a very simple and pragmatic way. For the sake of reflection consider yourself as an elderly patient with your individual diseases receiving drug products that you need to split or crush before it becomes your "personal medicine". Consider that you have the full intention to be adherent but every day face a pill box that you can hardly open. And when you have opened the pill box and pulled out the different drug products all basically look the same. Consider your desire to understand your therapy but the artificial drug product trade name is hard to spell and even harder to pronounce. Consider you want to understand your medication and you read the dosing instructions in the leaflet but it is not in line with the physicians dosing recommendation.

5.2. Adverse drug reactions in elderly

Due to the changes in vital functions, the existence of various disease conditions and polymedication, geriatric patients are a vulnerable patient group that develop serious adverse drug reactions [Delafuente, 2003]. Hanlon et al. found 35% of ADRs in elderly of which 63% required physicians contact, 10% emergency rooms and 11% led to hospitalization [Hanlon et al., 1997]. The Berlin Aging study, which is a multidisciplinary investigation of 70 to over 100 years old citizens of Berlin (Germany) with the objective of understanding the various issues this age group is facing in their daily life, studied the drug therapy of these elderly people and found that 17% of them made errors in their medication, 24% of them received a lower dose than needed and were under-dosed and a total of 80% of the elderly experienced some kind of ADRs [Burkhardt and Gladisch, 2003].

The impact of ADRs can be much more severe in an elderly than in a young adult. ADRs are considered a potential cause for falls (and resulting hip fractures), confusion and cognitive impairments, urticaria, dementia, excitations, dehydration and hypotension [Turnheim, 1998]. These ADRs however, can be avoided as Gurwitz et al. (2003) found that approximately 95% of these adverse drug reactions were predictable of which 28% were also preventable.

To determine drugs that should be avoided or limited in the therapy of the elderly, a list of potentially inappropriate medications (PIM) for elderly patients has been developed based on several criteria identified as critical in elderly patients [Beers, 1997]. However, PIM use is still the major source for adverse drug reactions, treatment failure and consequently hospitalizations in elderly patients [Gurwitz et al., 2005]. For example, Cannon et al. (2006) found that in long-term care facilities PIM were used by 31% of the elderly.

5.3. The impact of non-adherence and adverse drug reaction

Non-adherence to a drug treatment or ADRs during a therapy contributes significantly to health care costs.

The direct and indirect cost of non-adherence has been calculated at 100 billion USD per year and is described as 'America's other drug problem' [Hughes, 2004]. Murray et al. investigated the impact of multilevel, patient-centered interventions by a pharmacist to improve adherence in 314 patients with heart failure. During the 9-month intervention period the emergency department visits and hospital admissions were down by 19.4% in the intervention group and the annual direct health care cost savings were 2960 USD [Murray et al., 2007].

As a consequence of the ADRs in elderly the calculated costs related to hospital admissions of the elderly in the US are 80 billion USD. Other studies calculate 7.2 bio USD per year as a result of potentially inappropriate medication-use only [Fu et al., 2007]. Johnson and Bootman (1997) calculated, based on the assumption that 84% patients achieve an optimal therapeutic outcome, that the drug related morbidity and mortality costs would reach 76.6 billion USD in the US annually and that there is a potential saving of 45.6 billion USD possible through appropriate pharmaceutical care.

Ernst and Grizzle (2001) tried to calculate the costs that are associated with medications problems that are defined as any deviation from the expected treatment outcome. He concluded that the average cost associated with a treatment failure will be USD 977, while the creation of a new medical problem due to the medication will cost USD 1.105. In the case of medication that is a treatment failure resulting in a new medical problems, the costs will mount to USD 1.488.

When medication reviews were performed and advice given to patients aged 80 years an older the drug related hospital admission dropped by 16% and the admission to emergency departments by 47% [Gillespie et al., 2009]. With an average cost of USD 12.646 per hospital admission and USD 9.489 per long-term care admission due to a drug related problem [Ernst and Grizzle, 2001] interventions like medication reviews and patient advice can have a significant effect on the hospitalization and long-term care costs.

6. The elderly patient

Medicinal products represent one part of the entire disease management concept in the elderly; they play a dominant role in helping the elderly to remain independent in their own homes for a long time and as such contribute to mankind's longevity, quality of life, elderly people's independence and efficient use of health care resources.

To improve geriatric drug therapy, the elderly patient must be considered with his individual capabilities and limitations during the development of pharmaceutical products, as well as the medication management defined as self-care activity and following and managing a therapeutic regimen. The major age-related changes and differences compared to a young adult concern the physiological functions, the cognitive, visual, motoric and swallowing capabilities.

6.1. Physiological functions

With age the physiological and functional capacities of the body are changing progressively and might alter the absorption, distribution, metabolism and elimination (ADME) as well as the pharmacodynamic of drugs, leading to clinically relevant consequences with regard to safety and efficacy. Increasing prevalence for one or more chronic disease conditions, morbidity and co-morbidity in elderly as well as age independent factors like lifestyle (e.g. smoking, alcohol abuse) can further impact the ADME and pharmacological effect of drugs. With the rising likelihood of polypharmacy as a result of different chronic disease conditions the risk for modified pharmacokinetics and pharmacodynamic effects due to drug-drug interactions is adding further complexity to the drug therapy.

The age-related physiological changes that affect the pharmacokinetic profile can occur during drug absorption, metabolism, distribution and elimination. In a recent article, Klotz summarized the major changes and their estimated importance for the clinical results that are shown in Table 3 [Klotz, 2009].

Special attention should be drawn to the very old and frail patients. This patient group often develops a malnutrition stage and loses weight considerably. Continuing with the standard dose strength that has been determined and introduced at a much earlier life stage the patients are suddenly seriously overdosed [Ahmed et al., 2007].

Table 3
Age-related physiological changes and their pharmacokinetic consequences [Klotz, 2009].

Physiological changes in the elderly	Pharmacokinetic consequences
Increase gastric pH	Slightly decreased absorption (rarely clinical significant)
Delayed gastric emptying	
Reduced splanchnic blood flow	
Decreased absorption surface	
Decreased gastrointestinal mobility	
Increased body fat	Increased V and $t_{1/2}$ of lipophilic drugs
Decreased lean body mass	
Decreased total water	Increased plasma concentration of hydrophilic drugs
Decreased serum albumin	Increased free fraction in plasma of a few highly protein-bound acidic drugs
Increased α1-acid glycoprotein	Decreased free fraction of basic drugs
Decreased hepatic blood flow	First-pass metabolism can be less effective
Decreased hepatic mass	Phase I metabolism of some drugs might be slightly impaired
Decreased renal blood flow and glomerular filtration rate	Renal elimination of drugs can be impaired

6.1.1. Drug absorption

Drug absorption can be influenced by age-related changes in the gastric and intestinal physiology like the unstirred water layer, the membrane permeability or drug transport and the gastrointestinal blood flow.

