AAPS Advances in the Pharmaceutical Sciences Series 24

Sven Stegemann *Editor*

Developing Drug Products in an Aging Society

From Concept to Prescribing

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AAPS Advances in the Pharmaceutical Sciences Series

Volume 24

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ISSN 2210-7371 ISSN 2210-738X (electronic)
AAPS Advances in the Pharmaceutical Sciences Series
ISBN 978-3-319-43097-3 ISBN 978-3-319-43099-7 (eBook)
DOI 10.1007/978-3-319-43099-7

Library of Congress Control Number: 2016946327

Printed on acid-free paper

This Springer imprint is published by Springer Nature
The registered company is Springer International Publishing AG Switzerland

Foreword 1

Medical and pharmaceutical sciences have substantially progressed in providing effective treatments against acute and chronic diseases. Along with increasing wealth, life expectancy has nearly doubled during the past century and many diseases have lost their terrifying nature. The increasing longevity and number of old and very old citizens in our society is a fundamental and important achievement of modern medicine that is beneficial to all of us. However, an aging society does not come without challenges, especially in providing effective healthcare. Medical and pharmaceutical sciences are attacking these challenges in an evolving healthcare environment through innovative drug products and therapeutic interventions addressing diseases of the elderly.

The American Association of Pharmaceutical Scientists is pleased to support the development and publication of this book addressing the critically important issue of drug products and therapeutic interventions for an aging society. Bringing experts from around the world together, this book offers both broad and deep coverage. Beginning with healthcare perspectives from the United States, Europe, and Japan, this book provides insightful chapters on geriatric patients, clinical characteristics, and the process of aging. Chapters discussing the clinical development of drug products for older adults followed by in-depth treatises on product development considerations of multiple routes of delivery round out the first half of this book. The remainder of the text addresses drug therapy, therapeutic management in older adults, and specific regulatory guidance on geriatric medicines from a global perspective. A comprehensive, this book will provide a valuable resource to anyone actively engaged in the development of pharmaceutical products for geriatric patients around the world.

Greg Amidon
Walt Marlowe

Foreword 2

Increased longevity is one of humanity's major achievements, as people worldwide are living longer. By 2020, for the first time in history, the number of people in the world age 60 or older will outnumber the number of children under 5. By 2050, the global population age 60 or older is expected to total 2 billion, up from 900 million in 2015.

Yet this greater longevity comes with many challenges. In an aging world population, the growing burden of chronic disease will greatly affect older people's quality of life, and will increase the demand for safe and effective medications to manage and treat those diseases. Unfortunately, however, drug research and development has not kept pace with changing demographics.

Old age is the main risk factor for disease and, accordingly, most medications are used in older people. In addition, they often take several medications at the same time. Despite being the most frequent users of many drugs, older people are routinely excluded from clinical trials. Yet, marked aging changes in the response to medications, and the frequent presence of comorbidities, means that findings extrapolated from younger populations may not be directly applicable to their older counterparts. As a result, there is only limited evidence to support the efficacy and safety of many medications in older people, especially those who are frail or are taking multiple medications. As harm from medications is much more common in older people, it is critically important to start rethinking the drug development process and its regulation to improve drug safety and effectiveness for an aging and heterogeneous population.

Members of The Gerontological Society of America–the United States' oldest and largest scientific organization devoted to research, education, and practice in the field of aging—highlight the necessity of interdisciplinary research for understanding the aging process. Likewise, overcoming existing knowledge gaps to improve drug product development for older, very old, multi-morbid, and frail patients will require collaboration between the pharmaceutical industry, government regulators, gerontologists, clinical pharmacologists, and, of course, older people themselves.

This landmark book of articles from today's thought leaders and experts in the field sets the stage for filling these gaps. Its strength—reflected by the many disciplines of its authors—lies in recognizing that progress will only be made through multidisciplinary, multi-sector collaboration and the early inclusion of older patients in drug research and development programs. It provides a comprehensive overview of the important aspects of this critical issue, including the regulatory environment, the drug development process, product innovation, patient involvement, and the management of drug therapy. In doing so, it lays the foundation for improved outcomes for older patients, their families, and—ultimately—our global society.

James Appleby
The Gerontological Society of America

Preface

The provision of effective healthcare to society is a global mandate for all healthcare professionals around the world. Discovering, developing, and manufacturing drug products are the traditional roles of the pharmaceutical industry that continue to deliver on its promises through innovative medicines every year. Based on the evidence for the efficacy of these pharmaceutical drug products, physicians are rationally prescribing the medicines to patients as part of their overall treatment expertise. As the medical and pharmaceutical sciences evolve, society and patient populations are evolving too. Since the majority of acute and chronic diseases can be treated or managed very effectively today, life expectancy increases by an average of three months every year. Even though this demographic development did not come as a surprise, we were not well-prepared for the very rapid growth of old, very old, multimorbid and frail patients that have substantially changed the characteristics of the patients appearing in the daily practice of primary and secondary health care providers. Along with the evolution of the new patient populations, the provider's related treatment plans have also changed. Effective drug therapy for most of the chronic diseases today is achieved through interventions at more than just one clinical target, which leads to the prescription of two or three different drug products simultaneously. The results are treatment plans for more than one chronic disease that often imply the prescription of more than five drugs. This situation of polypharmacy complicates the preparation of the treatment plan for the prescriber as well as for the patient who has to manage these various therapeutic schedules.

With these changes in patient populations and therapeutic complexity, new challenges in healthcare and healthcare provision occur that require collaborative efforts throughout the entire community of healthcare professionals. Leveraging the knowledge and expertise of each discipline and stakeholder, starting from the drug development through to the medicine in the hand of the patients executing the therapy successfully are crucial elements that provide important insight into the disciplinary aspects of healthcare provision. Since patient drug utilization trajectories span across several decades, they shift from acquiring a single disease and

appropriate medicine to managing a multiple disease and polypharmacy treatment concept in later life. These trajectories develop into very demanding medication management tasks for this patient population. The problem is compounded by the symptoms inherent in these patients: their capabilities and reserves might fade with multimorbidity and higher age. Successful healthcare delivery will have to address this issue and transition from the treatment of single diseases to the personalized treatment of the patient with her or his individual risk-benefit profile and achievable health outcomes. Yet, even with this realization, the clinical development of a new drug and the relevant regulatory guidance and requirements remain focused on a single disease intervention concept to establish drug product safety and efficacy. The major aspects of product quality still refer to the product itself, its manufacturability and stability within the targeted quality specifications.

Considering that each healthcare professional and stakeholder has one's own disciplinary challenge, other challenges are common between the disciplines and will most likely be solved by concerted and synergistic procedures. This multidisciplinary approach is stimulated by the different perspectives and solving approaches generated by the disciplinary view. The advances in technology, such as genome sequencing, information technology, digitalization, and others, are holding significant promises for applications in and across future healthcare delivery. This book intends to provide an opportunistic view on the challenge of developing and providing better drug products to the evolving patient populations being multimorbid and much older than previous ones. The distinguished multidisciplinary author panel covers the majority of disciplines involved in the development, manufacturing, prescribing, and monitoring of drug products to the respective patient populations. Their individual chapters discuss the disciplinary challenges, provide expertise and knowledge, as well as describe initiatives towards solutions and improvements. The diversity of expertise shared throughout the chapters should stimulate and encourage the reader to go beyond one's own area of expertise and enter interdisciplinary discussions. Especially as the challenge and the research in the area of drug therapy to older and multimorbid patients continue evolving, multidisciplinary collaborations and discussions will be necessary to find practical as well as efficient solutions.

Graz, Austria Sven Stegemann

Contents

Part VIII Concluding Remarks

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Part I
Introduction

Healthcare Provisions in an Aging Society: U.S. Perspective

Ajoy C. Karikkineth

Abstract The number of the people 65 years and older continues to increase rapidly, both in absolute numbers and as a percentage of the population. The reasons are varied, including declining birth rates, improved life expectancy, and immigration. This is leading to significant demographic changes, changes in social structures, and economic stresses. However, the older population is a heterogeneous group, and a nuanced approach is required to deal with the challenges of this population. The old and very old patients are the major user group of medications and also the fastest growing population with the potential need for medicines [1]. The older population is frail, has different pharmacokinetics, experiences a greater number of side effects and has to deal with multiple medications with the potential for multiple drug interactions. No or inadequate medical insurance coverage, especially for medications, is compounded by decreased purchasing power due to lack of income, changing insurance rules, and increased out-of-pocket expenses for physician visits, hospitalizations, caregivers and care facilities. Developing drugs for this population is difficult, and is compounded by the lack of inclusion of this demographic in many drug trials for various reasons. Formulations of appropriate doses for the elderly, as well as appropriate packaging for ease of administration in this population with many physical challenges, are equally important. There is also a need for awareness, continuous training and sensitization of providers to these issues.

Keywords Elderly · Demographics · Medicare · Medications · Health

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S. Stegemann (ed.), *Developing Drug Products in an Aging Society*,
AAPS Advances in the Pharmaceutical Sciences Series 24,
DOI 10.1007/978-3-319-43099-7_1

Introduction

Provision of health care for the burgeoning population of older persons greater than 65 years of age is a very complex issue with many interlinked, complicated, and ever changing components.

A central and recurring theme that affects all aspects of health care is the economic aspect, both at the national level and at the individual level. At the national level, increasing expenditures and national debt has put pressure on Medicare and social security, and led to cost containment efforts. At the individual level, many factors such as decreasing incomes, dwindling employment, lack of housing, food insecurity, and need for long-term care services puts tremendous pressure on finances, and greatly influence how much health care and medications each individual can afford.

In the next few sections, we hope to outline the magnitude of the changing demographics, as well as the many life stressors, medical comorbidities, insurance coverage issues and access to primary care which impact the availability and access of the older population to medical care and medications. Even when medications can be afforded, adverse drug reactions, polypharmacy, and issues with dosage forms can affect compliance and ultimately the effectiveness of any prescribed medications.

Changing Demographics

Age Change

The traditional "pyramid" shaped population structure is evolving into a "100 floor skyscraper" population structure [2]. There were 44.7 million persons 65 years or older in 2013, which constituted 14.1 % of the U.S. population. The percentage is expected to increase to 21.7 % of the population by 2040 [3, 4]. Since 1900, the percentage of Americans 65+ has more than tripled, and the number has increased over thirteen times.

The older population itself is increasingly older. In 2013, the 65–74 age group was approximately 10 times larger than in 1900. Contrast this with a 4900 % increase in those greater than 85 years old [5]. Life expectancy was 47 years in 1900, and in 1991 it was 79 years for women and 72 years for men [6]. State wise, California has the largest number of elderly, while Florida has the highest percentage. Above age 65, women outnumber men by a ratio of 3:2, but at age 85 and over, the ratio is 5:2 [6].

Racial Changes and Immigration

The birth rate is higher among minorities than non-Hispanic whites. This is partly due to cultural factors, but also due to the higher average age of the current majority

population. Whites are the oldest group, with a median age over 42. This means that the majority of whites are almost past the childbearing age. By contrast, the mean age of Hispanics is 28, and Blacks and Asians have median ages in the early 30s. Additionally, most people who migrate are young and reproductively active. These factors lead to a growth rate differential between minorities and the traditional majority population. For example, 50.4 % of American children under the age of 1 belong to minority groups [7]. This differential growth rate will lead to the nation's transformation to a majority–minority population around 2042. Already California, Hawaii, New Mexico, Texas and Washington D.C. have minorities constituting greater than 50 % of the population. However, the decreasing immigration from Mexico may slow down the rate of this transformation.

Marital Status

Divorced and separated (including married/spouse absent) older persons represented only 14 % of all older persons in 2014. However, this percentage has increased since 1980, when approximately 5.3 % of the older population were divorced or separated/spouse absent. Separation is particularly traumatic in older persons, as it significantly impacts several aspects such as income, food security and access to services. The spouse is often the caregiver. 61 % of caregivers are women and 13 % of caregivers are aged 65 years and older [8].

Life Stressors

Income

Although Medicare provides health insurance coverage for most people 65 years and older, many health expenditure items are only partially covered or have high co-pays and deductibles, or not covered at all. For example, most Medicare plans do not cover dental procedures or stays in Assisted Living Facilities. As such, disposable income impacts utilization of health care [9–11].

The median income of persons 65 years and older is approximately $21,225, and 17 % of older adults reported incomes less than $10,000. Poverty rates are high among the older population—11 % for 65–74 year olds, and 16 % for those older than 75 years. Poverty rates are higher among women, Blacks, and Hispanics. Elderly White men have much higher median incomes than other groups. In 1992, their income was more than double that of elderly Black and Hispanic women ($15,276 vs. $6220 and $5968, respectively) [6].

Social security, rather than employment, is the major source of income for most of the older people. In 2014, 81.4 % of Americans age 65 and over were not working or actively seeking work [5]. In contrast, 86 % of older persons listed

Social Security as one of the major sources of income, and constituted 90 % or more of the income received by 36 % of beneficiaries (22 % of married couples and 47 % of nonmarried beneficiaries) [12].

Living Arrangements

The majority of older adults would like to stay in their current residences and in their current communities for as long as possible (aging in place). However, financial pressures, disabilities, multiple medical comorbidities, and lack of easy access to healthcare services often mandate that the older population require either additional assistance at home, or have to move to new neighborhoods, move in with family, or become institutionalized in long-term nursing facilities.

Among adults aged 50 and over, 82 % of whites, 58 % of blacks, 62 % of Hispanics and 70 % of Asians own homes. However, 37 % of those aged 80 and over pay more than 30 % of income for housing [13], a huge financial burden. Many older persons have disabilities, but only 1 % of houses have all the recommended accessibility features for persons with disabilities (American Housing Survey).

About 28 % of all noninstitutionalized older persons in 2014 lived alone. They represented 35 % of older women and 19 % of older men. The proportion living alone increases with advanced age. Among women aged 75 and over, almost half lived alone.

The percentage of older adults living in institutional settings such as nursing homes also increases dramatically with age, ranging (in 2013) from 1 % for persons 65–74 years to 10 % for persons 85+. 37 % of those 65 and over will receive care in an institutional facility at some point in their lives [13, 14].

Long-term services and supports (LTSS) costs about $192 billion annually. Two-third of the payments come from Medicaid and Medicare. This does not include informal care provided by family members and friends, which cost an additional $234 billion annually. Private insurance pays for only a small share of total spending on LTSS.

Most of the large multi-facility providers are publicly owned and managed as for-profit businesses [10]. There are exceptions; the largest operator in the US is the Evangelical Lutheran Good Samaritan Society, a not-for-profit organization that manages 6531 beds in 22 states, according to a 1995 study by the American Health Care Association [15].

Assisted living is one option for the elderly who need assistance with everyday tasks. It costs less than nursing home care but is still considered expensive for most people. Home care services may allow seniors to live in their own home for a longer period of time.

In the US, 67 % of the one million or so residents in assisted living facilities pay for care out of their own funds. The rest get help from family and friends and from state agencies. Medicare does not pay unless skilled nursing care is needed and

given in certified skilled nursing facilities or by a skilled nursing agency in the home.

Assisted living facilities usually do not meet Medicare's requirements. However, Medicare does pay for some skilled care if the elderly person meets the requirements for the Medicare home health benefit. Thirty-two U.S. states pay for care in assisted living facilities through their Medicaid waiver programs.

One relatively new service in the United States that can help keep the elderly in their homes longer is respite care. This type of care allows caregivers the opportunity to go on vacation or a business trip and know that their elder has good quality temporary care, for without this help the elder might have to move permanently to an outside facility. Another unique type of care cropping in the U.S. hospitals is called acute care of elder units, or ACE units, which provide "a homelike setting" within a medical center specifically for the elderly.

The Community Living Assistance and Support Services (CLASS) program provides home and community-based services to eligible participants [16, 17]. The Balancing Incentive Program provides financial incentives to States to increase access to noninstitutional long-term services and supports [18].

Changes such as greater rental assistance, additional funding for housing with supportive services, promoting, and subsidizing modifications to home and built environments to improve accessibility, better municipal zoning so that transportation and other services are within walking distance, and reorientation of state Medicaid programs to enable low-income households to age in the community, are much needed [13]. Significant opportunities exist for close cooperation of the government and private sector to tackle these challenges.

Food Insecurity

Food insecurity is often related to lower health utilization and a higher prevalence of medical disorders. Approximately 2.5 million (8.4 %) of households with older adults had experienced food insecurity in 2011 [19, 20]. Food insecure older adults had lower out-of-pocket expenditures than their food-secure counterparts, $1875 versus $310, respectively [19]. Increasing severity of food insecurity is associated with increasing likelihood of cost-related medication underuse [20–22]. Individuals with both cost-related medication underuse and food insecurity are more likely to be Hispanic or non-Hispanic Blacks, and have more chronic conditions [22].

Food insecurity in elderly persons is associated with a 60, 53, 52, and 40 % higher risk of depression, heart attack, asthma, and congestive heart failure, respectively [21].

It is very important that nutrition services recognize and provide services to cover those needs [22]. Different governmental programs such as Senior Farmers' Market Nutrition Program (SFMNP) and Nutrition Services Incentive Program (NSIP) try to tackle food insecurity among the low-income older population [23]. The federal government has appropriated nearly $1 billion to operate food and

nutrition assistance programs (funded through the Older Americans Act) for older adults who qualify (low income and some disabled) [24], but federal food and nutrition programs still only reach 6–7 % of the older at-risk population. Charitable programs such as Meals on Wheels try to bridge the gap.