Changes in the gastrointestinal motility occur frequently in disease conditions (e.g. Stroke, Parkinson's Disease, multiple sclerosis, etc.) and have been found difficult to investigate exclusively as a function of age [Orr and Chen, 2002]. Subtle changes in the upper esophageal sphincter functioning and a decline in gastric emptying of liquids and mixed meals are most likely to occur as a function of increasing age. Changes in the small intestinal motility do not occur until an age of 80 years and beyond. The colonic motility and the anorectal functioning are assumed to change with age as both, constipation as well as fecal incontinence is frequently seen in elderly [Orr and Chen, 2002]. These changes appear to be related to sensory losses due to region-specific loss of neurons [Wiley, 2002].

The gastric pH can increase with age due to an increasing incidence of achlorhydria. This can lead to an altered bioavailability of pH sensitive drugs or drugs with a pH dependent solubility [Gidal, 2006]. Ketoprofen for example exhibited a poor absorption from elderly with anchlorhydria and a gastric pH of >5 compared to elderly with a gastric pH < 5. Interestingly, when taken together with acidic juice, the ketoprofen absorption in achlorhydria patient was equivalent to the elderly with a gastric pH < 5 [Hurwitz et al., 2003].

The presystemic metabolism and efflux by cytochrome P-450 (CYP) 3A4 and P-glycoprotein (P-gp) in the small intestine has been described for many drugs. However, only very few studies have investigated the relationship of age on CYP and P-gp. Hamman et al. (2001) investigated the absorption of fexofenadine in 12 young (22–35 years) and 12 elderly (65–76 years) volunteers co-administered with the P-gp and CYP inducer rifampicin. The oral clearance of fenofexadine before and after administration of rifampicin was similar in both age groups and the P-gp activity as well as the P-gp induction upon rifampicin administration was not affected by age or sex.

Despite the above-described changes in the GI tract there is no evidence that oral absorption is changing as a result of increasing age [Cusack, 2004; McLean and Le Couteur, 2004].

6.1.2. Drug metabolism

Liver metabolism has been shown to decrease with age due to liver mass decrease of 20–30% and a hepatic blood flow decline of 30–50% [Cusack, 2004; Schmucker, 2001]. Aging has also been found to be associated with changes in the sinusoidal endothelium of the liver that could limit the availability of oxygen and other substrates for drug metabolism [Le Couteur and McLean, 1998]. However, the genotype related differences in drug metabolism are more important than the age-related changes and need to be taken into consideration for all age groups including the elderly in case a drug is substantially metabolized by one of the enzymes known for its genotype expression dependency (e.g. CYP 2D6) [Phillips and Van Bebber, 2005].

The effect of aging on the hepatic drug metabolism has been reviewed by various authors recently [McLean and Le Couteur, 2004; Cusack, 2004; Kinirons and O'Mahony, 2004]. The data confirmed an increasing inter-individual variability in drug metabolism with age, but found no clear evidence that age is an individual factor of declining metabolic enzyme activity. However, the clearance of highly metabolized drugs and the declining liver blood flow rate correlate quite well with the decreased metabolism seen in the elderly [McLean and Le Couteur, 2004]. Confounding factors like diet and food, frailty, smoking, co-morbidity, polypharmacy and alcohol intake are known factors contributing to the high inter-individual variability in older people [McLean and Le Couteur, 2004; Kinirons and O'Mahony, 2004].

Hepatic drug metabolism by CYP has been studied in various age groups ranging from 20 to >70 years of age. CYP metabolism showed a decline after the age of 40 years. The potential impact of this age-related decline of CYP was confirmed by the declining metabolism of phenazone. While the half-life of phenazone increased steadily with increasing age, the clearance remained stable between the ages of 20 and 49 years and declined significantly from 50 to 60 years of age and than stabilized at a low level. The authors concluded that early pharmacokinetic studies in drug development should include young (20–39 years), middle age (40–69 years) and elderly (>70 years) volunteers to evaluate the potential age-related clinically relevant effects in the targeted patient groups [Sotaniemi et al., 1997].

6.1.3. Drug distribution

Drug distribution can be altered with age by the changing body composition and the plasma protein levels.

With increasing age the total body fat increases and the total body water decreases. These changes can alter the volume of distribution (Vd) according to the lipophilicity or hydrophilicity of the drug compound. For lipophilic drugs the Vd can increase because of the up-take into the lipidic tissue along with a prolongation in the elimination half-life due to the re-diffusion of the drug from the fatty tissue [Cusack, 2004]. Clinically significant differences in the Vd and elimination half-life have been reported for the benzodiazepines [Woodward, 1999] lidocaine and chlormethiazole [Cusack, 2004]. For the more hydrophilic drugs a decrease of the Vd in elderly have been described for sotalol, antipyrine [Cusack, 2004], lithium and digoxin [Klotz, 2009].

After absorption of the drugs into the plasma, the drugs circulate to a great extent bound to plasma proteins while only a smaller portion of free drug is available for the pharmacological effect and metabolism. There is evidence that in elderly the plasma albumin concentration is slightly decreasing while the $alpha_1$-acid glycoprotein concentration remains stable or slightly increase [Klotz, 2009; Butler and Begg, 2008]. While acidic drugs bind to albumin, alkaline drugs bind to $alpha_1$-acid glycoprotein the degree of binding to plasma proteins is variable. Especially for drugs with >90% of plasma binding, a change in the plasma protein level or competition on the binding side with other high affinity drugs can significantly increase the free drug concentration [Cusack, 2004; Butler and Begg, 2008] and for drugs with a high extraction ratio and a narrow therapeutic window an increased drug effect or potential ADRs cannot be excluded [Benet and Hoener, 2002].

Recently, Butler and Beck reviewed the literature to evaluate the hypothesis that the metabolic clearance of drugs is declining with age independent from the extent of clearance [Butler and Begg, 2008]. As the level of plasma albumin, to which the majority of drugs are bound, have been described to decline with age and more significantly in elderly with severe acute illnesses, postoperative states and malnutrition states, the ratio of the bound and free fraction of a drug might also change. Butler and Begg could show that for the capacity limited drugs with high and low protein binding the free drug concentration is increasing for most of the drugs while the intrinsic clearance is declining [Butler and Begg, 2008]. The clinical relevance of the changes in protein binding by age is controversially discussed [Benet and Hoener, 2002] and the impact of altered plasma protein binding of drugs in elderly will require further investigation.

6.1.4. Drug elimination

The main route for drug and drug metabolite excretion is through renal tubular secretion in the urine. An age-related decline in the glomerular filtration rate has been demonstrated as a major factor for age-related changes in drug elimination. Aging of the kidney has also been described to be associated with various histopathologic changes like thickening of the intrarenal vascular intima, sclerotic changes of the glomeruli and decrease in renal weight [Muhlberg and Platt, 1999].

The renal clearance (glomerular filtration rate) is generally decreasing in two thirds of the population by 20–30% between the age of 30 and 80 years, however, the other third shows a stable renal clearance across this time span suggesting that the renal clearance is not necessarily impacted by numerical age [Klotz, 2009; Herrlinger and Klotz, 2001; McLean and Le Couteur, 2004].

Dose adjustment for the elderly to address the declining renal clearance has been proposed by Turnheim (2005). The two models proposed take into account the maintenance dose (D_m) corrected by either a factor Q, which is the sum of the extrarenal elimination fraction Q_0 and the renal elimination fraction Q_{renal} or the decline in the total clearance defined as the bioavailability of young multiplied by the clearance in elderly and divided by bioavailability in elderly multiplied by the clearance in young. Turnheim stated that both models are just average corrections based on either literature reported clearance data in young and elderly or truly measured clearance data in the individual.

Independent from aging, the renal function is known to decline as a result of several disease conditions like hypertension, vascular diseases and diabetes that are common in people over 65 years and they might be more important than aging itself [Melk and Halloran, 2001].

6.1.5. Pharmacodynamic

Age-related changes of clinical targets can result in changes of the pharmacological response to a drug. The changes of the physiology of organs and receptors can significantly differ from a healthy old or young individual and has been the subject of several review articles [McLean and Le Couteur, 2004; Hilmer et al., 2007; Turnheim, 2004].

The changing pharmacodynamics of cardiovascular and central nervous drugs are well described. With the increasing sympathetic activity with age β-adrenoreceptors of the heart are desensitized [Brodde and Leineweber, 2004]. The use of β-adrenoreceptor blockers has therefore been questioned and proven to be less effective in elderly compared to young adults [Hilmer et al., 2007]. Benzodiazepines are frequently used in elderly to treat sleeping disorders. Elderly appear to react more sensitive to benzodiazepines than younger, which could not be explained by pharmacokinetic changes that are also evident in elderly for this class of compounds. In general, elderly need a 2–3-fold lower plasma concentration of benzodiazepines for the same drug response than younger adults [Woodward, 1999].

6.1.6. Drug–drug interactions

Drug–drug interactions (DDIs) are the major challenge in polypharmacy and especially in the elderly as they are generally suffering from various diseases and consequently are exposed to multiple chronic drug treatments [Björkman et al., 2002; Nobili et al., 2009; Juurlink et al., 2003; Delafuente, 2003; Becker et al., 2008; Boobis et al., 2009; Bushardt et al., 2008]. The main types of DDIs are metabolism-based DDIs or transporter-based DDI which in both cases can be inhibited or induced leading to clinical consequences especially for co-administered drugs with a narrow therapeutic index or a steep dose–response curve. Moreover, DDIs often take place at the pharmacologic drug binding sites, whereby two drugs might work synergistically or antagonize the activity of one drug or both drugs together [Boobis et al., 2009]. Allergic reactions are another area of potential DDIs that are caused by histamine release from the mast cells or the basophiles by a drug. Drugs might also inhibit the diamine oxidase (DAO) or histamine-N-methyltransferase (HNMT) the main metabolizing enzymes of histamine and increase the histamine concentration [Boobis et al., 2009]. Drug or drug metabolites can compete on plasma protein binding sites increasing the free drug in the plasma that is responsible for the pharmacodynamic effect or for site effects in case of narrow therapeutic windows [Delafuente, 2003].

The frequency of DDIs in elderly outpatients across 6 different countries in Europe found prevalence for at least 1 potential DDI in 46% and at least 2 potential DDIs in 22% of the elderly of which one half cause ADRs and the other half suboptimal therapeutic effect. Beside the fact that the majority of drug combinations identified in the study where known, 90% of the potential DDIs could have been solved by simple dose adjustment [Björkman et al., 2002]. In another study, 674 geriatric outpatients taking more than one drug were evaluated focusing on the top ten most frequent interactions. In 300 of the patients (44.5%) 398 potential interactions were identified. 172 patients (25.5%) were identified with at least one side effect or a less than adequate treatment. In 111 patients (16.5%) changes to the actual medication regimes were proposed that led to an improvement in 80% of the patients that could be followed up [Tulner et al., 2008].

The frequency of DDIs has been found to be mainly dependent on the patient's age and the number of drugs. DDIs rose from 24% in patients between 60 and 74 years to 36% in patients over 80 years [Nobili et al., 2009]. The prevalence to experience a potential DDI has increased from 1992 to 2005 for people aged $\geq$70 years from 10.5% to 19.2% and for the life-threatening DDIs increased from 1.5% to 2.9% in the same period [Becker et al., 2008]. An increasing risk for serious DDI has also been suggested for elderly cancer patients as any pharmacokinetic and pharmacodynamic alterations of each anticancer treatment by polypharmacy can cause a deleterious drug effect [Tam-McDervitt, 2008]. The association between drug toxicity leading to hospitalization and DDIs has been investigated over a 7 years period for 3 major known drug toxicities hypoglycemia, digoxin toxicity and hyperkalemia. The likelihood for hospital admission was 6 times higher in glyburide patients treated with co-trimoxazole, 12 times higher for digoxin co-administered with clarithromycin and a 20 times increase for patients treated with an ACE inhibitor and potassium-sparing diuretics [Juurlink et al., 2003]. As many of the potential DDIs are predictable and preventable [Gurwitz et al., 2003], medication reviews have been suggested by several authors for elderly patients receiving polypharmacy to avoid inappropriate polymedication and "hyperpharmacotherapy" [Bushardt et al., 2008; Nobili et al., 2009; Björkman et al., 2002] and proven successful [Peterson et al., 2005; Tulner et al., 2008; Gillespie et al., 2009; Vinks et al., 2009].

6.2. Cognitive functions

Understanding the prescription of a medicine and establishing the medication schedule from different prescriptions is a complex and effortful cognitive task [Hutchison et al., 2006]. To follow through the established medication schedule, the implementation intention requires the development of an appropriate and achievable implementation plan on how and when the goal targeted action will be executed [Gollwitzer, 1999; Park et al., 2007]. The elderly have proven to be specifically good in implementing routines and automatic processes in their daily life [Park et al., 1999]. The majority of elderly suffering from various disease conditions have a real intention to follow the medication as prescribed by the physician [Park et al., 1999; Martin and Park, 2003]. With clear implementation plans and contextual cues medication management by the elderly can be facilitated, simplified and implemented as an automatic process in their daily routine.

Cognitive functions in general can be divided into working memory which is handling the effortful, complex management of information and activation of executive processes and the automatic cognition, which refers to information processing that can occur without conscious awareness and requires very little or no engagement of executive functions and complex information processing [Moscovitch, 1994]. The change in cognitive functions appearing with age is not a "uniform" process and cognitive functions might vary considerably across individuals as well as across cognitive domains in elderly. While selective attention in general has been shown to slow down with age, it is not affected by distraction differently from that at younger ages. When more attention tasks have to be processed at the same time, deficits are more likely with age, however, task specific training was able to convert some of these tasks into automatic processes that required less attentional resources [Glisky, 2007].