Neighborhood Factors

Individuals and patients, especially the elderly, are often dependent on myriad organizations providing hospice care, personal care services, mental health and substance use and abuse services, home-delivered meals, accessible transportation, school-based health care, and many other services. The patient centered medical home model being advocated for by the AHQRC calls for the interaction and the dissemination of information between physicians and these community resources [25, 26]. Neighborhood factors and crime affect perceived safety, leading to decreased utilization of walking and transportation [27–29], and decreased ability to coordinate these resources. Home care agencies which act to coordinate care between physicians and the community may find it hard to provide services in high crime areas. Connections between primary care and community services simply are absent or highly fragmented and disorganized to start with, and neighborhood factors could possibly exacerbate the problem.

Prevalence of Diseases

Introduction

Most of the older persons have at least one chronic condition and many have multiple conditions. In 2011–2013, the most frequently occurring conditions among older persons were: diagnosed arthritis (49 %), all types of heart disease (31 %), any cancer (25 %), diagnosed diabetes (21 % in 2009–2012), and hypertension (high-blood pressure or taking antihypertensive medication) (71 % in 2009–2012) [3, 5].

In 2009, the leading causes of death in men 65 years of age or older were heart disease, cancer, chronic lung diseases, followed by stroke. For women in the same age group, the causes were heart disease, cancer, stroke, followed by chronic lung disease [30].

In 2013 older consumers averaged out-of-pocket healthcare expenditures of $5069, an increase of 35 % since 2003. Older Americans spent 12.2 % of their total expenditures on health [31].

Dementia

Five to eight percent of people over the age of 65 have some form of dementia and the number doubles every 5 years over age 65.

Of those older than age 65 and 85, 11, and 32 %, respectively have Alzheimer's disease. It is estimated that 13.8 million people over the age of 65 will have the disease by 2050. It is the fifth leading cause of death for those ages 65 and older. In addition it is a leading cause of disability and poor health.

The percentage change in causes of death from 2000 to 2010 were as follows—breast cancer (−2 %), prostate cancer (−8 %), heart disease (−16 %), stroke (−23 %), HIV (−42 %). However, for Alzheimer's disease the percent change was +68 %. In 2013, Americans provided billion hours of unpaid care to people with Alzheimer's disease and other dementias. It is expected to cost Medicare and Medicaid 150 billion dollars in 2014 for health care, long-term care, and hospice for people with Alzheimer's and other dementias.

Disability

Nine percent (9 %) of those 65–69 years, and 50 % of those greater than 85 years, need assistance with performing activities of daily living [6]. Some type of disability (i.e., difficulty in hearing, vision, cognition, ambulation, self-care, or independent living) was reported by 36 % of people age 65 and over in 2013 [31, 32]. 96 % of institutionalized Medicare beneficiaries had difficulties with one or more ADLs and 83 % of them had difficulty with three or more ADLs [32, 33].

Depression

Major depression in older people ranges from 1 to 5 % for those living in the community to 12.5 % in those who require home healthcare and to 11.5 % in hospitalized persons [34]. This may partly be due to the fact that current diagnostic criteria may not be fully valid in the older population [35].

Prevalence of depression might be higher in older Hispanic women, and may vary by acculturation level [36]. Female sex, Native Americans, being separated or divorced, having low income, and being Asian or black are also associated with increased risk [37]. Women are more likely to receive treatment for depression than men [37]. Sub threshold depression may have a high prevalence in the older population, may be associated with significant impairment of psychosocial functioning, and early identification and management may prevent progression to major depressive disorder [38].

Depression in the older population increases their cardiac risk, and decreases their ability to rehabilitate [39].

Cardiovascular Diseases

Total costs for CVD in 2009 were $121.2 billion for patients 65 years of age and older [30]. Among men 60–79 years of age, 70.2 % have cardiovascular disease, 21.1 % have coronary heart disease, 6.2 % have had a stroke, and 7.8 % have heart failure. For women in the same age group, the corresponding percentages are 70.9, 10.6, 6.9, and 4.5 %, respectively.

Among men 80 years and older, 83.0 % have cardiovascular disease, 34.6 % have coronary heart disease, 13.9 % have had a stroke, and 8.6 % have heart failure. For women the corresponding percentages are 87.1, 18.6, 13.8, and 11.5 %, respectively.

Sixty six percent (66 %) of deaths due to cardiovascular disease occur in people 75 years of age and older, and 80 % of deaths due to coronary heart disease occur in people 65 years of age and older. High blood pressure is present in 63.9 % of men 65–74 years of age, and 72.1 % of men greater than 75 years of age. In women, the corresponding percentages are 70.8 and 80.1 %, respectively.

Cancer

Persons over 65 account for 60 % of newly diagnosed malignancies and 70 % of all cancer deaths [40–44], while the incidence of cancer in those greater than 65 years older is 10 times that for those younger than 65 years of age. There has been a decrease in the incidence of cancer [45], but the absolute increase in the number of older adults means that the total number of cases of cancer in those 65 years of age and older will sharply increase. Treatment efficacies, effects of comorbidities, psychosocial issues and different biology of cancer in the elderly may complicate diagnosis and treatment of cancer in this group [40].

Other

Frailty, sarcopenia, chronic inflammation, sensory impairments, are not easily classified as distinct disease entities, but play important roles in limiting the functioning and quality of life of the older population [2]. Differential aging (the natural diversity in the rates of aging), resilience, physical functioning, and nutritional status modify the ability of the older person to deal with the changes of aging [2].

Medicare

US Healthcare spending is on hospital care (31 %), physicians (21 %), drugs (10 %), and administration (7–25 %). A large proportion of this spending is on the elderly. Last-year-of-life expenses represent 22 % of all medical spending in the United States, 26 % of all Medicare spending, 18 % of all non-Medicare spending, and 25 % of all Medicaid spending for the poor.

Medicare is the US government's health insurance program for people 65 and older, people under age 65 with disabilities, and people of all ages with End-Stage Renal Disease [46, 47]. It is administered by the Centers for Medicare and Medicaid Services (CMS) and covers nearly 48 million Americans (15 % of the total population).

Medicare insurance consists of three parts. Hospital insurance (Part A) that helps covers inpatient care in hospitals (including critical access hospitals and skilled nursing facilities, but not custodial and long-term care), hospice care, and some home health care.

Medical insurance (Part B) that helps cover doctors' services and outpatient care and some of the medical services deemed necessary but not covered by Part A (i.e., some Physical and occupational therapy and some home health care).

Supplemental Medicare options that include Medigap, Medicare Advantage (Part C) and Medicare Prescription Drug Coverage (Part D), Medicare-approved supplemental insurance provided by private companies that helps lower prescription drug costs and helps protect against future hikes in drug costs [48, 49].

Medicare offers a choice between its traditional, open network, and fee-for-service plan and Medicare Advantage, where the federal government pays a private insurer for a net-work-based plan [49, 50].

The 2015 Medicare Trustees Report shows that Medicare solvency remains greatly improved since passage of healthcare reform with the Hospital Trust Fund paying full benefits until 2030 and the increase in per enrollee spending continuing to be lower than overall health spending. Implementation of the Affordable Care Act and other changes in the healthcare system, including payment and delivery system reforms that emphasize coordinated care especially for people with multiple chronic conditions, incentives that are reducing the rate of hospital readmissions, and a slowdown in payments to hospitals and private Medicare plans, are improving Medicare's financing. Solvency has improved by 13 years from the date that was projected before enactment of the Affordable Care Act and Medicare spending remained stable as a share of the economy. At the same time, millions of Medicare beneficiaries are receiving preventive screenings and wellness visits without copayments and increased help with their prescription drug costs.

Medicare Part A is primarily financed by payroll taxes on earnings that are paid by employees, employers, and the self-employed. Medicare Parts B and D are financed by payments from federal general fund revenues (about 75 %) and by monthly premiums charged to beneficiaries (about 25 %).

The standard Part B monthly premium for 2016 is projected to remain at $104.90 for about 70 % of Medicare. However, the standard monthly premium is projected to increase by a large amount for 30 % of beneficiaries not protected by the hold harmless provision.

Beginning in 2006, a prescription drug benefit called Medicare Part D was made available. Coverage is available only through insurance companies and HMOs, and is voluntary. Enrollees paid the following initial costs for the initial benefits: a minimum monthly premium, a $180 to $265 annual deductible, 25 % (or approximate flat co-pay) of full drug costs up to $2400. After the initial coverage limit is met, a period commonly referred to as the "Donut Hole" begins when an enrollee may be responsible for the insurance company's negotiated price of the drug, less than the retail price without insurance. The Affordable Care Act modified this measure.

Part D expenditures as a percent of GDP are expected to increase from 0.5 % in 2014 to 1.4 % in 2089. The average Part D monthly premium is $33.13 in 2015, and is estimated to be $37.66 in 2016. Parts B and D out-of-pocket costs will consume 36 % of the average Social Security check compared to 23 % in 2015.

With the enactment of the Affordable Care Act, the long-term outlook for Medicare is improving and spending per beneficiary is projected to continue growing more slowly than general health spending. However, Medicare faces a long-term financial challenge due to the large increase in the number of beneficiaries as baby boomers reach age 65 and overall healthcare inflation.

Affordable Care Act ("Obamacare")

Proposed Benefits

The overarching aim of the Affordable Care Act is to bend the healthcare, and especially Medicare, cost curve. About $700 billion dollars of cuts are proposed, and it is hoped that these would be achieved by increased efficiencies and other measures, without actually reducing critical services.

Improved care coordination and quality is incentivized by promoting various measures, such as proper transitions of care from inpatient to outpatient settings, value-based psurchasing, promotion of Patient Centered Health Care model, and penalizing readmissions and hospital acquired conditions [51].

By providing the ability to compare and shop for insurance coverage from a "marketplace", it would hopefully provide more choices and lower costs. Individuals cannot be penalized for preexisting conditions. As most elderly have multiple medical comorbidities, this measure could have a significant impact in reducing cost of insurance policies.

Prescriptions drugs will be more affordable, by decreasing the "donut" hole, which will be completely phased out in 2020. Preventive services such as selected cancer screening programs and immunizations will be covered with no deductible or co-pay on both Medicare and private insurances.

Anticipated Issues

By mandating significant payment reductions, it may decrease the number of physicians accepting Medicare, and thus decrease access to providers. By removing penalties for preexisting conditions and including free coverage for preventive services, it is likely that copayments and deductibles will increase.

Payments to Medicare Advantage plans have been reduced. Medical Advantage plans are "top-tier" Medicare plans provided by private insurers that cover added benefits such as coverage for eye exams and dental procedures. This may actually decrease the choices of insurance plans for some individuals.

Readmissions to hospitals within 30 days are penalized. However, many of the best hospitals in the nation, university teaching hospitals and tertiary referral centers often have the highest admission rates. To circumvent the fines, patients are often placed in "observation" level of care. While everything during the hospital stay mimics a regular inpatient hospitalization, patients are often responsible for co-pays similar to an outpatient visit, and this can run into the thousands of dollars for a 1–2 night stay. There is some evidence that poorer and less educated patients are more likely to return to the hospital for a variety of reasons, and thus, more likely to be penalized. Additionally, these stays do not qualify as an inpatient stay for Medicare's "3 Night Rule", which requires that a patient spend a minimum of 3 nights in the hospital in a qualified inpatient status, to be eligible for transfer to nursing facilities such as subacute rehabilitation facilities, thus cutting off access to critical services.

Increased focus on palliative services, revised recommendations with higher age cut offs for screening and preventive tests, are part of attempts at cost containment, which may adversely affect the health of the older population. Physicians are often paid for value and quality of services. Older people may be harder to get to goals of blood pressure, etc., and therefore may be dropped by physicians attempting to reach set targets. Pressure to discharge early may lead to unsafe discharges. Elderly have multiple co-morbid conditions, and often have unstable renal function, etc. They have higher average length of stay, which is looked upon as unfavorable. They require more transitions to nonacute care facilities which can take time and resources to set up, thus occupying hospital beds longer, which again is unfavorably looked at by hospitals.

Primary Care and Access to Health Care

Effective primary care intervention for older patients requires mutual understanding of the expectations and goals of all parties involved. There must be easily accessible patient information in the form of care plans, and specialist training for practitioners on complex care and multi-morbidity, discussing autonomy, goal setting, and shared care [15, 52].

Acceptance of Medicare varies by specialty, being accepted by 99 % of ophthalmologists but only 60 % of psychiatrists [16]. 82 % of physicians in general or family practice, and 80 % for physicians in internal medicine accept Medicare.

Acceptance of Medicare also varies by geographic area. While 91.2 % of physicians outside a metropolitan statistical area accepted new Medicare patients, only 82.9 % of physicians within such an area accepted Medicare [18].

Medicare eligibility is associated with increased access to a healthcare provider and increased cancer screening, in particular among low-income individuals [53]. However, past patterns of behavior may persist, and individuals who were uninsured before age 65 have 16 % fewer visits to office-based physicians, but 18 % more visits to hospital emergency departments [54]. Thus health coverage expansion alone may be insufficient to improve healthcare utilization.

The pattern of healthcare utilization is changing. In 1978, 62 % of visits by those 65 years and older were to primary care physicians, compared with 45 % in 2008. The percentage of visits to subspecialty physicians increased over the same period from 37 to 55 % [16].

Although Medicare covers many medical services for older adults, financial, personal, and physical barriers to both medical and dental care create racial, regional, and sociodemographic disparities in health status and use of health services in the United States [55]. Preventative immunization only reaches 23–49 % of the older adults at risk or susceptible. Blacks and the least affluent of the elderly have substantially lower rates of "self-initiated" healthcare utilizations such as physician office visits, influenza immunizations, mammograms, diagnostic testing, and cancer screening, although they have higher rates of emergency room visits [56].

Among Medicare beneficiaries, Blacks may receive poorer quality of care than whites [57], although other studies propose that psychosocial and physical barriers affect access to care among the elderly, and these may be influenced more by poverty than by race [58]. Doctor's lack of responsiveness to concerns may be a very important reason for decreased utilization of office visits [58].

The ACA has eliminated copayments for qualifying preventive services, like cancer screening and immunizations, under all Marketplace health plans and Medicare plans [59].

Medications

The sharp increase in the numbers of people aged 65 years and older, the heterogeneity of this group, together with altered pharmacokinetics and pharmacodynamics, polypharmacy, and multiple medical comorbidities, make medication management in the elderly a very complex and challenging process [60]. Those greater than 65 years of age constitute the fastest growing population with the potential need for medicines [1].

Development of medications for cancer can be difficult and beset by many hurdles. Clinical trials may be lacking due to lack of incentives, and when present

may not include older populations who may be more susceptible to side effects and therefore, less attractive as clinical trial subjects. Hurria et al. make the following suggestions to try and remedy this problem in the context of developing drugs for cancer treatment—use clinical trials to improve the evidence base for treating older adults with cancer, leverage research designs and infrastructure for generating evidence on older adults with cancer, increase US Food and Drug Administration authority to incentivize and require research involving older adults with cancer, increase clinicians' recruitment of older adults with cancer to clinical trials, and use journal policies to improve researchers' reporting on the age distribution and health risk profiles of research participants [61]. These principles should be broadly applicable to the development of drugs for other medical conditions as well.

Older adults represent a very heterogeneous group with many different subpopulations, and the oldest old (80+) may be a distinct subset [1]. As a whole, they have altered pharmacokinetics and pharmacodynamics due to various reasons.

The older adult has a different ratio of fat to protein to water (30:12:54) compared to the younger adult (18:16.5:60) [1]. Their ability to mount a compensatory physiological response is reduced [1]. Absorption is affected by various factors such as decreased gastric acid production, increased gastric emptying time and decreased gastrointestinal surface of absorption [1]. Delivery of inhaled drugs can be decreased due to a decrease in forced vital capacity with age [1]. Thinning of the skin and decreased tear production can impact the absorption of drugs administered via these routes.

Distribution is affected by decreased cardiac, renal, and hepatic blood flow, decreased volume of distribution of water soluble drugs and increased volume of distribution of lipid soluble drugs [62]. Metabolism is affected by decreased liver function and activity of liver enzymes such as the cytochrome P450 system, and decreased renal function [1, 62]. The above impairments may be further exacerbated by underlying medical conditions such as renal failure and cardiac failure [1]. Most scientific literature do not investigate the age appropriateness of medicine use by older adults [63].

The overall incidence of serious ADR was 6.7 % and of fatal ADR 0.32 % of hospitalized patients, making these reactions between the fourth and sixth leading cause of death [64]. Serious ADR is defined as an ADR that requires hospitalization, prolongs hospitalization, is permanently disabling, or results in death.

Nursing home patients appear to be particularly vulnerable to ADRs, and may be related to inadequate attention to the patients' history as well as to unrealistic therapeutic endpoints [65]. ADR may be related to polypharmacy, and this relationship may be exponential rather than linear. Drugs for hypertension, antiparkinsonian drugs, and psychotropics carry the greatest risk of adverse events, although the largest single number of adverse reactions is due to diuretics [66]. Electronic prescriptions and clinical decision support systems may decrease the number of ADRs [67, 68].

Approximately 70 % of older adults take OTC medicines along with their prescribed medicines, and in most cases this is not reported to the physicians [1].

Prescribing cascades are common, where one medicine is prescribed to treat the adverse drug reactions of another drug.