Decline in memory with aging has been described as a decline in processing resources and working memory account. As shown in Fig. 2, Park and Hedden (2001) found that certain tasks did not necessarily decline across the life span; instead they increase or remain at least stable over time like word knowledge (vocabulary).

They concluded that older adults have a rich set of information and experience that can balance the declining working memory and help perform prospective memory tasks, like adherence to medication regimens [Park and Hedden, 2001]. In general, the elderly try to compensate the declining cognitive functions by relying increasingly on their stable cognitive functions as an alternative strategy to performing a certain task. Further to this, the elderly do optimize their resources by becoming more selective in their goals, reducing the diversity of their activities to optimize their daily life including spending more time on compensational strategies like sleeping more often and longer during day time [Lang et al., 2002]. The performance of a prospective memory task was not found to be different between the elderly and young people unless there was an extensive background task during the retrieval phase. Even so, encoding and retrieval are relatively non-strategic and automatic processes, a certain amount of working memory seems to be involved in maintaining the intended reactions towards the signal in an activated mode [Einstein et al., 1997].

These results suggest that elderly can specifically focus on the medication schedule and that the performance of prospective memory tasks (taking the medication) is not affected by age unless the individual is exposed to a demanding situation simultaneously.

6.2.1. Using stable cognitive functions for medication management

Medication management needs to become a goal for the patient that she or he needs to execute continuously once a therapeutic medication schedule is defined. To attain a certain goal, plans need to be established on how the goal should be achieved. Linking an implementation intention (e.g. a medication schedule) to an anticipated situation or contextual cue (e.g. morning coffee) can initiate the goal directed medication intake as an automatic response to the situation or contextual cue [Gollwitzer, 1999; Park et al., 2007].

The usefulness of implementation plans has been studied by Chasteen et al. (2001) in the elderly with a mean age of 71 years. Participants who formed implementation intentions performed two times better in self-initiating the goal than the ones who did not form such implementation intentions. They concluded that even noticing the cue and processing the action required explicit memory or rehearsal; however, once noticed little memory was needed to execute the action. In a cohort of high-functioning best agers, Wallsten et al. (1995) found that about one third of the people used cues and routine activities to manage their medication intuitively as an implementation strategy. McDaniel and Einstein reviewed the retrieval of prospective memory when relying on automatic

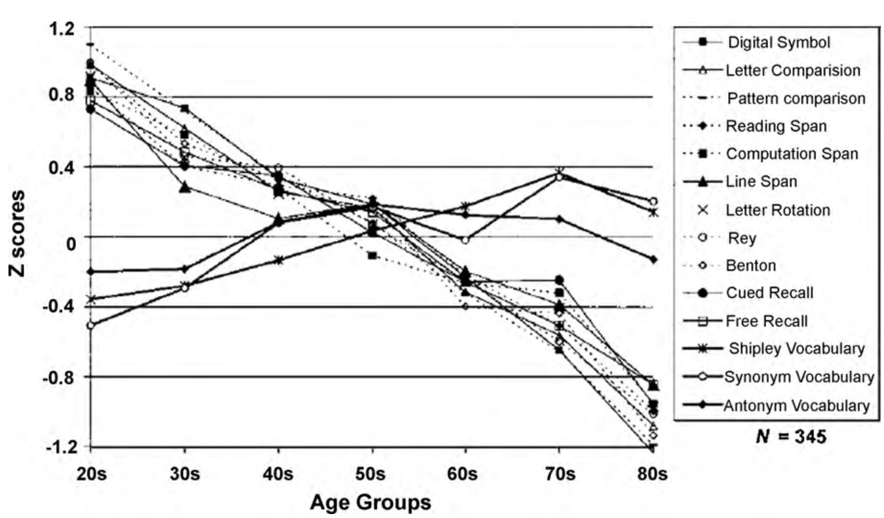

Fig. 2. Performance on measures of speed of processing, working memory, long-term memory, and world knowledge across the life-span [from: Park and Hedden, 2001].

processing. Their conclusion was that there are different strategies to retrieve a prospective memory task and that the probability of being successful depends on the prospective memory task itself, the targeted cues as well as the individual and the ongoing task [McDaniel and Einstein, 2000].

Medication adherence also depends on the life-style, which was found to be more favorable in elderly. When assessing 121 community-dwelling rheumatoid arthritis (RA) patients aged 34–84 years, Park et al. found that elderly patients despite declining cognitive capabilities were more adherent to the RA treatments than younger adults. The main reason was that the busy life-style in younger age distracts from the focus to take the medication, while the elderly, especially in serious disease conditions, structure their life around the medication schedules rather than the other way around [Park et al., 1999].

Using implementation intentions to perform a 4 time daily blood glucose measurement of nonpatients between 60 and 81 years of age demonstrated a significant improvement of performance. Non-patients were chosen to simulate the situation of newly diagnosed patients, to avoid prior experience and allow real testing of the effectiveness of the intervention and to assess the implementation intention effect by eliminating a motivation factor of newly diagnosed patients. The group who formed, rehearsed and deliberated implementation intentions (like where and how the blood glucose measurement would be done) performed significantly better with 50% more tests done over the study period of 3 weeks compared to the group that did not form implementation intentions [Liu and Park, 2004].

6.2.2. *Cognitive limitations to medication management*

To identify risk factors for poor medication management capabilities Ruscin and Semla investigated the capabilities of community-dwelling elderly with regard to the various tasks in medication management like reading prescriptions, interpreting medication instructions, opening pill boxes, etc. Cognitive impairment defined as a Mini Mental State Examination (MMSE) of MMSE < 24 as well as the physical abilities of daily tasks defined as Katz ≥1 were clear risk factors that an individual was not able to perform individual tasks and it was also found that these are independent individual risk factors for an overall poor performance in their medication management [Ruscin and Semla, 1996].

Ball et al. (2002) investigated the impact of intensive cognitive training programs on memory, reasoning and speed of processing in 2832 participants aged 65–94 years to improve mental abilities for independent daily living. Even so there was an immediate affect seen on all three training interventions the affect per se remained small and did not differ significantly from the untrained groups after 1 and 2 years post training. These results suggest that cognitive training does not improve the medication management performance of the elderly.

6.2.3. *Reduced cognitive demand in medication management*

As described earlier, medication schedules for elderly can be quite complex and cognitively demanding. The way of disseminating information and communicating with the patient is a critical component for comprehension and memory of the treatment plan. Shrank et al. reviewed the content and format of drug labels on the patient comprehension of these information and found that the patients expect to get information about indication, benefits of the drug, the treatment duration as well as the ADRs, in a format that is structured, easy to read and is using a simple language [Shrank et al., 2007]. In a group of older adults (mean age 70.4 years) medication instructions were delivered either in a categorized list, a simple list or in a paragraph and assessed for its preference and comprehension. Questions concerning the treatment instructions were more quickly answered form the listed instructions compared to the paragraph and the recall of information was best from the simple list, raising evidence that listed information help elderly in understanding their therapy more easily [Morrow et al., 1995].

Table 4
Ten "Best Practices" for developing effective print materials for patients [Wilson et al., 2009].

1. Use a clear, simple font
2. Maximize white space and avoid visual clutter
3. Employ list formats when possible
4. Provide supportive graphics only when appropriate
5. Chunk information into manageable pieces
6. Use concrete language
7. Avoid technical jargon
8. Stick to positive wording and avoid negations
9. Exclude distracting information and embellishments
10. Incorporate patients' perspectives and expectations

Wilson et al. tried to establish some "Best Practice" guidance (Table 4) towards delivering health care information in an effective way, by freeing up the working memory resources through elimination of unnecessary processing of poorly designed information material [Wilson and Wolf, 2009].

A good example on how important the clarity of medication instructions is has been provided by Beckmann, who asked to calculate the number of days a box of 40 pills would last if they have to take "two tablets morning and evening" roughly half of the people aged >77 years could not calculate this accurately. The authors noticed that the information was ambiguous and may be responsible for the wrong calculation [Beckman et al., 2005].

Another approach in reducing cognitive demand is the use of reminder systems to overcome the forgetfulness of the patient. While most of the reminder systems require the involvement of a human monitor, automatic medication tracking and reminder systems in the form of an auditory beep and visual alarm have been developed and investigated in the elderly. The reminding occurred either at the prescribed time of medication (time-based) or occurred only when the patient forgot the medication and was able to take the medication (context-aware). With 68.1% compliance without reminding, the compliance increased with the time-based reminding to 73.5% and the context-aware reminding to 92.3% [Hayes et al., 2009].

6.3. *Visual functions*

One of the major sensory organs leading human beings through life is the visual system. Medication management requires a clear identification of the medication as well as clear understanding of the medication by the patient. With the age-related decrease of visual functions, the elderly, and especially those 75 years and older, might lose a critical capability of clearly identifying the medication and their self-insurance of taking the right medicine.

The visual system encodes incoming information and transfers them to the working memory where they are processed into meaningful information for the individual. The visual performance has been shown in various investigations to be directly related to age. A 20-year-old human normally has a visual acuity of 1.0–1.5 (20/20–20/15 according to the Snellen index) which declines with age. A steep decline in the visual function happens normally between 80 and 90 years [Evans et al., 2002].

The estimation of the prevalence of visual impairment within the society is dependent on the criteria used. The WHO criteria defines blindness as a visual acuity of less than 0.05 (20/400 Snellen) and visual impairment as the best-corrected visual acuity of less than 0.3 (20/60) but no less than 0.5 (20/400) in the better eye, while the US criteria are more stringent and define blindness already as the visual acuity of 0.1 (20/200) and visual impairment as a best-corrected visual acuity of less than 0.5 (20/40) but better than

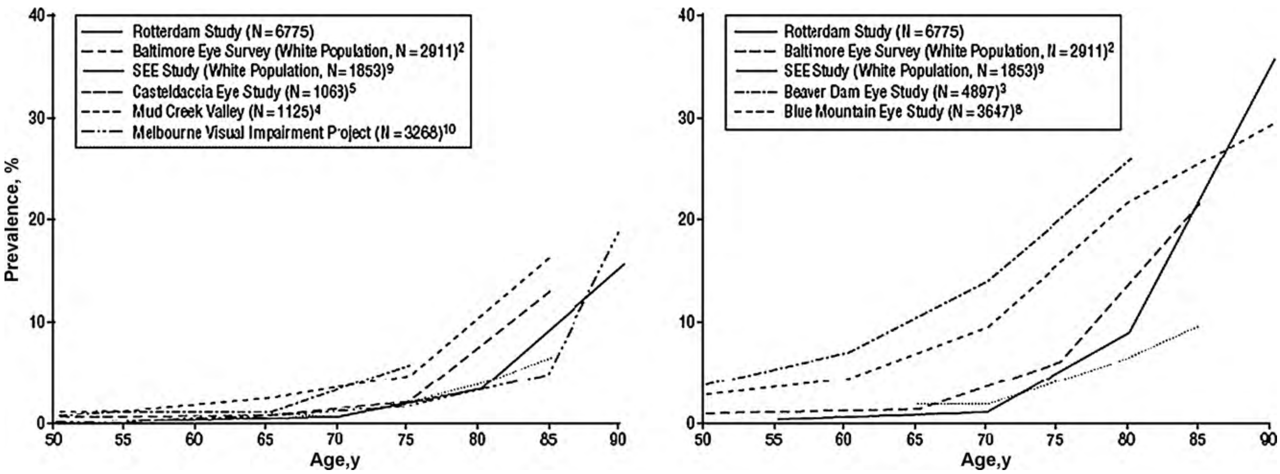

Fig. 3. Total prevalence of poor vision (blindness and visual impairment) as a function of age according to the World Health Organization criteria (left) and to criteria used in the Unites States (right) [Klaver et al., 1998].

0.1 (20/200). Depending on the criteria used, the number of people classified as blind or visually impaired varies from study to study. However, all studies provide clear evidence that visual impairment is a common problem in the age group ≥75 years [Klaver et al., 1998] (Fig. 3).

The causes for visual impairment and blindness differ depending on the age. Optic neuropathy and myopic macular degeneration was the predominant cause for blindness and visual impairment, respectively, in the age group younger than 75 years, while age-related macular degeneration and cataract alone or in combination with other eye diseases was the cause for blindness and visual impairment in people above 75 years. Interestingly, diabetic retinopathy was not found as a major cause for poor vision [Klaver et al., 1998]. With the increasing life expectancy as reflected in the demographic estimations (Table 2) visual impairment and blindness will be a predominant challenge for medication management by elderly.

6.3.1. Importance of colors in visual performance

Color perception is part of the early vision system and is preserved with age due to its over-learning in early childhood. A color stimulus attracts involuntary attention and is detected 5–6 fold better than a luminance spot. Repetition of colors can have a priming effect causing an automatic reaction to the color stimulus and that is preserved with age [Stegemann, 2005].

That elderly people maintain their ability to differentiate between different colors and color combinations of small oral dosage forms has been demonstrated by Hersberger. In the study including 50 volunteers aged 65–92 years 45 color combinations (monochromatic and bi-chromatic capsules) were assessed to see if they can be distinguished by the volunteers. Color combinations composed of white and yellow combined with light blue, red, green, dark blue and purple were found to be the most suitable color combinations, while color identification was slightly difficult with dark color combinations of brown, dark blue and purple [Hersberger, 1997]. To enhance product identification and differentiation between different products the use of colors in drug product design has been suggested [Stegemann, 2005].