Regular medication review and use of criteria such as START, STOPP, and BEERS criteria are important. However, these criteria may not always be sufficient, and may need to be combined with implicit criteria [69].

Anticholinergics, sedatives, and psychotropic medications are particularly problematic in the older population. Psychotropic medications are a particular problem in long-term care facilities. Antipsychotics and benzodiazepines are often prescribed to nursing home residents without an appropriate indication. One review found that more than one quarter (26 %) of nursing home residents used an antipsychotic medication, 40 % of whom had no appropriate indication for such use. Among the 13 % of residents who took benzodiazepines, 42 % had no appropriate indication [70].

Anticholinergic and sedative drug exposure is associated with poorer function in community dwelling older people, both cross-sectionally and longitudinally [71–73], as well as in older adults living in self-care retirement villages [74]. Anticholinergic drug burden was associated with greater difficulty in balance, mobility, slow gait, chair stands, grip strength, upper extremity movements, activities of daily living and with poor performance on the Mini-Mental State Examination, while sedative drugs were associated with impaired grip strength and mobility difficulties in older women [75]. Total anticholinergic burden was associated prospectively with mortality and cardiovascular disease in a general population [76].

Patients treated with neuroleptic medications, especially clozapine, showed autonomic dysregulation, and cardiac repolarization changes [77]. Patients prescribed typical and atypical antipsychotics had relative and absolute dose related prolongation of the QT interval, and increases in risk of ventricular arrhythmia and sudden cardiac death [78–82]. The combination of antipsychotic and antidepressant drugs may increase the risk further, especially at the time of an acute coronary event [82].

The patient and caregiver, if any, must be involved in the decision making process. Medication times, doses, routes, packaging, and reminders should be tailored for each patient, keeping in mind individual patient characteristics, physical frailties, disabilities, memory problems, etc.

Adherence is a complex issue with social, economic, health care system, therapy, condition, and patient related aspects. Route of administration, size, shape, texture, taste, smell, labeling, and packaging can all impact compliance with medications.

Future—Opportunities for the Pharmaceutical Industry

The provision of drug therapy starts with the early development of a pharmaceutical product, and as old and very old patients are becoming the predominant user group for many medications, it becomes very important that the pharmaceutical industry

keep this group in mind while developing drugs [83]. The use of genomic information for tailoring drug therapy to the individual, increased availability and use of healthcare information, and the greater involvement of the patients in the decision making process provide opportunities to improve the prescription of medications [84]. System improvements in pharmaceutical manufacturing processes like Process Analytical Technology (PAT) and Quality by Design (Qbd) promise to increase the efficiency of drug development and provision [84, 85]. Public engagement workshops may help to highlight concerns faced by patients and caregivers, and help identify changes that need to be made in drug manufacturing and provision [86]. A greater understanding and utilization of frameworks for the development of improved therapeutic entities based on existing drug products may help to harness the clinical experience of these existing drug products, so as to reduce cost and time in the provision of new therapies or new dosage forms of existing therapies [87]. Innovative approaches such as the Polypill need to be pursued.

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Healthcare Provision in an Aging Society—The European Perspective

Peter Crome and Joanna Pleming

Abstract This chapter aims to set out an overview of current practice for the treatment of older patients in Europe. It focuses on established health services for the elderly and current prescribing practice in the context of European health policy. It details the roles of the professional health bodies within Europe including the European Medicines Agency (EMA) and European Union Geriatric Medicine Society (EUGMS) and patient charters including that of the PREDICT partnership. It explores some of the overprescribing and underprescribing issues in older people specific to Europe. The healthcare system for older people in England is described in some detail and compared to a number of other European countries, thereby providing a context for prescribing opportunities and challenges in the continent.

Keywords Healthcare in Europe · EUGMS (European Union Geriatric Medicines Society) · EMA (European Medicines Agency) · NICE (National Institute for Health and Care Excellence) · PREDICT

Introduction

Physicians treating older people and older people themselves have long been concerned about the risks and benefits of pharmacotherapy. Issues of adherence, polypharmacy, potentially inappropriate medications, high rates of adverse events, and altered kinetic and dynamic responses, together with the poor evidence base for

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S. Stegemann (ed.), *Developing Drug Products in an Aging Society*,
AAPS Advances in the Pharmaceutical Sciences Series 24,
DOI 10.1007/978-3-319-43099-7_2

treatment in the over-75s and those with multimorbidity, all make prescribing problematic. These factors need to be considered in the context of improved diagnosis (e.g. scans), new medicines for newly identified conditions, the increased prevalence of conditions such as diabetes (although others are in decline), national policies and guidelines and the greater emphasis on secondary prevention for conditions such as stroke and heart disease. These issues have gained more prominence as the result of demographic changes and the growing recognition that older people are not a homogenous group (see Box 1). In this chapter some of these issues are explored from a European perspective.

Older People in Europe

Demography of Aging in Europe

Europe is aging, and as it does so, it pulls a larger and larger proportion of the population out of work and into retirement. Life expectancies in European countries are some of the highest in the world and continue to increase. Over the last 50 years, life expectancy at birth in the 28 European Union Countries (EU-28) has increased by approximately 10 years and between 2001 and 2013, the median age of the population in Europe increased in all of the EU-28 countries, from a minimum of 2.1 years in Lithuania and up to 6.4 years in Estonia [1].

The aging population is, in part, contributed to by low birth rates. Fertility rates in the EU-28 have decreased since the baby boom of the 1940s–1960s and stayed relatively low. This trend is partly explained by European families having fewer children and parents waiting longer before starting families [2].

The aging of the population will also lead to an increase of the percentage of the population classified as the oldest old, >80 years. This proportion of the population is growing faster than any other and is projected to increase by more than twice as much again between 2013 and 2080 [3] (Fig. 1).

Life expectancy for women in Europe is, on average, longer than that of men, estimated at an extra 5.5 years of life in 2013. This longevity comes at a cost, however, with most of the later years being subject to activity limitations. The gap in "healthy life years" is much less significant between sexes, only equating to 0.1 years [4]. The growth in the elderly population has resulted in the elderly consuming an ever increasing proportion of health resources, with the over 65s accounting for 70 % of hospital bed days in the UK [5].

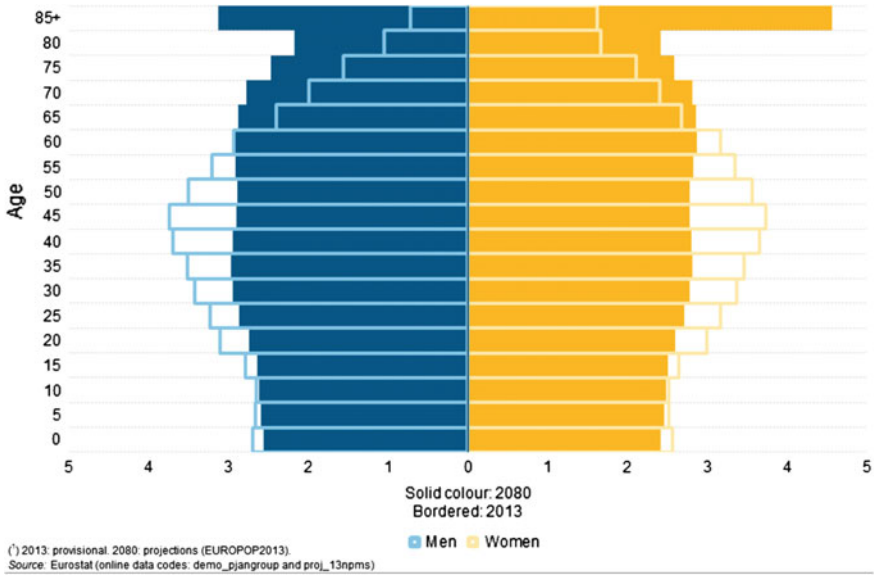

Fig. 1 Projections of population spread with the *bordered color* representing actual figures from 2013 and the *solid color* the projections for 2080 (*Source* Eurostat)

Prevalence of Diseases/Disability in Europe

The Dutch National Institute for Public Health and the Environment (RIVM) prepared a report to review the impact of chronic disease on the population of pre- and post-retirement age in the European Union. It reported the substantial burden of four main chronic diseases—cardiovascular disease, cancer, COPD, and diabetes. It notes the lack of good data on trend prevalence but states that the total number of people with chronic disease is expected to increase due to the aging population and the continued prevalence of lifestyle risk factors. It also notes significant differences between individual countries within the European Union [6].

In the UK, The Alzheimer's Society estimates that one in six people aged 80 or over have dementia at a financial cost of £26 billion per annum. It also estimates that only 44 % of people with dementia in the UK receive a diagnosis. The prevalence is increasing. By 2015 there will be 850,000 people with dementia in the UK and this number is expected to rise to 1 million people by 2025 [7]. Alzheimer Europe used projections from UN populations statistics for 2012 to estimate that dementia affects on average 1.5 % of the entire population of the European Union, the lowest in Romania and Slovakia at 1.07 % and highest in Italy at 2.09 %. It also notes that as more than half of dementia goes undiagnosed, these figures are in all likelihood, much higher [8].

There are also 157,000 new strokes per year in the UK [9]. The increase in prevalence of stroke in the elderly is paralleled in other European countries. Engstad et al.'s literature review in 2012 highlighted that, in Nordic countries, prevalence has increased due to a combination of improvement in care quality causing decreased lethality and a slower fall in incidence than increase in the proportion of the oldest old in the population [10].

European countries vary in the percentage of their GDP that is spent on health. OECD data shows that the proportion of GDP spent of health rose from 7.3 to 8.3 % between 1998 and 2008. There was almost twofold variation between countries with France spending 11 % of their GDP on health, whereas it was only 6 % in Cyprus and Romania [11]. The financial issues facing European health services as a consequence of the 2008 recession coupled with inflationary pressures (including their drug budgets) are obvious. Maximizing efficiency in a time of resource limitation whilst improving health in later years is a public priority across Europe. Keeping costs down whilst at the same time developing a national fiscal environment that encourages pharmaceutical innovation remains a challenge.

Medication Use in Europe

An Introduction to Overprescribing and Underprescribing

Medication use in older people and its regular review formed one of the pillars of the UK National Policy on Older People [12] that suggested that older people should be broadly categorized into three groups [12]:

(1) Active and independent older people—those entering old age
(2) Transitional Phase—the bridge between 1 and 3
(3) Frail older people with a higher level of care needs and increased vulnerability.

We have illustrated the difference in care needs between these groups with two vignettes (Box 1).

Box 1 The Diverse Faces of Aging: Two case vignettes highlighting the differences in heath needs and prescribing considerations between two older patients

THE DIVERSE FACES OF AGEING
Older Person 1

Personal Situation
65-year-old married female office worker. Works part-time and plans to retire in about two years. Two children and three small grandchildren. Her mother, 87, lives in a retirement apartment. Plays an active role in grandparenting and wishes to continue this. Life expectancy 20 years.

Medical Conditions

Type 2 diabetes and hypertension. No physical or mental health complaints. Slightly overweight. Blood pressure usually about 150/90. Osteopenia on dexa-scanning.

Drug Treatment Issues

Realizes that she may need treatment for hypertension, diabetes, and osteopenia.

Wants to know what the risks are without drug treatment and what the benefits are for people like her, not for the entire population.

Prepared to put up with mild side-effects if there is substantial benefit.

Wants a simple drug regime that fits in with life style.

Older Person 2

Personal Situation

85-year-old widow. Admitted to a nursing home following a fall in which she fractured her right femoral neck. Limited mobility. Can only walk with the help of a walker. Her children are now retired. She enjoys visits from her grandchildren and great-grandchildren. Can only leave the home in a wheel chair. Life expectancy 3 years.

Medical Conditions

Type 2 diabetes, hypertension, and osteoporosis. Blood pressure usually about 150/90. Glucose slightly raised.

Drug Treatment Issues

Concerned about side-effects, particularly risk of hypoglycaemia and whether the drugs will produce worthwhile benefits.

The requirements in health provision differ greatly between these two groups. A lack of recognition that these two groups of patients have different care needs and medication requirements can create issues with overprescribing or underprescribing. Older Person 1 will benefit from active primary care for example, interventions to help her maintain a healthy BMI, actively manage cardiovascular risk factors, and monitor bone density, intervening when necessary. These interventions will keep her healthier for longer, keeping her out of hospital, limiting her cardiovascular risk and improving her quality of life. She is motivated to accept treatment but requires the time to be informed of benefits and risks to improve adherence. She will be on most of this medication for the rest of her life with no notable change to how she feels on a day-to-day basis. It may be tempting to restrict some medications as she is an older adult but this may lead to underprescribing for someone who may live for a further 30 years. Older Person 2 requires multidisciplinary comprehensive geriatric assessment with focus on maintaining and strengthening

existing function, regular medication review and advanced care planning. Antihyperglycaemic medication is indicated to prevent a hyperosmolar state but care should be taken that glycaemic control is not too strict as the long-term benefits will not be realized with a limited life expectancy and the risk of hypoglycaemia is higher and more dangerous. Overprescribing should be avoided with consideration made of quality of life and a shift in focus made from broad cardiovascular prevention to targeted prevention (e.g., bone protection in a patient at risk of falls) and symptom control.

Medications are prescribed by the general practitioner, hospital doctors during hospital admissions and other health professionals. This can lead to a lack of empowerment by any one professional to review an individual's medications meaning that medications are started and not stopped, or that an indication that has changed is not recognized, for example anticholinergics for benign prostatic hypertrophy continued after a long-term catheter has been inserted, increasing the risk of falls and delirium with no further benefit to the patient. In hospital there is a focus on short-term treatments, the acute care setting is not conducive to chronic medication review, and general practitioners may feel disempowered to change specialist prescription started sometimes decades previously, e.g., antidepressants. There can be limited communication between primary and secondary care [13].

In a study performed in 2005, Fialova et al. showed that polypharmacy (graded as 9 or more medications) was reported by 22 % of adults >65 years in home care in Europe [14].

Health Services for Older People

Discussion of Public Health Services with Individual Country Examples

There is a general consensus in Europe that the provision of health services for older people is a national rather than an individual responsibility. How this is organized varies from country to country and even within countries from region to region. There is also a scheme that allows citizens or residents from one country to receive health care in another European country as if they were a citizen/resident of that country. To facilitate this, a European Health Insurance Card is available for travelers.

In the UK, the National Health Service (NHS) is free at the point of use for both primary and hospital health services. It is primarily funded by general taxation; there is no hypothecated health tax. The method of funding varies throughout Europe with some countries using state funding to cover the cost of health care, others use mandatory health insurance (both for profit and not for profit insurers) and top-ups or co-payments may be required. Private health care is used to a variable degree in all European countries and often allows greater flexibility to

choose the care provider, e.g., consultant or hospital, and chose the timing of appointments.

Every person in the UK is registered with a general practitioner (GP). These doctors work from community-based practices which contain from one to several GPs. GPs are generalists and act as gatekeepers to hospital outpatient services, referring patients to secondary care, usually via a paper or web-based referral form. If cancer is suspected, the NHS has a "two—week wait" pathway in which patients are triaged and seen by the specialist team within two weeks from the date of referral. Specialist secondary care is practiced in hospitals, generally not geographically placed within primary care centers. Some specialist referrals, for example specialist Parkinson's disease clinics, are set in a multidisciplinary outpatient department with patients being seen by doctors, specialist nurses and physiotherapists within the same outpatient hospital visit. Specialty referral to geriatric medicine can be to several discrete outpatient services, for example, falls clinics, old age psychiatric services, or general geriatric outpatients. Some hospitals provide admission avoidance services. These can offer, for example, direct access by GPs to a consultant geriatrician via telephone for advice or to take a referral to see an older person in a specialist clinic to avoid what would otherwise lead to an admission to hospital. Admission avoidance appointments are typically longer and have access to occupational therapists, physiotherapists, and in some cases social services to organize home care packages, blood tests, and scans on the same day. Some departments have links with community-based nursing packages, through which nurses visit patients in their homes to administer intravenous medications and measure observations.

In the UK, most older people with care needs are cared for in their own home. Social care services in the UK are means-tested with those who have higher need care-packages prioritized. Occupational therapists in the community and allied to hospitals make recommendations as to the safest and best place for care to be delivered, making home visits to assess whether equipment or adaptations would enable living at home for longer. Older people who require more supervision can be offered sheltered or residential housing with a warden on site to make regular calls to check on residents. Nursing homes are usually a final step providing 24 h nursing care for those with severely disabling illness and requiring round the clock assistance. Medical care to nursing homes is provided either by GPs or, in some countries (e.g., the Netherlands) by nursing home physicians. In England, social care is facilitated by the Local Authority. In those who cannot pay, this is fully funded. There is a wide spectrum of social care outside the UK with significant reliance on informal care in some countries, depending on culture and GDP.

On admission to hospital in England, a decision to admit or discharge must be made within four hours. There are specialist pathways for some conditions, for example, fractured neck of femur and stroke, mobilizing members of the multidisciplinary team early, to decrease morbidity and mortality. Throughout the UK, geriatricians are involved in the care of older surgical patients and orthopedic patients, with a proven benefit to outcomes [15, 16].

A key focus of NHS reform in the UK in recent years has centered around integrated care—the development of a more holistic, person-centered system avoiding the fragmentation and compartmentalisation of different care episodes. Integrated care aims to deliver care to a patient in a location best suited to the patient, meeting their physical, mental, and social care needs. Geriatric patients are well suited to this approach, and their health and social care needs will increasingly be met through integrated care. Over time, changes in the way health care is financed and regulated will promote provision of integrated care. Admission avoidance and ambulatory care clinics, increasingly present in UK hospitals, provide an increased range of services to outpatients so that they can remain out of hospital or be discharged home earlier [17, 18].

Alongside the move to integrated care, there will be a shift in provision of care and prescribing away from hospital specialists and toward other health workers in the community, including specialist nurses. This will mirror the shift to nurse-led care that has already been seen in other disciplines. An example of nurse-led care which has been highly successful and widely adopted throughout the NHS is in the treatment of heart failure. Specialist heart failure nurses are usually allied to cardiology departments and work within hospitals or from a community base, also performing domiciliary visits. Nurse practitioners provide coordination of care with a multidisciplinary approach combining patient education, dietetics, medication review, and prescription including uptitration of heart failure medications. Nurse-led intervention in this area, particularly in elderly and isolated patients, has shown benefits not only in clinical and cost-effectiveness, but also in quality of life [19].

There is much variation in the number of physicians and the division between general practitioners and specialists in Europe [20]. Throughout Europe there are 3.3 physicians/1000 population, the highest number being in Greece (6/1000) and the lowest in Turkey (1.5/1000). There is even greater variation in the proportion of physicians who are general practitioners—54.5 % in Romania, 4.5 % in Greece, with an overall European figure of 25 % [11].

Prescribing for Older People

National Guidelines and Cost-Effectiveness Arrangements

The responsibility for prescribing for long-term conditions varies by country (Table 1). In the UK, the management of long-term conditions is the responsibility of the general practitioner (e.g., essential hypertension, Type 2 diabetes, hypercholesterolaemia, COPD, and hypothyroidism). Some specialist (and usually more expensive) medications are prescribed by specialists in hospital (e.g., chemotherapeutic agents, monoclonal antibodies, and drugs for HIV/AIDS). Shared care guidelines are in existence whereby treatment is initiated by specialist and then

Table 1 Simplified comparison of key features of health services for older people in seven European Countries (excluding private sector)[a]

	UK	Germany	Italy	Belgium	Netherlands	Cyprus	Lithuania	Czech Republic	Greece
If an older person becomes ill whom do they see in the public health service? (Non-emergency)	GP	GP or specialist	GP	GP or specialist	GP	GP	GP	GP	GP
Who pays for the consultation?	State	Health insurance	State	Health insurance	Health insurance	Mostly state	State	Health insurance	State
Are there co-payments?	No	No	No	Yes (25 % paid out of the pocket by the patient)	No	Yes (3 euro co-payment)	No	Sometimes but not usually	No
If drugs are prescribed, does the patient have to pay?	No	Yes 10 Euro per drug prescribed up to a ceiling of a total healthcare expenditure of 3 % of the family income per year, reduced to 1 % of the family income in individuals with chronic conditions	No If the patient wants a brand instead of a generic one then he has to cover the difference in price	Yes Depending on drug, e.g., diabetes drugs are free but tranquilizers are not reimbursed	Yes At least 300 euro own risk for all insured patients, this includes also costs for medicines. For some drugs all costs have to be paid for depending on the insurer	0.5 euros per drug	Partly	Varies according to drugs	No

(continued)

Table 1 (continued)

	UK	Germany	Italy	Belgium	Netherlands	Cyprus	Lithuania	Czech Republic	Greece
Are there any restraints on what the GP/primary care physician can prescribe?	If approved by NICE, drugs have to be provided by health service. Local formularies may vary from district to district	No (but the insurance company will ask questions if prescribing costs are very high, and the GP has to justify costs)	Yes Many drugs require a specialist prescription	Some Only a few very expensive drugs	Yes All GPs are not allowed to prescribe all drugs, health insurance companies have a preferred list of medicines that are allowed to be prescribed, these lists could be different from company to company	Some Restricted list of drugs stipulated by state	Some GP prescribing is monitored. Some medications can be prescribed only by specialists	Yes Some drugs are prescribed by specialists controls by health insurers	No Drugs usually prescribed by brand name
Do specialists provide primary care?	No	Yes	No	No	No	No	No	No	No
Who monitors chronic conditions?	GP	GP and specialists	GP	GP and specialists	GPs and specialists	GP	GP	GPs and specialists	GP

(continued)

Table 1 (continued)

	UK	Germany	Italy	Belgium	Netherlands	Cyprus	Lithuania	Czech Republic	Greece
Do GPs have financial incentives to prescribe?	Yes For GPs to meet targets for prescribing preventive treatments	No (but the insurance will ask questions if prescribing costs are very high, and the GP has to justify costs)	No	No	Yes Incentives from health insurance companies to prescribe the cheapest drugs	No	No	No GPs leave prescribing to specialists if possible	No
How do patients see geriatricians?	On referral from GP	Only in hospital	Mainly only available in the hospital with a GP referral or as a private visit	Mostly in hospitals	Mostly in hospitals	Self-referral or by doctors' recommendation	On referral from GPs	Only in hospital	Not a developed specialty
How is geriatric medicine practice different from the UK?		Only provided in hospital. No community geriatricians, no visits to nursing homes and no day hospitals	Mainly provided in the hospital. Few specialists are available in the community and in nursing homes	Geriatric day hospitals in every hospital. Mandatory internal medicine liaison	Only provided in hospital Geriatricians visit nursing homes at the request of nursing home physicians	Few private geriatricians only	Few geriatricians	Only in hospital—mainly university hospitals	As above

(continued)

Table 1 (continued)

	UK	Germany	Italy	Belgium	Netherlands	Cyprus	Lithuania	Czech Republic	Greece
In hospital are there any constraints on prescribing?	Hospital formularies and policies e.g. antibiotic prescribing	No	No	Different formulary in every hospital	Yes, some hospitals do not allow prescription of very expensive drugs, most of the time this not relevant for geriatricians	Restricted formulary stipulated by state	No	No	Local hospital formulary. Essentially all drugs and brands are available
Are there financial incentives to prescribe?	Quality and outcomes framework (QOF)	No	No	No	No	No	No	No	
Who pays for hospital care?	State. No co-payments	Insurance	State. No co-payments	Insurance plus out of pocket payment by the patient (25 %)	Insurance	Either the state pays fully, or partially and patient makes modest contribution, or pays full cost (various criteria e.g. income, chronic illnesses, number of children)	State	Health insurance	State

(continued)

Table 1 (continued)

	UK	Germany	Italy	Belgium	Netherlands	Cyprus	Lithuania	Czech Republic	Greece
Who pays for drugs in hospital?	State. No co-payments	Insurance plus 10 euro per day hotel costs up to a ceiling of a total healthcare expenditure (also include prescriptions, travel to hospital, etc) of 3 % of the family income per year, reduced to 1 % of the family income in individuals with chronic conditions)	State. No co-payments	The hospital	Insurance	As above	State	State	State

[a]There may be differences in how services are provided for between different regions in the same country, e.g., at Laender level in Germany and at country level in the UK

devolved to GPs (e.g., cholinesterase-inhibitors for Alzheimer's Disease and novel oral anticoagulant medications).

Older people are exempt from prescription charges. At a practice level there are incentives for GPs to prescribe some medications in order to qualify for additional payments by meeting defined thresholds. Examples include anti-osteoporosis medication, antihypertensives, and lipid lowering drugs.

The ability of physicians to prescribe within state health systems is controlled by a variety of mechanisms. For example, in England and Wales, the National Institute of Health and Care Excellence (www.nice.org.uk) assesses the clinical and cost-effectiveness of new medications. As a general rule those drugs which are above the £20,000–£30,000 per quality adjusted life year (QALY) Incremental Cost-Effectiveness Ratio threshold will not be approved. At the present time manufacturers of anticancer drugs can apply to a special Cancer Drug Fund if their application to NICE is rejected. NICE approved drugs have to be made available through the NHS. In addition to its appraisal role NICE also produces evidence-based guidelines for the management of common geriatric medicine problems, e.g., delirium, dementia, falls, and continence. In France, the Haute Authorité de Santé is an independent organization evaluating both the health system and health care products as well as the organization of health systems including public health (www.has-sante.fr). Hospitals will have local formularies listing which drugs are recommended for what conditions and in some countries these controls will apply to community prescribers as well.

The cost of medications is a major health issue in Europe. The number of prescriptions in the community has increased to 1000.5 million in 2012, a 62.2 % increase over 2002. The total ingredient cost actually fell compared to 2011 largely due to the expiry of patents on widely prescribed drugs (e.g., atorvastatin). Free prescriptions accounted for 90 % of prescriptions of which 60 % were older people [20].

In most countries there is a conflict between the desire to reduce costs of medications (whether paid for by the state, insurers or the public directly) and the desire to promote the pharmaceutical industry as a source of employment and tax revenue.

In most European countries co-payment for prescriptions is required, often varied according to the cost of the drug or to the wealth of the patient (see Table 1). A useful summary of how prescribing is monitored is found at http://www.icf.uab.es/es/pdf/publicacions/DU_inventory_countries.pdf.

European Actions

Human Rights

Physicians in many European countries have taken the view that many of the issues surrounding drug treatment in older people can be considered within the framework of Human Rights. The European Convention on Human Rights, ratified after the events of the Second World War, includes the Right to Life (Paragraph 1),

The Right for Respect for Private and Family Life (Paragraph 7) and the Prohibition of Discrimination (Paragraph 14) [21]. National law is subject to this convention but not all rights are absolute and interpretation varies. All of these principles may be violated if governments do not set in place systems to ensure that older people are not denied safe and effective mediations. The European Union contains within its charter on fundamental rights at Article 25 "the Union recognizes and respects the rights of the elderly to lead a life of dignity and independence and to participate in social and cultural life" [22].

The EU Charter of Patient's Rights (2002), although not specifically addressed to older people, affirms a patient's right to fundamental rights when applied to healthcare. Article 35 of the Charter provides for a right to health protection as the "right of access to preventive health care and the right to benefit from medical treatment under the conditions established by national laws and practices". Article 35 also specifies that the Union must guarantee "a high level of protection of human health," meaning health as both an individual and social good, as well as health care. This formula sets a guiding standard for the national governments: do not stop at the floor of the "minimum guaranteed standards" but aim for the highest level, notwithstanding differences in the capacity of the various systems to provide services.

These conventions have served as models for the development of other charters that are more specific as regards the health of older people. The European Charter of the Rights and Responsibilities of Older People in need of long term care and assistance states at article 1.2.9 "protection from all medical and pharmaceutical abuse, maltreatment or drug use or denial of treatment" [23].

European Medicines Agency

The European Medicine Agency (EMA) is the body that regulates medicines in almost all European Countries (i.e., European Union and the European Economic Area). It has two principal functions in relation to medicines for older people—the authorization for marketing and pharmacovigilance. Information about the EMA is available on its website www.ema.org.eu. Some medications may also be authorized through national licensing bodies.

An important step in the development of European Medicines policy for older people was the publication of the report on adequacy of guidance [24]. This report analyzed the data submitted for 10 new drugs and compared the data submitted to standards recommended by the International Commission on Harmonization [25]. It concluded that in general, dossiers were compliant with the guidance, however there was scope for improvement. Amongst the suggestions were for professional bodies to define elderly, very-elderly, and frailty, the need for further discussions on increasing the number of older people recruited into studies and to systematically appraise the exposure of older people to a medication.

The EMA has produced a geriatrics medicine strategy which has its vision "… ensuring that medicines used by geriatric patients are of high quality, and appropriately researched and evaluated, throughout the lifecycle of the produce, for use in this population" and "improving the availability of information on the use of medicines for older people, thereby helping informed prescription" [26]. Amongst the actions advocated in the report is to give advice on numbers of older patients to be included in studies, the special needs of older people, age-specific end points, the identification of validated tools to measure safety in and effect in "frail" older people. Postmarketing monitoring in people with comorbidities was also recommended. To assist in this work a "virtual" geriatric expert group has been established [27]. One piece of work this group is taking forward is to develop definitions of physical and mental frailty and of comorbidity to guide drug development for these import subgroups of older people.

Recent reports on the implementation of the strategy have reviewed scientific guidelines and product information [28, 29].

An analysis of 28 guidelines produced in 2011–2013 showed that two were fully compliant with ICH E7. Of the 18 guidelines which were adopted over this period, one-third did not take into account comments made to rectify the situation [28].

The report on product information contains a more detailed account of information deficiencies and the responses of manufacturers. Examples included the need for further cardiovascular safety data, the requirement for post-authorisation follow-up because of the small number of older people included in the original submission, warnings about the lack of safety information about older people and the requirement to include a specific warning about falls risk [29].

Thus it can be seen that the EMA is taking on board the concerns of professionals about the present state of information about drugs in older people and addressing issues within their areas of competence. The EMA is producing a further reflection paper covering scientific literature, practical issues, and a gap analysis describing how existing authorisations do not meet the needs of older people. This is due to be published in 2016.

Actions on Representation of Older People in Clinical Trials

As has been described above, the EMA has taken some steps to increase the number of older people in clinical trials of investigational medical products. However the issue goes beyond solely new products to affect both existing drugs and devices. The underrepresentation of older people in trials has been reported upon by a number of investigators. As an example, in 2011, Cherubini et al. [30] found that a quarter of clinical trials for heart failure had an arbitrary upper age limit and that over 40 % had one or more unjustified exclusion criteria [30]. The European Union Geriatric Medicine Society, the umbrella group for European societies, has established a pharmacology special interest group that lobbies on this and other issues with the EMA and other agencies [31].

European geriatricians have also undertaken collaborative research on this issue. For example the PREDICT study has reported on both professional and patient/carers views on the under-representation of older people [32, 33]. This work led to the production of a European Charter on Patients, Rights in Clinical Trials that has been endorsed by many European Geriatric Medicine Societies and other professional organizations (Box 2).

Box 2 Key Elements of the PREDICT Charter

- Older People have the right to access evidence-based treatments—they should demonstrate effectiveness in people of their age.
- Older people should be not be discriminated against in recruitment for clinical trials.
- Research Ethics Committees, Sponsors, medical Journal Editors, and regulators should review all studies critically for unjustified exclusion based on age, other illnesses, disability, and other drug treatments.
- Clinical trials should be designed so that older people can participate easily.
- Researchers should be trained to conduct clinical trials in subjects with communication, sensory, mobility, or cognitive problems.
- Trial sponsors should recognize that older people may need extra support to participate in clinical trials.
- Clinical trials in older people should be as safe as possible.
- Outcome measures should be relevant to older people.
- Clinical trial sponsors should involve older people and carers in the design of clinical trails.
- Researchers should respect the values of each older person as an individual.
- Older people should be able to withdraw from a clinical trial without detriment to other treatment and their overall care.

The European Forum on Good Clinical Practice, a multidisciplinary organization that brings together academics, clinicians and the pharmaceutical industry, has produced a report on Medical Research For And With Older People In Europe (EFGCP) [34]. This report is targeted toward clinical trials undertaken for regulatory purposes. However, it is of relevance to all clinical trials (drugs and non-drugs) and covers ethical issues such as consent/assent, and risk assessments as well as topics such as numbers needed, inclusion and exclusion criteria, and outcome measures.

The European Union Geriatric Medicine Society (EUGMS) is a federation of national societies that is also promoting the inclusion of older people in clinical trials (www.eugms.org). Its pharmacology section's goals include promoting the inclusion of older people in clinical trials, to promote appropriate prescribing including the STOPP and START criteria (see below) and to develop pharmacogenetic research in older people. It has lobbied the EMA to establish additional requirements for

authorisation for drugs that will be used in older people. These would require the recruitment of very old people as well as those with multimorbidity and disability. They have suggested that companies that comply with additional recommendations might be "rewarded" with a longer patent for their product [31].

Actions on Inappropriate Prescribing and Failure to Prescribe Appropriate Medications

The repeated finding that older people are more susceptible to the side-effects of drugs led to the development of lists of drugs which were deemed inappropriate outright or for specific conditions. The most widely employed and studied are the Beers criteria which have regularly been reviewed, most recently in 2012 [35]. Other investigators have developed alternative lists of medications to be avoided. [36] reported on the prescribing of inappropriate medication in six European countries using both the STOPP criteria and the then Beer's criteria [36]. They reported that the overall prevalence of potentially inappropriate medications ranged from 34.7 % in a Czech hospital to 77.3 % in a Swiss hospital whilst for the Beer's criteria the range was 22.7–43.3 % in the same two hospitals. These authors also reported that potential prescribing omissions averaged 59.4 % across the six European hospitals [36]. Since this paper was published there has been a further update of the STOPP/START criteria [37].

One of the criticisms of the use of criteria is that there has not been robust clinical trial evidence that using criteria such as STOPP/START or Beers has improved patient outcomes. This is now being tested in a controlled six nation trial in Europe funded by the EU (SENATOR study—http://www.senator-project.eu/). In this study 1800 patients will be randomized to have their medication assessed against a computerized version of the STOPP criteria or to standard care. A range of outcomes will be measured.

Prescribing Toward End of Life

Whilst there is consensus that prescribing drugs other than those that will provide symptomatic relief for those older people in their last few days of life is futile there is debate as to whether the same principle is true for patients in their last years of life. There are practical and ethical difficulties for physicians who have extolled patients to take statins and antihypertensive drugs for years only to tell patients that on reaching a certain age or a certain stage in their disease that they should stop the drugs as they are no longer necessary.