To investigate the perseverance of color perception in high age and even in people with cognitive impairment a study was performed comparing 95 year normal old with 80 year normal old and 80-year-old Alzheimer Disease (AD) patients. Color discrimination and naming was identified as quite well preserved in all populations tested and no significant differences were observed in color perception. Minor differences were found between the groups for the people with medium or low visual functions as well as Mini Mental State Examination (MMSE) score below 26 [Wijk et al., 2002]. Further studies have investigated the aspect of AD in relation to color discrimination, naming and preference. Twelve AD patients were compared with 12 normal subjects aged >80 years without identifying a significant difference between the two groups. The authors conclude that color cues and color contrasts in the environment can help guide AD patients in their daily life [Wijk and Sivik, 1995]. To identify the specific capabilities of AD patients with mild, moderate and severe disease states with regard to color discrimination, naming and preference another study was performed with 50 patients. Color discrimination was better in the yellow and red area and was affected for blue and green. A degree of severe dementia had a negative impact on color naming; however, no differences were seen with regard to color preference and degree of severity of AD [Wijk et al., 1999].

6.3.2. Visual impairment and medication management

Reading and understanding prescription labels is the basis for an individual to develop his proprietary medication scheme and follow through the medication. For the elderly 65 years and beyond, this has been identified as a challenge. From 325 elderly patients (mean age 78.1) from an ambulatory care center prescription labels could not be read by 38.8% and had not been fully understood by 67.1% of the elderly [Moisan et al., 2002]. While the study did not find a correlation with the compliance of these elderly, there is clearly a lack of information that may or may not be important to the medication schedule for an elderly patient and remains a potential source for medication issues. It can be assumed that the use of pictograms supported by discriminatory colors and identifying marks will facilitate reading and understanding of the important information and consequently improve the medication management of elderly with visual impairments.

The elderly try to compensate mild cognitive impairments through visual capabilities and they have been found to do this successfully in managing their medication. In 335 elderly aged 73–82 who had either poor cognition (MMSE 24) or good cognition (MMSE 30) it has been demonstrated that higher visual acuity, stereopsis and contrast sensitivity is directly related to the ability to fill pill boxes with two drug products correctly [Windham et al., 2005]. As visual acuity supports reading the instructions or letter/symbols on the dosage form, contrast sensitivity in the discrimination of the dosage forms and stereopsis in the management of the pill box and the dosage form placing, the importance of clear and differentiable dosage forms to improve the management and pill box filling of multiple medications becomes evident.

To further support the declining visual acuity and ability to read a standard 12-point type size prescription label in the elderly, clear information and instructions could be delivered through holograms, pictograms and colors. Especially when medication instructions are delivered in pictures, the attention can be drawn to the important details and circumvent the need to draw this information from complex textual information [Katz et al., 2006].

6.4. Motoric functions

Motoric functions change gradually with age and more severely by various secondary diseases in the form of degenerative disease of the musculo-skeletal, vascular or central nervous system. Affected are hand forces, fine-motoric tasks and sensory perception that are required to manage our daily tasks. Losing these motoric functions can have a direct impact on medication management as it might restrict easy access to or modification of the drug products by the elderly patients, which is basically the base for adherence and compliance.

Motoric functions described as Activities of Daily Living (ADL) were introduced by Katz et al. (1970) as the most important physical capabilities for independent living. The deterioration of motoric functions is often the result of other degenerative disease conditions like osteoporosis, rheumatoid arthritis, osteoarthritis or degenerative processes in the CNS like Parkinsons Disease. Motoric functions have also been found to be directly related to the cognitive status of the elderly and start to be impacted already in early dementia [Scherder et al., 2008].

6.4.1. Impact of motoric functions on pharmaceutical packaging

For medication management, a certain level of hand motoric functions are required in order to take out the medication of the pharmaceutical packaging, put them into a medication organizer, take them out of a medication organizer again and eventually manipulate the medication, for example splitting a tablet before bringing the small dosage form into the mouth. The decrease in hand motoric function is a gradual process that is progressing gradually from an age ≥65 years and that becomes apparent at an age of ≥75 years. The most important changing hand functions are the hand force and gripping strength (muscle and tendon strength), griping and pinching activities (intrinsic bones and joints) as well as sensory functions (cutaneous and motor nerves). Overall the age and potential disease related changes of the hand functions impact various abilities that are directly related to medication management which requires a certain set of fine-motoric capabilities [Carmeli et al., 2003].

Pharmaceutical packaging is designed to protect the product from the outside environment as well as to prevent children's access. With declining motoric functions geriatric patients have been found to have huge difficulties in opening child-resistant bottles or releasing the drugs from blister packs. In a study 50 older people aged 60 years and above were given different child-resistant and non-child-resistant medication bottles and blisters for opening experience. All older people were able to open the different non-child-resistant packaging presentations, but were unable to open the standard child-resistant ones. With increasing complexity of the packaging opening mechanism, like aligning tabs or arrows of cap and bottle for opening, the inability to open the packaging was most significant. The most appropriate child-resistant packaging was a simple push and turn cap on a bottle, whereas the larger cap sizes with instructions in bold and colored contrast on the cap turned out to be the most suitable for elderly [Keram and Williams, 1988].

Table 5
Frequency of failure in opening medication containers ($n = 120$) (presented in order of increasing frequency of failure) [Atkin et al., 1994].

Container/task	Unable to open	Percent unable
Screw top	10	8.3
Flip top	17	14.2
Blister pack	25	20.8
"Dosett"	29	24.2
Foil wrap	36	30.0
Child-proof	68	56.6
Break tablet	87	72.5

The ability of 120 elderly with a mean age of 81 years to open pharmaceutical packaging and handle their medication (breaking tablets and managing a dosett, a 7-day medication organizer) has been investigated by Atkin et al. (1994). This patient group had an average of 4.43 medications per day, ranging from 0 to 13 different medications per day. In this study population, 78.3% were unable to open at least one of the medication containers or break a tablet. The difficulty to split tablets was the dominant area of failure, but even the opening of the 7-day medication organizer could not be performed by 24% of the elderly and consequently they are neither able to fill their own medication organizers nor to take out the medicines again for the intake (Table 5). Moreover, managing medication packaging as well as splitting tablets has been found to be significantly influenced by visual capabilities as well as general cognitive functions.

These results do not come as a surprise taking into account that beside the motoric limitations elderly are less capable in understanding complex medication regimen and have increasing visual impairments that simply prevent them from reading the opening instructions on the leaflet or packaging label [Beckman et al., 2005]. Simply not being able to open the medication container or packaging might create a substantial frustration and loss of self-confidence in the individual leading to modification or discontinuation of the medication schedule that could easily be avoided by an age appropriate packaging.

6.4.2. Impact of motoric functions on dosage form manipulation

Besides selecting the right drug, geriatric patients often require lower doses than healthy volunteers or adults with a single disease condition tested in clinical trial programs. Rodenhuis et al. found that only in 46% of the cases a dosage form with a lower dose was available, while in the other 54% the dose strength needed for a geriatric patient was not available and dosage form splitting by the patient was required. Especially in elderly, dose titration is often used as a practical solution to identify the right maintenance dose for an elderly patient [Rodenhuis et al., 2004]. According to this study, tablet splitting is performed in 31% as a lower dose was needed, in 17% the patient choose to take a lower dose by himself and in 13% to facilitate swallowing. The subdivision of the scored tablet led to problems in 55% of the cases of which dysfunction of the score line was the major reason (42%), which was judged by 31% of the patients as an unacceptable problem.