The process of "de-prescribing" has been operationalized by Garfinkel in Israel and has been taken up by physicians in Europe [38]. Garfinkel et al. undertook a systematic deprescribing exercise in nursing home residents with what they called the "geriatric-palliative" methodology [38]. An example quoted was to stop nitrates if there had been no chest pain for 3 months. Although not a randomized trial they found that the one year mortality in the study group was 21 % compared to 45 % in the control group. Acute care referral was also reduced—30 % in the control group and 11.8 % in the study group. They discontinued 332 drugs in 119 patients and had to reintroduce 33 drugs in 21 patients. Antihypertensives, H_2 blockers, and nitrates were the drugs most frequently discontinued [38]. Garfinkel and Mangin [39] have also described successful drug discontinuation in community-dwelling older people [39]. Scott et al. have advocated a similar approach with a 4-step decision tree: no benefit, harm outweighs benefit, symptoms stable, or non-existent, preventive drug benefits unlikely to be realized because of short life expectancy [40].

Conclusion/Discussion

Older people and their families want access to the most effective and safest medications. Within health care systems, where there is co-payment for prescription drugs, then they want such co-payments to be reasonable. What might be considered reasonable will vary from country to country. Evidence from the PREDICT study shows that older people want their drugs to be tested by clinical trials with relevant outcomes. Trials may need to be modified to meet the needs of older people with multiple morbidities and frailty. "Real-life" trials with minimum exclusion criteria and simple meaningful outcomes such as, e.g., AD2000 or PDMed, or adaptive trials which allow for modification of design and the introduction of new drugs, are two ways to improve recruitment of older people into trials. There also needs to be recognition that taking medication does pose physical and psychological burdens in addition to financial burden. Toward the end of life consideration needs to be given to reducing or stopping medications for which there is unlikely to be benefit. These factors also need to be set in the context of governmental concerns about the costs of medication and the need to have a thriving manufacturing and research arms for their pharmaceutical industry, for there are still many conditions of later life for which there are no drug treatments with any significant benefits.

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Healthcare Provisions in the Aging Society: Japanese Perspectives

Naoko Muramatsu

Abstract As the home of the oldest population in the world, Japan is transforming its healthcare system to prepare for year 2025, when all the first baby boomers will be aged 75 and older. Japan achieved universal medical insurance and long-term care insurance systems in 1961 and 2000, respectively. A core vision of the ongoing reform efforts is the Community-Based Integrated Care System, where the whole community (the local government, professionals, and residents) works together to integrate various services (e.g., housing, medical and health care, long-term care, and daily living support and services) so that older adults, even with cognitive impairment and without family support, can remain in the community with dignity until the end. Many of challenges and opportunities associated with population aging in Japan are shared by other aging societies. Global co-learning (or two-way learning) is essential for developing innovative products, services, and systems to promote healthy aging in communities.

Keywords Community-based integrated care system · Universal insurance for medical and long-term care · Healthy aging · Health care reform · Global co-learning

Introduction

Japan is experiencing population aging at a rate that is unprecedented in the world. The ongoing population aging challenges Japan's healthcare provision that is based on universal medical insurance and long-term care insurance systems established in 1961 and 2000, respectively. To illustrate Japan's efforts and vision to establish sustainable healthcare and long-term care systems, this chapter starts with a brief review of factors that have made Japan the home of the world's oldest population,

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S. Stegemann (ed.), *Developing Drug Products in an Aging Society*,
AAPS Advances in the Pharmaceutical Sciences Series 24,
DOI 10.1007/978-3-319-43099-7_3

followed by key features of the Japanese healthcare system and on-going reform efforts, and concludes with implications and recommendations for the global community of aging societies.

Japan's Population is the Oldest in the World and is Getting Even Older

Japan's population is the oldest in the world. As of 2014, one in four people in Japan is 65 or older; the 65+ population is projected to account for approximately one-third of the total population by 2030 and 40 % by 2050 [1]. Population aging in Japan has been rapid, although the rate has been surpassed by Korea and China in recent years [2, 3]. As in many other developed and developing countries, fertility decline has been the major driving force for population aging. The post-World War II baby boom was brief (1947–1949), and the number of births per woman has declined rapidly. The total fertility rate declined from 4.54 births per woman in 1947 to 2.04 in 1957 [4]. As the average age of mothers at childbirth gradually increased (from 25.6 in 1970 to 30.4 in 2013), the total fertility rate dropped to a record low of 1.26 in 2005, then has increased slightly up to 1.43 in 2013, much lower than the replacement level of approximately 2.1 that is required to keep a population stable. Declines in mortality among older adults also accelerated population aging in Japan. Japan's population is not only aging but also declining in size simultaneously. The total population of Japan peaked at 128 million in 2004 and is projected to shrink to 75 % of its peak size by 2050.

As a result, Japan has a top-heavy, shrinking population pyramid. As the population aged 70 and over grows rapidly, young populations will become smaller between 2005 and 2030. The ratio of older persons aged 65 or older to the working-age persons aged 20–64 is rising rapidly. And so is the age dependency ratio, or the ratio of the size of the population aged 65 and older that are likely to be "dependent" on the support of others to the size of the working-age population capable of providing such support. In 2010, Japan had 36 persons aged 65 and over (compared to 19 in the U.S.) for every 100 persons aged 20–64; in 2050, Japan is expected to have 72 older persons (compared to 36 in the U.S.) for every 100 working-age persons [5].

Population aging is no longer restricted to rural areas that experience outmigration of young people. Japan is ahead of other countries in experiencing rapid population aging in urban communities. The demographic conditions described above have been the major driving force for a series of healthcare reforms that have been implemented over the last several decades in Japan. To understand recent healthcare reforms, let us first review basic features of Japan's healthcare system.

Universal Access and Excellent Population Health for Relatively Low Healthcare Costs

Japan has achieved highest levels of population health and good access to health care for relatively low costs. Life expectancy at birth has rapidly improved from 1950 (61.5 among women and 58.0 among men) to the highest level in the world. Women's life expectancy at birth was the highest in the world for three consecutive years at 86.3, and men's the third highest at 80.5 in 2014. Healthy life expectancy is also the highest in the world, both for men and women [6]. This high level of population health has been attributed to an excellent public health system, healthy life styles, and egalitarian health care systems [7]. Japan achieved universal health insurance coverage in 1961 by gradually extending coverage to different groups of populations over time [8]. According to OECD Health Statistics, the share of health expenditures in Gross Domestic Products (GDP) in Japan was lower than the OECD countries' average (e.g., 6.8 % vs. 8.1 % in 1995). However, the share of health expenditures in GDP has been rising in recent years due to escalating healthcare expenditures and slow economy. In 2013 Japan's total health spending accounted for 10.3 % of Gross Domestic Products, 1 % higher than the OECD countries' average [9].

Japan's Healthcare System

Under the universal health insurance system, all the people in Japan are required to enroll in a health insurance program. Although premiums and co-payments are somewhat different depending on their age and income, the same set of services are covered by health insurance programs regardless of age or income.

Over 3000 insurers exist in Japan. They cover four groups of people: (1) employees of large companies and government employees (approximately 1400 insurers), (2) employees of small- and medium-sized companies, (3) self-employers and pensioners under 75 years of age, for which approximately 1700 municipalities serve as insurers, and (4) people aged 75 and older. Subsidies from the national and local governments reduce disparities in benefits across the four types of programs [10].

Relatively low health expenditures are achieved by the government's strong control over medical fees and drug prices through fee schedules that are revised every other year [8, 11, 12]. The fee schedules, which cover over 4000 services and 15,000 drugs [13], set the fees that insurers pay to healthcare providers or pharmacies, and stipulate conditions for payment. These fee schedules are applied uniformly to every provider, service, and product throughout Japan and are used to guide the healthcare system towards desired goals. Japan has the highest number of hospital beds among OECD countries, 13.4 beds per 1000 population, compared to the OECD average of five beds in 2012 [14]. Japanese hospitals are known to have

long hospitalizations [15]. This is partly because hospitals have often played the role of long-term care facilities for older adults. Concerned about long hospitalizations that contribute to escalating medical care costs, the government took various measures to reduce hospital length of stays. However, Japan's average length of stay for acute care remains the longest among OECD countries, 17.5 days in 2013, compared to less than 5 days in the United States and less than 8 days in United Kingdom and Canada [16].

Long-Term Care

Over the past 40 years, Japan's long-term care system has made drastic transformations. Traditionally, Japan relied on "Ie" or family system, where the eldest son was legally responsible for taking care of family needs and, in return, inherited most family assets. Eldest sons' wives were expected to care for their parents-in-law and other members with caregiving needs. This family system was officially abolished after World War II. However, societal caregiving norms remained, and women have long been expected to provide physical care for their husband's older parents and their husband. Population aging and growing elder care needs have put excessive burden on the healthcare system and family caregivers. After a series of initiatives to develop long-term care infrastructures (e.g., The Gold Plan of 1989, and The New Gold Plan of 1994), the Japanese government started a public long-term care insurance system throughout Japan with the slogan, "from family care to societal care;" in 2000 [17, 18, 19].

This new system has made long-term care the right of older adults in Japan. This is a major departure from the pre-2000 long-term care programs based on means-tests. As a social insurance, the long-term care insurance program requires residents of Japan to start contributing to the long-term care insurance system at the age of 40 and allows beneficiaries to receive long-term services and supports (nursing home services. home care, adult day services, and other community-based services, but not money) based strictly on physical and mental care needs, regardless of their income or family availability at the age of 65 (or younger people with aging-related diseases, such as Alzheimer's disease). Nation-wide standardized care needs certification system assesses applicants' care need levels and assigns their needs to one of the seven categories. Municipalities are the insurers. Those who are certified can receive needed services up to the maximum amount allowed for each care need level, in consultation with care managers. This system is jointly financed by premiums paid by people aged 40 to 64 and beneficiaries aged 65 and older, and by municipal, prefectural, and national-level governments [20].

While the financing of the long-term care insurance program is tightly controlled by the government via the fee schedule similar to medical care insurance, the delivery system for home and community-based services is dominantly private. At the outset, the Japanese government provided financial incentives to encourage the

private sector to develop a market for home and community-based services. The long-term care insurance system has been rapidly accepted by Japanese people and become part of their everyday life.

How Population Aging Manifests Itself in Health Care and Communities?

By early 1990s, population aging has become a priority policy issue in Japan. Given that fertility drives population aging, the course of population aging was anticipated several decades before the large tide of older people hit the nation. However, we do not "feel" and "see" how it is like to be in a super-aging society until it actually arrives. Currently in 2015, one quarter of the Japanese population are aged 65 and older. Signs of population aging are now seen and felt not only in healthcare settings but in the community.

If you visit cities or villages in Japan, it will not take much time for you to notice home care agency offices, long-term care facilities, and vans that transport older adults to or from adult day services. If you visit community hospitals in Japan, especially those with long-term care beds, you would be struck by the fact that most beds are occupied by frail older adults with multiple chronic conditions, many of whom have difficulties eating, breathing, or remembering. According to the governmental statistics, 68 % of all the hospital beds in Japan were occupied by people aged 65 and older and 49.3 % by people 75 and older [21], and the average length of stay of discharged patients aged 75 and older was 50.2 days in 2011 [22]. Older patients with multiple complex medical needs and disabilities (e.g., people who need oxygen tank or percutaneous endoscopic gastrostomy [PEG] tube) have difficulties finding places to go after hospitalization, either in long-term care facilities or home and community-based settings.

Population aging is evident not only in rural areas but also in urban cities. A large number of people who permanently moved from rural areas to urban communities to rebuild Japan after World War II are now over 80 years old. Many of them still live in large apartment complexes built in the suburbs of metropolitan areas in 1950s and 1960s. The surrounding parks and streets which used to be filled with young children are now replaced by quiet scenes with older people slowly walking by [23].

Living arrangements and traditional caregiving norms are changing [24]. Multigenerational living arrangements were the norm in the past. Now, fewer and fewer adult children live with their older parents. As a result, one in four households in Japan are "elderly" households that consist only of older couples or older persons living alone [25]. Given that one-third of people aged 75 and older living in the community need assistance with daily living, how to care for older couples or persons living alone with disabilities is a major issue in Japan. Families remain the main caregivers for older people in Japan as in any other society. In 2010, 64 % of

primary caregivers were coresident family members (spouses [26 %], children [21 %], child's spouses [15 %]), and close to 70 % of those coresident family caregivers were women. It is important to note that over 60 % of those family primary caregivers were aged 60 or older. In particular, 21 % of male caregivers were over 80 years old [26]. Thus supporting those older caregivers is another important issue.

The absolute number of the oldest old is large and increasing rapidly in major metropolitan areas (i.e., Tokyo, Osaka, and surrounding prefectures) that have lower levels of family and community support than in rural areas. Among all the prefectures, Tokyo will have the largest increase in the number of people 75 and older in Japan (743,000 people) between 2010 and 2015 [25]. Japan now has close to 60,000 centenarians or 46.21 centenarians for every 100,000 people [27].

The number of deaths is rising rapidly as well. Although mortality rates are declining in all age groups, the number of deaths among people aged 80 and older is increasing and is expected to rise with the aging of baby boomers. In 2014, 1.27 million people died, and more than 70 % of deaths occurred among people 75 and older [28]. The number of deaths in Japan is expected to peak at 1.7 million in 2040 [29]. This trend suggests rising end-of-life care needs and services for people at advanced ages. In Japan where cremation is a custom, cremation facilities in some areas have difficulties meeting the demand [30].

Japan is facing major challenges from population aging. The first major challenge is how to support the growing number of older adults with limited or no family support. This challenge is not limited to care for frail, dependent older adults who are eligible for long-term supports and services covered by social long-term care insurance. There are many older adults who are not yet disabled enough to receive formal long-term supports and services, but need social contacts to maintain and monitor their health and safety. Second, dementia is increasingly prevalent. Approximately 4.4 million people (15 % of people aged 65 or older) have dementia, and an additional 3.8 million people are estimated to have mild cognitive impairment. Of particular importance is how to support people with severe or mild cognitive impairment, especially those living alone or living only with a spouse who is also cognitively impaired [25]. Third, integration of medical and long-term care is sorely needed, but is still lacking. People with advanced ages have both medical and long-term care needs, but home and community-based systems are not set up to care for complex medical needs of older adults in home or community settings. Further efforts are needed to make medical care available for home-bound older adults with complex medical needs. Fourth, end-of-life care needs are growing in the home and community settings, especially among older adults at advanced ages living alone. Over 60 percent of adults would like to receive end-of-life care at home [31], but healthcare and long-term care systems often do not allow dying at home. As of 2012 only 10 % of deaths occurred at home, down from 80 % in 1950s. These home deaths include cases where older people die at home alone, without anybody knowing, only to be discovered after a while (e.g., 2733 cases in Tokyo in 2013) [32].

Japan's Healthcare Reforms for 2025: Community-Based Integrated Care System

In 2025 all of the first baby boomers, approximately 8 million people born in 1947–1949, will be 75 years or older. Japan has started a series of health care reforms to prepare itself for year 2025. From then on, the baby boomers will accelerate the rate of increase in medical and long-term care utilization. The proportion of people certified to have long-term care needs grows with age, especially after ages 80 (15 % for ages 75–79, 30 % for ages 80–84, 50 % for 85–89, 80 % for 95+) [25]. In the meantime, the size of the population aged 65 and older will continue to grow and is expected to peak at 39 million people in 2042. The proportion of adults aged 65 and older will continue to grow to approximately 40 % in 2060.

Japan's existing social security system was designed in the context of social norms and economic conditions of the 1970s, such as life-time employment among men supported by full-time house wives, high economic growth, and elder care that relied on co-residing family members in multigeneration households. In early 1990s, the economic bubble burst, and in a depressed economy, low fertility has become a major social issue. Clearly, the existing social security system would not be sustainable for the current Japanese society with low birthrates, reduced life-time employment opportunities, an economy that increasingly relies on more unstable or temporary jobs, and rapidly declining multigenerational households.

A series of reform discussions and proposals emerged, which led to the Comprehensive Reform of Social Security and Tax [33, 34], through which Japan initiated a series of attempts to reform the social security system and to secure financial resources. In 2012, the government enacted laws related to Comprehensive Reform of Social Security and Tax. One of these laws, the Social Security System Reform Promotion Law, specified fundamental principles and established the Social Security Reform National Committee consisting of 15 expert members. This Committee's report, submitted to Prime Minister Abe in August 2013, clarified the overall vision of social security system reforms for 2025 and addressed the needs of people at different life stages, including stable employment, child care support, reducing income inequality, and housing needs. The new social security systems would rely on each individual's "self-support," informal "mutual support" (e.g., grass-roots community services, volunteer activities, informal social support of families and friends), and support networks involving not-for-profit organizations. The report clarified the vision for integrating medical care and long-term supports and services as well as that for the community-based integrated care system, indicating the need for shifting emphasis from medical care to long-term supports and services, and from institutions (e.g., hospitals) to community-and home-based services. These guidelines assumed tax reform, specifically raising sales tax to finance medical and long-term care service reforms. The subsequent law of December 2013 set timelines for a series of reform items in the areas of child care support, medical and long-term care, and public pension systems, to be implemented over the next decade through 2025.

The core of the healthcare reform vision is the Community-Based Integrated Care System, which was first proposed in 2003 in a study group set up by the government, initiated in 2006 as part of the 2006 LTCI reform [35], and promoted further in 2012 and subsequent years [36]. The basic idea is that the existing medical, welfare, and long-term care systems will not be able to support the rapidly growing number of the oldest old in 2025 and thereafter. To establish a fundamentally different healthcare system, the whole community (i.e., the local government, professionals, and residents) needs to work together to integrate various services (e.g., housing, medical, caregiving, disease and disability prevention, and daily living support services) and develop a network to provide "community-based integrated care" that help people who want to remain independent in their own home and community as long as possible so that they can live a life with dignity until the very end. The "community" is defined in this context as a daily living area where needed services can be provided within 30 min when requested (or within a 30-min walking distance), more specifically, a middle-school district (or a primary school district in a metropolitan area), covering approximately 20,000 residents.

The Community-Based Integrated Care System involves several fundamental elements [25, 37]. First, housing is the fundamental basis for older adults. Housing can be older adults' own homes or residential care homes, but it should be in the community where older adults used to, or want to live. The second critical element is access to medical services in the community. This can be accomplished through outpatient visits or in-home medical services (e.g., physician house calls, home health nurse visits). Of particular importance is timely hospital discharge planning that involves multiple professionals (physicians, nurses, rehabilitation, and long-term care professionals, home helpers, care givers) so that older adults can live in a step-down medical facility, a rehabilitation facility, or in the community, without worries after leaving the hospital. The third element is access to long-term supports and services (e.g., day services, home care) when needed. Older adults, even those living alone with severe physical disabilities or cognitive impairment, should be able to receive needed care and continue to live in the home. Long-term care institutions (e.g., nursing homes) need to be integrated into the community. Fourth, the community-based integrated care center assesses older residents' needs, identifies the community's social resources, and coordinates supports and services for older adults. This center established in each "community" as defined above involves public health nurses, social workers, and care managers who work as a team. Fifth, older adults are conceptualized as providers as well as recipients of services. Older adults with reserved capacities are expected to participate in social activities and prevention programs to stay healthy, and play active roles as volunteers or members of community groups that support the integrated care system.

The community-based care system encourages older adults and their families to articulate their preferences of their life styles and to develop their plans for the last stage of their life, especially where and how they want to live and with whom. Building on essential daily life and welfare services that older adults need for community living (e.g., meal preparation, basic economic resources to purchase daily necessities), the community-based care system needs to develop three

essential services to be integrated: (1) medical and nursing services, (2) long-term care and rehabilitation, and (3) public health and prevention services. In particular, Japan puts special emphasis on public health prevention services (i.e., promoting physical activity and healthy eating to maintain functional abilities, chronic disease prevention) to minimize medical and long-term care needs among growing older populations. Since 2006, prevention services have been incorporated into long-term care insurance benefits (for older adults certified to have long-term care support needs) and community-based support services (for older adults who have not yet developed disabilities).

The conceptual framework of the community-based integrated care system serves as a common goal for all parties involved, especially municipalities and other local governments. Communities vary greatly in terms of available economic and social resources, the size and the proportion of older adults, and cultures. As long-term care insurers, municipalities are charged to plan and implement community-based integrated care systems that suit unique characteristics and resources of their communities. The Ministry of Health, Labor and Welfare mandates municipalities to conduct needs assessment and quantitative analysis of facility and personnel resources available in the communities, and to obtain an in-depth understanding of the needs and social resources availability in the community through qualitative data obtained from community care conferences (where professionals such as care managers, social workers, and public health nurses of the daily living community area meet at least once a month to discuss difficult cases and issues faced by the community, as mandated by the long-term care insurance law for each daily living area). The Ministry publicly shares on their website best practice examples of local initiatives to develop their own community-based integrated care systems to further promote this system throughout the country [36].

The government realizes that public resources are limited. Thus the community-based integrated care system assumes "self-support" (doing what you can do yourself, such as health management, and purchasing housekeeping and meal delivery services with personal resources) combined with "mutual support" (informal support, such as mutual help among neighbors, support from volunteers and non-profit organizations), "joint support" and "public support" (welfare services for older adults and the poor, elder abuse services, funded by general revenues).

Conclusion

Social institutions such as social security systems resist changes and lag behind rapidly changing demographic, social, or economic conditions [38]. As described above, Japan is trying its best to reduce such time lag by reforming the social security system towards 2025, the beginning of the peak aging society. Development of community-based integrated care systems throughout Japan is an example of such on-going social experiment efforts that global aging communities

should monitor. As the first country to experience the super-aging society, Japan provides a sneak preview of societal impact of population aging that other countries may face in the future. Japan learned a lot from other countries in developing their aging policies and should offer opportunities for other countries to learn from its lessons and experience.

Good news is that the trend of population aging is relatively easy to predict, given that countries usually know the size of the population born each year and when they become age 65 or 75. Japan's examples may inspire other countries to foresee the future and take necessary actions early enough so that the society is ready to meet the needs of aging populations in the future. This is especially important for rapidly aging countries including newly industrialized countries, such as China, Singapore, South Korea, Hong Kong, Taiwan, India, and Brazil.

Rapid population aging has coincided with the economic slow-down in Japan as in many other countries. This poses challenges and opportunities. The Ministry of Health and Welfare designated 2014 as Health and Prevention Year 1 [39]. And the Japanese government has adopted strategies to attain a healthy aging society, such as striving to promote the world's top-level provision of medical care, new health service development, innovative use of information and communication technology for high-quality, efficient healthcare provision, and the sharing of Japan's health technology with other countries [40]. Growing older populations will increase demand for drugs and products for treating aging-related diseases and improving the quality of late life, making Japan an attractive market for pharmaceutical products. Japan is reforming drug pricing policies to promote healthcare cost-effectiveness and innovation [41–46].

Innovative ideas and products are needed to support new cohorts of older people with fewer or no children and family members to rely on, people with dementia and their family, and end-of-life care. Also needed is collaboration among medical, public health, and long-term care professionals, including physicians, pharmacies, dentists and dental hygienists, rehabilitation professionals, nutritionists, direct care workers, caregivers, and older adults themselves. Direct care workers, such as home helpers, who interact with older adults, should be important parts of care teams. Community-based coordinated care will need to involve industries and talents that were not traditionally considered in medical and long-term care systems, such as electricians and gas companies, home deliverers, and convenience stores ubiquitous in Japan. In a society where close to 40 percent of people are 65 and older, like the one that is expected in Japan in 2055, older adults themselves are critical resources for developing community-based mutual support and coordinated care systems that fit unique characteristics of their own communities.

Many of the issues related to population aging discussed above are not unique to Japan; they are common issues faced by any aging societies, such as needs for multidisciplinary team work, barriers against adoption and maintenance of health promotion and prevention behaviors among older adults, challenges of medical and long-term care integration, increasing reliance on community resources, and slow

economic growth. While each country is unique in terms of cultural, historical, and political conditions, we should find common elements. It is crucial to promote global co-learning (or two-way learning) for developing innovative products, services, and systems to support healthy aging in communities.

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Part II
The Patient(s)

Old, Very Old and Frail

Jean-Pierre Baeyens

Abstract Becoming older is not easy in our society due to insufficient preparations for the geriatric population. Older persons are often excluded from the everyday lifestyle of society. Ageing becomes a solitary process. One issue is that drugs are mostly used by older persons, but these older persons are not included in clinical trials. While problems occur when people became frail, frailty can be reversed. Thus, the geriatric patient has to be approached differently from the adult patient.

Keywords Frailty · Oldest old people · Growing older · Geriatric patient

Introduction

Ageing already begins before birth. It has been proven that the age of the parents at the birth of the child is one of the determinants of the life expectancy of the offspring. The older the parents are, the shorter the life expectancy of the offspring [1].

Malnutrition (obesity or deficiencies in food or vitamins) will have a negative influence on life expectancy [2, 3]. Moreover, it is proven in several animal experiments that caloric restriction extends life expectancy. This is, of course unethical, to test in humans.

Ageing is not only a biological process but also a psychological process. Some older people feel young at heart and act younger, while others feel older early in life and act old.

1. Why the term "elderly" is banned

The term "elderly" is still frequently used, and apparently so in most languages. The term "elderly" is not only used in many newspapers and other media but also in peer-reviewed journals. Many older persons do not appreciate this word since it has

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S. Stegemann (ed.), *Developing Drug Products in an Aging Society*,
AAPS Advances in the Pharmaceutical Sciences Series 24,
DOI 10.1007/978-3-319-43099-7_4

a negative connotation. It focuses on the end of life, and by extension, on the exclusion of the older person from society, etc.

The General Assembly of the United Nations[1] (UN) decided in 1995 to recommend the usage of the word "older person" or "older people" instead of "elderly," for all languages. Using the word "older" insists on the comparison between "younger" and "older." A 30-year-old is older than a 20-year-old, and an 80-year-old is younger than a 90-year-old. The underlying idea is that as long as a person's age is compared with another person's age, one is not classified in the "elderly" group.

2. Who is old?

In 1890 Mr. Krupp[2] (Germany) decided to introduce a paid retirement for older people, implementing the range of what can be categorized as an older age. However, Mr. Krupp was afraid this measure would cost him dearly, and so he assigned his accountant to determine the right age for his workers to retire, in such a way that the cost incurred on his company would be as low as reasonably possible. His accountant calculated that using the age of 65 was safe—the life-expectancy of the average person, at that time, was only 46 years. Therefore, using the age 65 as the marker for "old" age has no scientific base; it has only an economic basis, originating more than hundred years ago.

In 1963, the United Nations introduced the age of 60 to define older age. At the same time, they realised that there was a rather large span between the ages 60 and 122, 122 being the highest age ever reached by a human being in France named Madame Calment. They decided to introduce the concepts of the 3rd Age (between 60 and 74) and the 4th Age (75 and older). The UN considered people of the 3rd Age to be still active and travelling, etc., and considered people of the 4th Age to be rather house-bound and more frequently dependent on others.

Fast forward 50 years, people in Western Europe, North America, and Australia are living 3 months longer, with every passing year. As a result, the 3rd Age has moved ten years (now between 70 and 84) and those of this age range are, nonetheless, still very active until the age of 84. Consequently, the 4th age has also been pushed ten years forward. To further elucidate on the arbitrary quality of the "older" age range, popular magazines for "older people" successfully increase their market share by claiming that their magazines are fit for people of 50 years and older.

To conclude, to define "old age" simply by using the patients' birthdate or his "calendar age," is inaccurate. We, geriatricians, never look at the "calendar age" of our patients, because it is dangerous to do so. Treatment decisions are based on the functionality of each person, and not based on the "calendar age" of our patients.

[1]Resolution General Assembly 50/141.

[2]https://www.dss.gov.au/sites/default/files/documents/06…/jun96.pdf.

3. Physiology of ageing

Modern theories about ageing are centred on the gradual diminution of the homeostasis of the ageing body. Reserve capacity diminishes gradually with ageing. The problem is that there are very important physiological differences that vary between individuals. The kidney function is an excellent example: the mean decrease of renal function is 50 % at 80 years. The differences between individuals, while excluding patients suffering from kidney disease, are very important; the function decrease varies between 20 and 80 % [4]. These same important differences among older individuals are seen in other organ systems, for instance the functional decrease in the pulmonary capacity.

There is more and more evidence that the decrease of this functional capacity depends on the activity level of each individual older person. Keeping a good activity level keeps functional capacity at a higher level.

4. Drug use by older people

One of the key issues in healthcare for oldest-old people is polypharmacy, which is currently a hot topic. Unfortunately, daily clinical practice has not changed, despite all the discussion. One in three hospital admissions of people of this age group is related to the use of medicines [5].

A primary issue is that Evidence-Based Medicine (EBM), with its fixed guidelines for each disease, leads to the prescription of many drugs, especially for patients who suffer from numerous chronic diseases. Clearly, the current standard medical practice is incompatible with the needs of older patients. These drugs often have contradictory effects, and the combination of all these drugs often induce adverse drug reactions (ADR). Some patients demonstrate poor compliance and only take a selection of the prescribed drugs, often a poor decision made without professional guidance. Geriatricians tackle this problem by prioritizing drugs; they reduce the number of drugs, only keeping the drugs which are essential for each individual patient. This is a difficult task, proving to be one of the more important skills of geriatricians.

A second issue is the total absence of drug testing in the oldest-old people [6], who typically have different pharmacodynamics and pharmacokinetics from patients in other age groups. Geriatric patients frequently have totally different reactions to drugs and drug combinations from the standard testing pool. The exclusion of frail patients in dedicated clinical trials is, in fact, a case of “elder abuse”!

5. The concept of “growing” older

In our modern society there is a tendency to regard ageing as a progressive decrease in capacities. Older people have to retire because they are no longer productive. This view is detrimental, not only for older people, but also for society as a whole. Older people are capable of doing more than travelling, dancing, making fun, and drinking whisky. Older people have a rich life experience. Decreasing organ function is compensated by new skills.

Importantly, it has been shown that physical, mental, and psychological inactivity increases the risk of involution of many functions, thereby increasing the risk of developing several diseases. A notorious example is early retirement, which increases the risk of developing Alzheimer's or Dementia [7–9].[3]

It is important to look at what improves with aging, not only at what is decreasing. Nowadays, many employers prefer older employees over younger ones for some specific jobs.

6. What is frailty?

In the last 15 years, the concept of frailty was developed and has spread. Fried [10] tried to standardize and validate a screening method and defined several criteria for this term: unintentional weight loss (5 kg in one year); self-reported exhaustion; weakness (grip strength); slow walking speed; and low physical activity.

These criteria allowed clinicians to divide patients into three groups: no frailty, intermediate frailty (1 or 2 criteria present) or frail (3 or more criteria present). Dr. Frieds' study demonstrated a major difference in mortality between the 3 groups: the possibility of 3-year mortality had rates of 3, 7 and 18 % respectively; 7-year-mortality was 12, 23 and 43 % respectively. The decreasing mobility (disability) after 3 years was 23, 40, and 51 % respectively; after 7 years, the rates were 41, 58, and 71 % respectively.

One conclusion of the study was that frailty is a physiological syndrome. It delineates frailty from comorbidity and disability. Frailty causes disability, independent of clinical and subclinical diseases. Frailty begins by affecting mobility tasks before causing difficulties with ADL.

Another method used to define frailty is the SOF index (Study of Osteoporotic Fractures) [11], which may be an easier method compared to the Fried's study and uses the following criteria: weight loss (≥ 5 % between two examinations), inability to rise from a chair (5 times without using the arms), poor energy (a NO answer on the question "Do you feel full of energy?"). There is frailty when two or three of these criteria are present. Simply put, if no criteria are present: ROBUST; if one component is present: INTERMEDIATE STAGE; if 2 or more component are present: FRAIL.

This SOF index looks easier to use in the daily practice of a General Practitioner (GP).

B.Vellas started a systematic screening of the older population in GP-practices. The patients suspected of frailty are sent to the G.F.C. (Geriatric Frailty Clinic) for assessment of frailty and prevention of disability. With this approach, it seems possible to increase life expectancy without disability [12].

[3]Delaying retirement may reduce Alzheimer's risk. Mayo clin Health Lett 2014, May, 32, 6, 4.

7. "The geriatric patient"

The definition of the geriatric patient was defined by the UEMS-Geriatric section (Union Européenne des Médecins Spécialistes) in Malta in 2006.[4]

The key words found in this definition are: polypathology, polypharmacy, frailty, and risk of losing functionality.

The most important part in the care for the geriatric patient has to be delivered by the GP and the multidisciplinary team at the home of the patient or at the replacement home (nursing homes are home-replacement facilities, not mini-hospitals). When the geriatric patient's functionality diminishes, ideally, the GP should refer this patient to the Geriatric Unit in the acute hospital or to the geriatric day-hospital, and not to an "organ specialist" in the hospital. A multidisciplinary team will take care of the patient. This team consists of a geriatrician, geriatric nurse, geriatric physiotherapist, occupational therapist, social worker, dietitian, speech therapist, and a psychologist. This team will perform a Comprehensive Geriatric Assessment. Treatment is adapted and rehabilitation is started from day one of admission.

This model is proven very effective since 1983 by Rubenstein [13], and later by many others, including the Cochrane library.

Rubenstein's study in 1983 was shocking; indeed, the mortality rate of geriatric patients treated in conventional medical units was twice that of those treated in acute geriatric units. The risk of placement in nursing homes was twice in conventional units and the functionality of patients was 2.5 times lower after treatment in conventional medical units in one year.

The total of the health-care expenses per patient per year was diminished by $2.500US, if passing through the acute geriatric unit.

With this knowledge, it is difficult to understand why there is not yet a geriatric department in every general hospital in the world (as is now the case in Belgium!). In fact, this lack of presence is a case of "elder abuse".

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Age and the Process of Aging

Paul A.F. Jansen

Abstract The epidemiological transition, with a rapid increase of the proportion of the global population aged over 65 years from 11 % in 2010 to 22 % in 2050 and about 32 % in 2100, represents a challenge for public health. More and more old persons have multimorbidities and are treated with a large number of medicines. In advanced age, the pharmacokinetics and pharmacodynamics of many drugs are altered. In addition, pharmacotherapy may be complicated by difficulties with obtaining drugs or adherence and persistence with drug regimens. Safe and effective pharmacotherapy remains one of the greatest challenges in geriatric medicine. In this chapter the process of aging is described and the influence of age on pharmacokinetics and pharmacodynamics is presented. Information needed for appropriate prescribing of medicines to older patients is provided.