Manipulation of dosage forms is a critical factor for potential medication errors. With a frequency of 24%, tablet splitting is a frequent manipulation operation. In 8.7% tablets were split that were not suitable for splitting and 3.8% were split that were not even allowed to be splitted [Quinzler et al., 2006]. An alternative drug product was available only in 62.5% of the cases, leaving 37.5% of prescriptions without a suitable alternative.

Analyzing the performance of splitting dosage forms, various authors have reported significant weight variations of the individual parts after splitting as well as loss of product due to powdering and fragmentation [Van Santen et al., 2001]. The theoretical weight of tablet halves of a cyclobenzaprine–HCl tablets divided by a split-

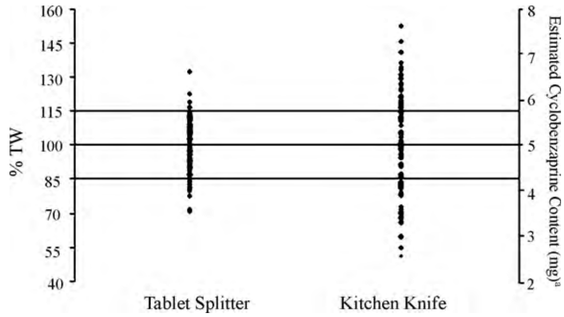

Fig. 4. Deviation of tablet fragments from theoretical weight and estimated drug content for tablets split by a tablet splitter or kitchen knife [Cook et al., 2004].

ter or a kitchen knife were found to be 69.4–130.2% which is equivalent to a dose range of 3.47–6.51 mg for a targeted dose of 5.0 mg as shown in Table 4 [Cook et al., 2004]. Product loss due to splitting of different drug products has been found to be as high as 14% for halved and up to 27% for quartered dosage forms [Biron et al., 1999] (Fig. 4).

Geriatric patients, due to their limited and varying motoric capabilities might have even a higher challenge for accurate splitting of the dosage forms as the accuracy of splitting has been found to be dependent on the method of splitting [Van Santen et al., 2001].

6.5. Swallowing functions

The most preferred and major route of drug product application is the oral route. Solid oral dosage forms are generally swallowed intact. Due to dysphagia, disease conditions or simply due to polypharmacy and the number of medications that need to be swallowed each day elderly people experience problems with swallowing of solid oral dosage forms.

Swallowing is a complex coordinative process between different nerves and muscles that is impacted as a function of age. Swallowing capabilities are declining in elderly or are directly disordered by certain disease conditions common in elderly like Parkinson's disease or cancer [Ekberg and Feinberg, 1991; Sheth and Diner, 1988].

Swallowing difficulties have been described as a major health care problem in elderly that advances with increasing age, affecting 50% of patients in nursing homes [Nilsson et al., 1996]. Swallowing difficulties may lead to sticking of the dosage form in the throat or to aspiration of the particles or parts of the dosage form into the lungs. Swallowing issue will therefore have a direct impact on medication adherence.

Swallowing medications is mainly an effortful process directing the patient to swallow hard with oral and pharyngeal muscles [Hind et al., 2001]. It is estimated that 26% of patients have difficulties with swallowing [Andersen et al., 1995] and 22% of people over 55 years of age are affected by dysphagia [Hind et al., 2001]. In 61% of dysphagia patients swallowing a tablet caused difficulties and even when oral dispersible dosage forms were used 39% showed difficulties in swallowing [Carnaby-Mann and Crary, 2005].

Only a very few studies have been performed to compare different dosage forms regarding their ease of swallowing. One study found that capsules were perceived as easier to swallow than coated tablets and coated tablets easier than un-coated tablets. The perceived ease of swallowing was also dependent of the size of the medication and smaller sizes are generally preferred [Overgaard et al., 2001].

Swallowing will become even more difficult in polypharmacy conditions, when several different oral products have to be swallowed over the day as well as co-committing diseases can reduce the capabilities of proper swallowing [Beckmann Gyllenstrand, 2007]. More research is needed to understand the medication swallowing issues in elderly, how this impacts medication management and adherence and how these issues can be overcome by more appropriate dosage forms.

7. Discussion

The elderly are one of the most fragile patient population and it should be our common goal to dedicate a special attention to their well-being. The elderly represent an extremely heterogeneous patient population that differs significantly in terms of functional capabilities, their morbidity and co-morbidity without any relationship to the numerical age. Due to the increasing probability to develop chronic diseases with age, elderly are the main user group for medicinal products. As such, the medicinal products contribute to the increasing life expectancy of humans and the maintenance of the individual's health and independence, but unfortunately also to medication related problems.

7.1. The elderly's view on geriatric drug therapies

With increasing age, especially beyond 75 years, some of the major vital functions change and the risk to develop disease conditions are increasing. There is clear evidence that people beyond 65 years of age are prone to develop several age-related and chronic disease conditions and they are therefore the major user group of prescribed medicines. At the age of 85 years it is quite common that people suffer from various disease conditions and take 5–10 different medicinal products per day. Together with declining vital functions like metabolic, cognitive, visual, motoric and swallowing functions, medication management becomes a complex task for the individual that requires not only clear implementation plans but also age adequate medicinal products. Beckman calculated that 57.6% of people aged 77–79 years, 61.4% aged 80–84 years and 79.9% older than 85 years have difficulty in their medication management [Beckman et al., 2005]. When asked what could help them to better manage their medication, people of the same age (75–97 years) responded that simplification, visual and tactile cues as well as bringing the medication management into a routine are important strategies to improve their medication management performance [Swanlund, 2010].

Investigating the physical ability of patients to read the medicine label, open the medicines container, understand the instructions and calculate the therapy length and change on a receipt, 66% of elderly patients (≥75 years) did not meet the criteria for medication management. Importantly, there was a discrepancy in their self-assessment and the real ability of the medication management ability [Beckmann Gyllenstrand, 2007; Hind et al., 2001]. When asked about difficulties with managing the medication, no one responded that the difficulties would prevent them from taking the medicines. However, in order to manage medication, several interventions have been reported like asking advice from professionals and non-professionals, reading leaflet information and using tools like knifes and a pair of pliers to crush or split the tablets [Beckmann Gyllenstrand, 2007]. However, the discrepancy between self-reported medication management and the identified medication management performance suggest that non-compliance or improper use will be the result of the negligence of the difficulties elderly face and how they manipulate the medication to manage.