Keywords Process of aging · Age-related pharmacokinetic changes · Age-related pharmacodynamic changes · Appropriate prescribing

Introduction

The worldwide population, within the age group 65 years and older, has increased rapidly in the last century and a further increase is expected. The proportion of the global population over 65 years old increases from 11 % in 2010 to 22 % in 2050 and about 32 % in 2100 [1, 2]. In Western Europe between 2010 and 2060, the number of people over 65 will grow from 17.4 to 29.5 % of the total population. The number of people over 80 will nearly triple to 12 % [3].

The aging of the world's population is the result of several factors: installation of sewers and improvement of portable water, improvement of quality of food and preservation of food, better housing, education, more attention for physical condition, and developments in medical sciences [4]. Prevention and treatment of

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S. Stegemann (ed.), *Developing Drug Products in an Aging Society*,
AAPS Advances in the Pharmaceutical Sciences Series 24,
DOI 10.1007/978-3-319-43099-7_5

infectious and cardiovascular diseases and development of anaesthesiology medicines and technics have, amongst others, contributed considerably to the increase in life expectancy. An epidemiological transition in the leading causes of death, from infectious disease and acute illness to noncommunicable chronic diseases and degenerative illnesses, is happening. Developed countries in North America, Europe, and the Western Pacific already underwent this transition, and other countries are at different stages of progression. The epidemiological transition, combined with the increasing number of older people, represents a challenge for public health. More and more old persons have multimorbidities and are treated with five medicines or more. In advanced age, the pharmacokinetics and pharmacodynamics of many drugs are altered. In addition, pharmacotherapy may be complicated by difficulties with obtaining drugs or complying with drug regimens. Safe and effective pharmacotherapy remains one of the greatest challenges in geriatric medicine. In this chapter, the process of aging is described, the influences of age on pharmacokinetics and pharmacodynamics are presented, as well as the information that is needed for health care professionals to prescribe appropriately.

The Process of Aging

Aging is intrinsically complex, being driven by multiple causal mechanisms [5]. Aging is the gradual, lifelong accumulation of subtle faults in the cells and organs of the body [6]. This tendency for faults to accumulate is countered by the action of an extensive array of error-preventing and error-correcting systems. However, maintenance and repair are costly. Although genes influence longevity, it has been shown that genes account for only about 25 % of the variance in human lifespan [7, 8]. Single-gene mutations with major effects on lifespan, as well as dietary restriction, appear to act via wholesale adjustment of metabolic investments in the hundreds of specific maintenance and repair pathways that collectively result in the aging of the organism, as manifest in the form of age-related frailty, disability, and disease [5].

The ‘disposable soma theory’ is in essence the investments in durability and maintenance of somatic (nonreproductive) tissues to be sufficient to keep the body in good repair [6]. The distinction between somatic and reproductive tissues is important because the reproductive cell lineage, or germ line, must be maintained at a level that preserves viability across the generations, whereas the soma needs only to support the survival of a single generation through the normal expectation of life in the wild environment, with some measure of reserve capacity.

Aging is a continuous process, starting early and developing gradually, instead of being a distinct phase that begins in middle to late life [6]. Damage to DNA is likely to play a role in the lifelong accumulation of molecular damage within cells, since damage to DNA can readily result in permanent alteration of the cell’s DNA sequence. Cells are subject to mutation all the time, both through errors that may become fixed when cells divide and as a result of reactive oxygen species, or free

radicals induced damage which can occur at any time. Oxidative damage is among the most important, accounting for large numbers of oxidative hits per cell per day [6].

In many human somatic tissues, a decline in cellular division capacity with age appears to be linked to the fact that the telomeres, which protect the ends of chromosomes, get progressively shorter as cells divide [9]. This is due to the absence of the enzyme telomerase, which is normally expressed only in germ cells (in testis and ovary) and in certain adult stem cells. Telomere shortening is greatly accelerated in cells with increased levels of stress. A growing body of evidence suggests that telomere length is linked with aging and mortality [10]. Not only do telomeres shorten with normal aging in several tissues (e.g., lymphocytes, vascular endothelial cells, kidney, liver), but also their reduction is more marked in certain disease states.

However, damage can also affect any of the macromolecules that make up the cell, as well as those that form extracellular structures such as cartilage and bone [6]. In particular, damage to protein molecules occurs to a considerable extent, and accumulation of faulty proteins contributes to important age-related disorders such as cataract, Parkinson's disease, and Alzheimer's disease.

At least five major elements contribute to the individuality of the human aging process: genes, nutrition, lifestyle (e.g., exercise), environment, and chance [6]. Poor environments may adversely affect an individual's opportunity to do the optimal things for healthy aging in terms of nutrition, lifestyle, etc. In particular, a poor environment can reinforce a tendency for the older person to suffer social isolation, which in turn can exacerbate psychological and physical deterioration. On the positive side, the understanding that we now have of the biological science of human aging supports the idea that the aging process is much more malleable than has hitherto been recognized. This opens the way to a range of interventions that may improve health in old age and extend quality life [6]. All in all, aging is best explained as the balance between investments in fitness and investments in body maintenance: if investment in body maintenance is not optimal, aging occurs.

Age-Related Changes in Physiological Function

The process of aging varies between people and even the decrease in function of different organs may vary within one person. In general, the highest level of, for example, muscle strength, bone density, and kidney function is reached at the age of 30 years. After this age, a gradual slow down will happen with diminishing of function of most organs. An accelerated decrement in muscle strength is seen in women above the age of 55 years, probably because of menopause [11]. After the age of 30 years glomerular filtration rate (GFR) will decrease in general by 1 ml/min/year. Therefore, a patient in his eighties has at mean a GFR of about 60–70 ml/min. However, the variability between older persons is very large. A validation study of GFR calculation methods in geriatric patients showed that all

methods, the modification of diet in renal disease (MDRD), chronic kidney disease-epidemiology (CKD-epi), and Cockcroft and Gault (CG), slightly overestimated GFR with few percentages [12]. In individual patients, however, large deviations from the values of the sinistrin clearance were found, as well as overestimating as underestimating kidney function up to 30 ml/min. Therefore, it is important to have a look at the muscle mass of an individual patient. The measurement of weight in relation to the height, hand-grip strength, walking velocity, and balance, measured for example with the Short Physical Performance Battery, gives a good impression of the functionality of a patient, and it is related to frailty, risk of falls, and life expectancy [13, 14]. Next to poor balance and falls, mental performance is also of importance. With increasing age, more and more patients suffer from dementia caused by Alzheimers disease and/or vascular dementia. This may have a large impact on the sensitivity for the effects and adverse effects of medicines and especially of lipophilic medicines, as most psychotropics. For appropriate prescribing the knowledge of changes in pharmacokinetics and dynamics in patients are therefore important.

Epidemiological studies in old persons may show changes of the effect of diseases. For example, the Leiden 85-plus study found that old persons with hypertension had a better life expectancy in comparison with persons without hypertension [15]. This may have consequences for prescribing drugs for primary or secondary prevention. However, it is possible that the effect of low blood pressure, for example, caused by end-stage heart failure, influences the results. Therefore, only randomized controlled trials may give an answer of it is worthwhile to treat, e.g., hypertension or hypercholesterolemia in patients over 80 years [16, 17]. However, participants recruited to clinical trials are likely to have been healthier than the general very elderly hypertensive population. In consequence, the applicability of the results to the wider elderly population has been questioned, so that uncertainty remains as to whether treatment benefits also extend to the frailer elderly people. A recent study showed no evidence of an interaction between treatment effect and frailty [18]. Both the frailer and the fitter older adults with hypertension appeared to gain from treatment.

Longitudinal aging studies may give many answers on the way the aging process happens and changes over time. Monitoring of the Framingham Study population since 1948 has led to the identification of the major cardiovascular disease risk factors—high blood pressure, high blood cholesterol, smoking, obesity, diabetes, and physical inactivity—as well as a great deal of valuable information on the effects of related factors such as blood triglyceride and HDL cholesterol levels, age, gender, and psychosocial issues [19]. New diseases, which have had little attention, become more important, as it is the case for heart failure with preserved ejection fraction in older patients [20]. The primary aim of Longitudinal Aging Study Amsterdam (LASA) has been to study the determinants, trajectories, and consequences of physical, cognitive, emotional, and social functioning in relation to aging [21]. One of the many results of the LASA study is that weight loss, due to social reasons, was not associated with mortality suggesting that not all unintentional weight loss is harmful. The increased mortality risk of other causes of

unintentional weight loss may be related to underlying disease. Intentional weight loss was not associated with mortality [22].

Age-Related Changes in Pharmacokinetics

With increasing age and because of change in body weight, several changes in pharmacokinetics are present in many elderly people. Especially, changes in volume of distribution and renal clearance (CL) are of clinical importance [23, 24].

Drug Absorption

Pharmacokinetic studies on the effect of aging on drug absorption and gastric emptying have provided conflicting results. Several studies have not shown age-related differences in absorption rates for different drugs [25–30]. The greatest age-related change in oral bioavailability and plasma concentrations is likely to occur with drugs that exhibit a significant first-pass effect (>80 %) [31]. For drugs absorbed by passive diffusion, there is low-grade evidence for age-related changes. In general, no adaptation of the dose is needed because of the aging process.

First-Pass Metabolism and Bioavailability

There is a reduction in first-pass metabolism with advancing age. This is probably due to a reduction in liver mass and, for high clearance drugs, the consequential reduction in blood flow. The bioavailability of drugs which undergo less-extensive first-pass metabolism, such as opioids, propranolol, verapamil, and metoclopramide, can be significantly increased in the elderly. For these drugs, a low start dose is adviced. By contrast, the first-pass activation of several pro-drugs, such as the angiotensin-converting enzyme (ACE) inhibitors enalapril and perindopril, might be slower or reduced [31]. However, this is not clinically relevant due to the chronic usage.

Drug Distribution in the Body

Significant changes in body composition occur with advancing age, such as a progressive reduction in the proportion of total body water and lean body mass. This results in a relative increase in body fat. Hydrophilic drugs tend to have smaller volume of distribution (V) resulting in higher serum levels in older people

(e.g., gentamicin, digoxin, lithium, and theophylline). The consequence may be that the loading dose should be chosen lower than in young adults. The reduction in *V* for water-soluble drugs tends to be balanced by a larger reduction in CL, with a smaller effect on elimination half-life ($t^1/_{2el}$). By contrast, lipophilic drugs (e.g., benzodiazepines, morphine, and amiodarone) have a lower water solubility so their *V* increases with age. The main effect of the increased *V* is a prolongation of half-life. Increased *V* and $t^1/_{2el}$ have been observed for drugs such as diazepam, thiopental, and lidocaine. The consequence is that older patients may have adverse effects, even days after cessation of the therapy [23].

Protein Binding

Acidic compounds (e.g., diazepam, phenytoin, warfarin, acetylsalicylic acid) bind mainly to albumin, whereas basic drugs (e.g., lidocaine, propranolol) bind to alpha-1 acid glycoprotein. Although no substantial age-related changes in the concentrations of both these proteins have been observed, albumin is commonly reduced in persons with malnutrition, cachexia, or acute illness, whereas alpha-1 acid glycoprotein is increased during acute illness. The main factor which determines the drug effect is the free (unbound) concentration of the drug. Although plasma protein binding changes might theoretically contribute to drug interactions or physiological effects for drugs that are highly protein-bound, its clinical relevance is limited for most of the drugs [32]. However, for some medicines, e.g., phenytoin, drug effects may enhance and more ADR could be seen with low albumin concentrations [33].

Drug Clearance

Liver

Drug clearance by the liver depends on the capacity of the liver to extract the drug from the blood passing through the organ (hepatic extraction ratio) and hepatic blood flow. Drugs can be classified into three groups according to their extraction ratio (*E*): high ($E > 0.7$, such as dextropropoxyphene, lidocaine, pethidine, and propranolol), intermediate (*E* 0.3–0.7, such as acetylsalicylic acid, codeine, morphine, and triazolam), and low extraction ratio ($E < 0.3$, such as carbamazepine, diazepam, phenytoin, theophylline, and warfarin). When *E* is high, the clearance is rate-limited by blood flow. When *E* is low, changes in blood flow produce little changes in clearance. Therefore, the reduction in liver blood flow with aging mainly affects the clearance of drugs with a high extraction ratio. Of importance is also the reduction in liver volume up to as much as 30 % across the adult age range. This results in a reduction in clearance of a similar magnitude [34]. Several studies have

shown significant age-related reductions in the clearance of many drugs metabolized by phase-1 pathways in the liver. These involve reactions such as oxidation and reduction. The amount of total cytochrome P 450-metabolizing enzymes (CYP) is decreased in patients over 70 years of age with about 30 % [35]. By contrast, phase-2 pathways (e.g., glucuronidation) do not seem to be significantly affected with the exception of morphine [36, 37]. However, in general the reduction in hepatic clearance is not of clinical relevance and dose reduction is not needed.

Kidney

The age-related reduction in GFR affects the clearance of many drugs such as water-soluble antibiotics, diuretics, digoxin, water-soluble beta-blockers, lithium, non-steroidal anti-inflammatory drugs, and newer anticoagulant drugs like dabigatran and rivaroxaban. The clinical importance of such reductions of renal excretion is dependent on the likely toxicity of the drug. Drugs with a narrow therapeutic index like aminoglycoside antibiotics, digoxin, and lithium are likely to have serious adverse effects if they accumulate only marginally more than intended. In elderly patients the serum creatinine may be within the reference limits, while renal function is markedly diminished. Estimation of the creatinine clearance or GFR with the CG, the MDRD, or the CKD-epi equations may be helpful. However, these methods are not yet validated very well in frail elderly patients, and therefore one should be careful when using these equations [38–40]. The study of Drenth et al. in 16 geriatric patients, with a mean age of 82 years (range 71–87), showed that, on average, all formulas slightly overestimated GFR: CG +0.05 (95 % CI −28 to +28) ml/min/1.73 m^2, CG with ideal body weight (IBW) +0.03 (95 % CI −20 to +20), MDRD +9 (95 % CI −16 to +34) ml/min/1.73 m^2; and CKD-EPI +5 (95 % CI −20 to +29) ml/min/1.73 m^2. In individual patients, there were, however, large deviations [12]. The formulas classified kidney disease correctly in 69 % (CG), 75 % (CG with IBW), 44 % (MDRD), and 69 % (CKD-EPI) of the participants, respectively. A list of drugs whose dosage should be adjusted in case of decreased renal function is presented in Table 1.

Age-Related Changes in Pharmacodynamics

Studies of drug sensitivity require measurement of concentrations of drug in plasma, as well as measurement of drug effects. Pharmacodynamics are determined by concentrations of the drug at the receptor, drug–receptor interactions (variations in receptor number, receptor affinity, second messenger response, and cellular response), and homeostatic regulation. Few data are available on pharmacodynamic differences in very old persons [41]. Some important pharmacodynamic age-related changes are illustrated in Table 2.