7.2. The elderly as a patient

Until today a systematic and common understanding of the "elderly" as a patient and medicines user has not yet been established. As a basis for individuals care planning Morris et al. proposed a general assessment of broad area of cognition, communication, vision mood, behavior, ADL, self-performance and continence to identify specific areas at risk for decline, which can than be evaluated in depth using clinical assessment protocols (CAPs) [Morris et al., 1997]. These assessment protocols were constantly developed further into an interRAI suite that was shown to be reliable across different care settings [Hirdes et al., 2008]. Martin and Park proposed a questionnaire to investigate quickly the medication adherence of the elderly patients based on busyness and routine. The questionnaire is based on 11 question items and showed good correlation in rheumatoid arthritis patients [Martin and Park, 2003].

Within the context of geriatric drug therapy we suggest defining the "elderly" as a person that experience age-related limitations in managing the daily life and has at least one age-related chronic, medical condition. Considering the complexity of geriatric drug treatment and medicines, we should notwithstanding be able to identify clinical, therapeutic and personality communalities among certain elderly patients that help us to identify, define and assess subpopulations and their respective limitations, capabilities and needs. Based on the results of patient assessments, medication selection and medication management should lead us to a clear understanding of the individual elderly and what therapeutic strategies will be most suited for this individual.

The importance of adapting the therapy to the age and not treating elderly like "standard adults" has been demonstrated by Peterson et al. They investigated the prescription of excessive dosing of psychotropic drugs in 3718 elderly inpatients and the potential impact of adapting to a recommended standard dose for the elderly. In this study 5% of the patients received a 10-fold higher dose than needed and 10.8% of the patients received a drug that was not recommended for elderly. The intervention in form a dosing and drug guidance tool in the ordering system reduced the 10-fold dose prescription to 2.8% and the non-recommended drug use to 7.6%. The improvement of appropriate prescriptions for elderly resulted in a significant decrease of falls from 0.64 to 0.28 falls per 100 patient days showing the potential of a simple drug and dose adjustment on critical ADRs [Peterson et al., 2005].

Taking into account the lack of knowledge as well as limited diagnostic resources in a standard health care setting, the geriatric dosing strategy "start low and go slow" still seems to be the most practical guideline suitable in medication initiation of mono therapies or as add-on polypharmacy of older patients in the standard ambulatory setting. Because polypharmacy might develop over time and by several different medical physicians, more regular revisions of medication schedules of older and especially frail patients by physicians and pharmacists are needed to secure optimal drug therapy in elderly.

The elderly patients do have in principle an intention to receive an effective treatment as well as to adhere to the prescribed therapy once the medical intervention is understood. Nevertheless, the patient is the most important factor in adherence to a medication schedule and therefore the elderly patients must be understood and their needs addressed in the prescription, the medicinal products and the medication management.

7.3. The common responsibility of geriatric drug therapy

Geriatric drug therapy must be seen in a multidisciplinary context of a true medication management concept aiming for an effective and safe therapeutic regimen that can be independently and adherently managed by people of 65 years and beyond (Fig. 5).

Drug discovery and the clinical development program will have to reflect the therapeutic relevant geriatric patient group early on. Appropriate geriatric dosage form will have to be provided and go along with doctors prescribing patterns. Medication management will be supported by simplifying the medication regimen and the use of medication management tools like medication organizers [Beckman et al., 2005] and patient's advice on implementation intention and situational cues to turn the medication management into an automatic cognitive process [Gollwitzer, 1999].

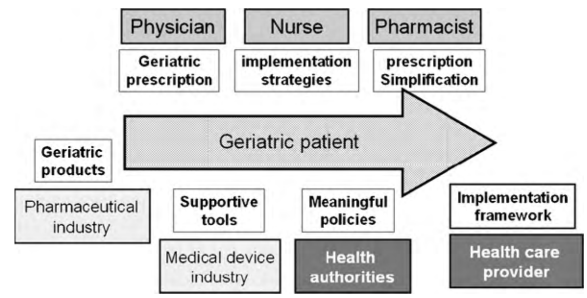

Fig. 5. Geriatric medicines in the context of geriatric medication management.

Practically, an appropriate geriatric drug therapy should allow the doctor to select the starting dose from various available individual dose strengths. The individual drug products and their respective dose strengths should be easily identifiable and distinguishable by main features like color, shape or imprint. The oral dosage forms should be dispersible in order to be applicable to patients with swallowability issues of larger single units otherwise alternative drug delivery systems should be used.

Drug product information must be easy to read and precise. The use of user-friendly packaging concepts (easy accessible, with pictogram, etc.) will facilitate the daily medication preparation by the elderly but also the pharmacists and care givers. They can be supported by simple visual charts and pictograms in conjunction with respective medication management tools and devices. Pharmacists and care givers can make use of these product features when helping the elderly to transfer the medication management into an automatic process, and indentifying the most appropriate situational cue for the individual patient.

Developing more appropriate dosage forms for elderly will also be a challenge for process development and commercial manufacturing as the paradigm of large batch product manufacturing will have to be revisited. Pharmaceutical engineering will therefore play an important role in providing flexible ways of manufacturing many different dose strengths yet being easy to distinguish and commercially effective.

Health care providers will have to provide the structural and commercial framework for the implementation of geriatric drug therapy and geriatric medication management into the daily practice of the patients because more appropriate geriatric drug therapy alone will not be sufficient to improve the elderly medication management practices towards adherence and compliance without the necessary medication management intentions and strategies.

There is clear evidence that substantial improvements in geriatric drug therapy are possible. We postulate that a systematic application of the various identified and proven strategies to improve geriatric drug therapy will synergistically improve the overall therapy and therapy management in this patient population. Table 6 lists some of the identified specific needs of the elderly and some respective possibilities to address these needs by appropriate interventions (Table 6).

Finally, it is important to keep in mind that appropriate geriatric drug therapy will allow senior citizens to receive the most appropriate drugs and an individualized treatment regimen which they can easily follow through and stay independent as long as possible. The economic benefits of just delaying the dependency by one year while life expectancy increases by one year, will lead to a consider-

Table 6
Specific needs of geriatric patients and the possible ways to address these needs.

Specific needs	Possible solutions
Clinical trials in geriatric patients	Include healthy and specific subpopulations
Age specific ADRs	Investigate critical ADR's in elderly
Dose strengths covering the declining metabolic capacity and drug–drug interactions in polymedication conditions	Lower dose strengths to allow dose titration
Simplify drug product identification even in a mono- and polymedicational context	Colored or specifically shaped dosage forms
Simplified medicines information through the use of pictograms, adapted labeling	Larger font and simple wording in leaflet, product picture on the pill-box
Suitable age adequate packaging to access the drug product with motoric capability limitations and diseases	e.g. low strength screw top
Easy to swallow oral dosage forms options	Convertible into multiparticulates or sprinkle, prefilled oral liquid dosage form options
Decrease pill burden	Modified release formulation, dual or multiple release formulations or combination products
Complex medication schedules	Define implementation strategies and contextual cues
Supportive device tools	Medication organizers with medication control or alert systems
Potential medication errors in polypharmacy	Easy and clearly identifiable drug products

able reduction in long-term care expenditures from 2000 to 2050 [European Study of Long-term Care Expenditure, 2003].

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