Table 1 Adjustment of dosage in renal insufficiency [24]

Ace inhibitors	Decreased renal function and dose adjustment
Benazepril	Clcr 10–30 ml/min: start with 2.5–5 mg once daily. Adjust dosage based on effect
Captopril	Clcr 10–30 ml/min: start with 12.5–25 mg once daily. Adjust dosage based on effect until 75–100 mg/day
Cilazapril	Clcr 10–30 ml/min: start with max. 0.5 mg/day. Adjust dosage based on effect until max. 2.5 mg/day
Enalapril	Clcr 10–30 ml/min: start with max. 5 mg/day. Adjust dosage based on effect until max. 10 mg/day
Lisinopril	Clcr 10–30 ml/min: start with max. 5 mg/day. Adjust dosage based on effect until max. 40 mg/day
Perindopril	Clcr 30–50 ml/min: max. 2 mg/day; Clcr 10–30 ml/min: max. 2 mg every two days
Quinapril	Clcr 30–50 ml/min: start with 5 mg/day; Clcr 10–30 ml/min: start with 2.5 mg/day. Adjust dosage based on effect
Ramipril	Clcr 20–50 ml/min: start with max. 1.25 mg/day. Adjust dosage based on effect
	Clcr 10–20 ml/min: insufficient data for sound advise
Trandolapril	Clcr 10–30 ml/min: start with max. 0.5 mg/day. Adjust dosage based on effect until max. 2 mg/day
Zofenopril	Clcr 10–50 ml/min: start with max. 7.5 mg/day. Adjust dosage based on effect until max. 15 mg/day
Antibiotics	
Cefalosporins	
Cefalexine	Clcr 10–50 ml/min: prolong interval to once per every 12 h
Cefalotine	Clcr 50–80 ml/min 2 g every 6 h; 30–50 ml/min 1.5 g every 6 h; 10–30 ml/min 1 g every 8 h
Cefamandol	Clcr 50–80 ml/min 2 g every 6 h, in case of life-threatening infection 1.5 g every 4 h
	Clcr 30–50 ml/min 2 g every 8 h, in case of life-threatening infection 1.5 g every 6 h
	Clcr 10–30 ml/min 1.25 g every 6 h, in case of life-threatening infection 1 g every 6 h
Cefazoline	Clcr 30–50 ml/min: 500 mg every 12 h; 10–30 ml/min: 500 mg every 24 h
Cefradine	Clcr <30 ml/min: contra-indicated
Ceftazidim	Clcr 30–50 ml/min: 1 g every 12 h; 10–30 ml min: 1 g every 24 h

(continued)

Table 1 (continued)

Ace inhibitors	Decreased renal function and dose adjustment
Ceftibuten	Clcr 30–50 ml/min: 200 mg every 24 h; 10–30 ml/min: 100 mg every 24 h
Cefuroxim parenteral	Clcr 10–30 ml/min: standard dosage every 12 h
Fluoroquinolones	
Ciprofloxacin	Clcr 10–30 ml/min: 50 % of normal dosage
Levofloxacin; ofloxacin	Clcr 30–50 ml/min: 50 % of normal dosage; Clcr 10–30 ml/min: 25 % of normal dosage
Norfloxacin	Clcr 10–30 ml/min: prolong interval to once every 24 h
Nitrofurantoin	
Nitrofurantoin	Clcr <50: contra-indicated. Risk of neuropathy and failure of therapy
Macrolide	
Clarithromycin	Clcr 10–30 ml/min: 50 % of normal dosage with normal dose frequency
Penicillins	
Amoxicillin/clavulanate	Clcr 10–30 ml/min: standard dosage every 12 h (orally, i.v. of.im.)
Benzylpenicillin	Clcr 10–30 ml/min: dosage dependent of indication. Consider intended effect, risks of overdosage and underdosage
Piperacillin	Clcr 30–50 ml/min: max. 12 g per day in 3 or 4 doses; Clcr 10–30 ml/min: max. 8 g per day in 2 doses
Piperacillin/tazobactam	Clcr 30–50 ml/min: piperacillin/tazobactam 12 g/1.5g per day in 3 or 4 doses Clcr 10–30 ml/min: piperacillin 4 g/0.5 g every 12 h
Tetracyclines	
Tetracycline	Clcr 10–30 ml/min: maintenance dosage 250 mg once daily
Antidiabetics	
Metformin	Clcr 30–50 ml/min: start with twice daily 500 mg; Clcr 10 to <30 ml/min: contra-indicated
Sulfonylurea (ex. Tolbutamid)	Clcr <50 ml/min start with half the dosage
Antihistaminics	
Acrivastin	Clcr 10–50 ml/min: 50 % of normal dosage OR prolong interval to 1–2 × per day
Cetirizine/Levocetirizine/Hydroxyzine/ Fexofenadine/Terfenadine	Clcr 10–50 ml/min: 50 % of normal dosage

(continued)

Table 1 (continued)

Ace inhibitors	Decreased renal function and dose adjustment
Antimycotics	
Fluconazole	In case of >once daily dosing regimen: Clcr 10–50 ml/min: normal starting dosage, decrease maintenance dosage until 50 % of normal dosage
Flucytosine	Clcr 30–50 ml/min: prolong interval to once every 12 h, then based on serum plasma concentration
	Clcr 10–30 ml/min: prolong interval to once every 24 h, then based on serum plasma concentration
Terbinafine	Clcr 10–50 ml/min: 50 % of normal dosage
Antiparkinson drugs	
Pramipexole	Clcr 30–50 ml/min: start with 0.125 mg (=0.088 base) twice daily, then based on effect/adverse events
	Clcr 10–30 ml/min: start with 0.125 mg (=0.088 base) once daily, then based on effect/adverse events
Antithrombotics	
Dabigatran	Clcr <30 ml/min: contra-indicated
Eptifibatide	Clcr 10–50 ml/min: normal starting dosage, then 50 % of normal dosage
Tirofiban	Clcr 10–30 ml/min: 50 % of normal dosage
Antiviral medication	
Acyclovir orally	Decrease dosage used for herpes zoster treatment: Clcr 10–30 ml/min: 800 mg 3 times a day
Amantadine	Start with 200 mg, maintenance dosage: Clcr 50–80 ml/min: 100 mg once daily
	Clcr 30–50 ml/min: 100 mg every 2 dayen; Clcr 10–30 ml/min 100 mg every 3 dayen@@@
Cidofovir	Clcr <50 ml/min: preferably do not use
Famciclovir	Clcr 30–50 ml/min: normal dosage every 24 h; 10–30 ml/min: 50 % of normal dosage every 24 h
Foscarnet	Clcr 30–80 ml/min: dosage according to schedule manufacturer; <30 ml/min: do not use
Ganciclovir	INDUCTION: Clcr 50–80 ml/min: 50 % of normal dosage every 12 h; 30–50 ml/min: 50 % of normal dosage every 24 h; 10–30 ml/min: 25 % of normal dosage every 24 h

(continued)

Table 1 (continued)

Ace inhibitors	Decreased renal function and dose adjustment
	MAINTENANCE: Clcr 50–80 ml/min: 50 % of normal dosage every 24 h; 30–50 ml/min: 25 % of normal dosage every 24 h; 10–30 ml/min: 12.5 % of normal dosage every 24 h
Oseltamivir	Clcr 10–30 ml/min: 50 % of normal dosage OR normal dosage but double interval
Ribavirine	Clcr 10–50 ml/min: dosage based on hemoglobin concentration
Valacyclovir	Clcr 10–80 ml/min: adjust dosage according to schedule manufacturer
Valganciclovir	Clcr 30–50 ml/min: 50 % of normal dosage plus double interval
	Clcr 10–30 ml/min: 50 % of normal dosage twice a week
Beta-receptor-blocking drugs	
Acebutolol; Atenolol	Clcr 10–30 ml/min: 50 % of normal dosage
Bisoprolol	Clcr 10–20 ml/min: start with 50 % of normal dosage. Then max. 10 mg/day
Sotalol	Clcr 30–50 ml/min: max 160 mg/day; Clcr 10–30 ml/min: max. 80 mg/day
Calcium antagonists, dihydropyridine type	
Barnidipine	Clcr <50 ml/min: contra-indicated
Digoxin	
Digoxin	Clcr 10–50 ml/min: decrease initial dosage by 50 %, then go to 0.125 mg/day. Next adjust dosage based on clinical symptoms
DMARDs	
Anakinra	Clcr <30 ml/min: contra-indicated
Methotrexate	Clcr 40–70 ml/min: 50 % of normal dosage. Clcr <40 ml/min: based on serum plasma concentration
Gout medication	
Allopurinol	Clcr 50–80 ml/min: 300 mg/day; 30–50 ml/min: 200 mg/day; 10–30 ml/min: 100 mg/day
Benzbromarone	Clcr <30 ml/min: contra-indicated
Colchicine	Clcr 10–50 ml/min: 0.5 mg/day
H2-antagonists	
Nizatidine; cimetidine; famotidine; ranitidine	Clcr 10–30 ml/min: 50 % of normal dosage, once daily
Hypnotics, sedative agents, anxiolytic drugs, antipsychotics	
Chloral hydrate	Clcr <50 ml/min: preferably do not use
Meprobamate	Clcr 10–50 ml/min: 50 % of normal dosage OR double dosage interval

(continued)

Table 1 (continued)

Ace inhibitors	Decreased renal function and dose adjustment
Risperidone	Clcr 10–50 ml/min: 50 % of normal dosage, then based on effect and adverse events
Muscle relaxants	
Baclofen	Clcr 10–50 ml/min: start with 5 mg once daily, then adjust based on effect and adverse events
Tizanidine	Clcr 10–30 ml/min: start with 2 mg once daily, then increase dosage slowly based on effect and adverse events. End with increasing the dose frequency
NSAIDs	All NSAID's: Clcr <30 ml/min: consider if chronic use is indicated. Check renal function previously to and 1 week after start
OPIOIDs	
Morphine	Clcr 10–50 ml/min: dosage based on effect and adverse events. Be alert to accumulation of M6G
Tramadol	Clcr 10–30 ml/min: decrease dose frequency to 2–3 × per day In case of retard tablet max. 200 mg per day
Ethambutol	Clcr 10–50 ml/min: 50 % of normal dosage
Vertigo medication	
Piracetam	Clcr 30–50 ml/min: 50 % of normal dosage; Clcr 10–30 ml/min: 25 % of normal dosage
Xanthine derivates	
Pentoxifylline	Clcr 30–50 ml/min: 400 mg twice daily; Clcr 10–30 ml/min: 400 mg once daily

Calculate the creatinine clearance or GFR (http://nephron.com/cgi-bin/CGSI.cgi). For Crcl <10 ml/min consult the nefrologist

Table 2 Selected pharmacodynamic changes with aging

Drug	Pharmacodynamic effect	Age-related change
Antipsychotics	Sedation, extrapyramidal symptoms	Increased
Benzodiazepines	Sedation, postural sway	Increased
Beta-agonists	Bronchodilatation	Decreased
Beta-blocking agents	Antihypertensive effects	Decreased
Vitamin K-antagonists	Anticoagulant effects	Increased
Furosemide	Peak diuretic response	Decreased
Morphine	Analgesic effects, sedation	Increased
Propofol Verapamil	Anesthetic effect Antihypertensive effect	Increased Increased

Anticoagulants

A number of studies have shown that the frequency of bleeding events associated with anticoagulants therapy and response to warfarin increase with age [41, 42]. There is evidence of a greater inhibition of synthesis of activated vitamin K-dependent clotting factors at similar plasma concentrations of warfarin in elderly compared to young patients. If vitamin K-antagonists (VKAs) are monitored carefully, age in itself is not a contraindication for treatment and, as presented in an Italian study in the very old, the VKAs have acceptable low rates of bleeding incidents [43]. Concerning the new anticoagulants, edoxaban, dabigatran, rivaroxaban and apixaban, prescribers should be aware of the differences between well-controlled trials and daily practice, especially concerning adverse drug events (ADEs). If prescribed to the elderly, appropriate doses should be used [44].

Cardiovascular Drugs

Calcium Channel Blockers

Although elderly subjects are less sensitive to the effects of verapamil on cardiac conduction, older people do show a greater drop in blood pressure and heart rate in response to a given dose of verapamil [41]. This might be explained by an increased sensitivity to the negative inotropic and vasodilatating effects of verapamil, as well as diminished baroreceptor sensitivity. Diltiazem also shows age-related changes in metabolism, but these changes do not appear to affect blood pressure or heart rate response [45]. The administration of diltiazem as a bolus injection causes greater prolongation of the PR interval (dromotropic effect) in young than in elderly subjects [23].

Dihydropyridines initially have a greater effect on blood pressure in elderly persons, possibly due to an age-related decrease in baroreceptor response. The greater effect may be transient and disappears in about 3 months [41].

Beta-Blocking Agents

Reduced β-adrenoreceptor function is observed in advanced age. Both β-agonist and β-antagonist show reduced responses with age [41]. This is secondary to impaired β-receptor function due to variations in receptor confirmation, alterations in binding affinity to the guanine nucleotide subunit (G_s), or receptor downregulation. The total number of receptors seems to be maintained but the post-receptor events are changed because of alterations of the intracellular environment. The responsiveness of α-adrenoreceptors is preserved with advancing age.

Central Nervous System-Active Drugs

Many drugs affecting the central nervous system (CNS) cause an exaggerated response in older persons. Elderly patients are particularly vulnerable to adverse effects of antipsychotics, such as extrapyramidal motor disturbances, arrhythmias, and postural hypotension. Agents with anticholinergic effects can also impair cognition and orientation in patients with a cholinergic deficit such as those with Alzheimer's disease. Advanced age is also associated with increased sensitivity to the CNS effects of benzodiazepines. Postural sway is increased and patients are more likely to lose their balance after triazolam administration [46]. The sedative effects of midazolam are much stronger with the regular given dose [47]. The exact mechanisms responsible for the increased sensitivity to these drugs with aging are unknown. However, drugs may penetrate the CNS more readily with advancing age. For example, functional activity of the P-glycoprotein efflux pump in the blood–brain barrier is reduced by aging [48]. Reported differences for the benzodiazepines could be due to differences in drug distribution to the CNS.

Anesthetic agents generally show an increase in sensitivity in the elderly. For example, propofol sensitivity increases with age [49]. Neuromuscular blockers do not show increased sensitivity, and lower dosing requirements are primarily due to altered pharmacokinetics [49]. Sensitivity of opioids increases by about 50 % in elderly individuals [50, 51].

Variability in Response to Medicines

Older people display considerable variability in responses to medicines, as well as beneficial effects as adverse effects [52]. Patients may benefit from antipsychotics for delirium and behavioral and psychological symptoms in dementia. Many other antipsychotics do not show benefit, but do have adverse effects [53]. About half of the patients treated with haloperidol suffer extrapyramidal motor disturbances, independent from daily dosage or serum haloperidol concentration [54]. A change in pharmacogenetic factors was not present. Another example is the variable response on anticoagulants. VKAs are associated with a significant risk of adverse outcomes leading to hospitalization in older people. Age, weight, and genotype account of pharmacokinetic (CYP2C9) and pharmacodynamic (VKORC1) determinants account for about 60 % of the variability in warfarin dose requirements [55–57]. The variability in drug response is multifactorial and the consequence of changes in organ function, body composition, post-receptor response, homeostatic reserve, and comorbid disease [58, 59]. Also, pharmacogenetic factors may play a role. Frailty is increasingly recognized as a phenotype that is predictive of adverse health outcomes in older people [60]. Inflammation associated with frailty has the

potential to significantly alter drug transporter and metabolizing enzyme expression contributing to variability in drug clearance [61]. Changes in gene expression involve a very small fraction of genes [62]. All in all, the variabilities in responses to medicines are unlikely to have a strong pharmacogenic component [62].

Information Needed for Appropriate Prescribing to Older Patients

Since in the pre-authorization phase older people are often excluded from clinical trials [63–67], the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH), a committee of the drug regulatory authorities and the pharmaceutical industry of Europe, Japan, and the United States, developed a guideline for studies involving older individuals, focusing, from a legislative point of view, on what investigations should be carried out in older people, and what information should be reported in the pre-authorization dossier of a new medicinal product [68]. Even though the guideline is not mandatory, a sponsor or pharmaceutical industry has to provide authorities with convincing reasons why it is not following these recommendations. This ICH E7 guideline, adopted in 1994, has been updated by the questions and answers document in 2010 [69]. The ICH E7 guideline, however, might not reflect the needs of healthcare professionals in clinical practice. The study of Beers et al. showed that information about age-related differences in adverse events, locomotor effects, drug-disease interactions, dosing instructions, and most respondents considered information about the proportion of included 65+ patients necessary. Clinicians considered information significantly more important than the nonclinical respondents about the inclusion of 75+, time-until-benefit in older people, anticholinergic effects, drug–disease interactions, and convenience of use [70]. The EMA's Committee for Medicinal Products for Human use (CHMP) has established a Geriatric Expert Group, to provide scientific advice on issues related to the elderly. An European Geriatric Medicine Strategy is launched in 2011 [71]. Information is available on www.ema.europa.eu. In the Netherlands the Expertise center Pharmacotherapy in Old Persons is raised to improve effective and as safe as possible pharmacotherapy (www.ephor.eu). Adequate information is critical for optimal patient-individualized drug use. Recently, the Geriatric Expert Group has discussed about information of crucial importance when considering the use of medicinal products in geriatric patients. Table 3 shows which information in my opinion should be available in the pre-authorization phase to provide prescribers information for appropriate prescribing to older patients. If the information is not present it should be gathered as soon as possible in the post-authorization phase.

Table 3 Information needed for appropriate prescribing of medicines to older patients

1. What is the number of patients included ≥65 year?
2. What is the number of patients included ≥75 year?
3. What is the number of patients included ≥85 year?
4. Are >100 persons included over 65 year in diseases also present in the elderly?
5. Is the majority of database ≥65 year in diseases characteristically associated with aging?
6. Are the patients included in the studies reasonably representative of the older population suffering from the disease/condition?
7. Are subjects excluded based on age, if so what is the reason?
8. Are subjects excluded on base of comorbidities, if so which comorbidities and what is the reason?
9. Are subjects excluded with comedication, if so which comedication and what is the reason?
10. Is a post-authorization efficacy study in older patients planned?
11. Is a post-authorization safety study in older patients planned?
12. Is a single-dose PK study in subjects >65 year available?
13. Is a single-dose PK study in subjects >75 year available?
14. Is a multiple-dose PK study in subjects >65 year available?
15. Is a multiple-dose PK study in subjects >75 year available?
16. Is drug accumulation to be expected and to what extent?
17. Is the PK studied in renal dysfunction?
18. Is the drug metabolized with a high extraction ratio?
19. Is the drug metabolized via CYP 450?
20. Is the drug depended of drug transporters like PgP?
21. Has the drug a narrow therapeutic dose range?
22. Are there clinical relevant drug–drug interactions?
23. Are there important drug–disease interactions?
24. Are there age-related differences in efficacy?
25. Are there age-related differences in dose-response?
26. Is the time-to benefit (TTB) of the drug of importance, if so is the TTB calculated in the elderly?
27. Are there age-related differences in adverse effects?
28. Have the drug anticholinergic effects, if so to what extent?
29. Does this drug increase the risk of delirium, if so to what extent?
30. Does this drug increase the risk of dizziness, if so to what extent?
31. Does this drug increase the risk of falls, if so to what extent?
32. Have the drug sedative effects, if so to what extent?
33. Have the drug orthostatic effects, if so to what extent?
34. Have the drug effects on the locomotor system, if so to what extent?
35. Have the drug effects on haemostasis, if so to what extent?
36. Have the drug effects on food intake, if so to what extent?
37. Are effects of quality of life studied in patients >65 year
38. Is the drug intake studied in older persons? (e.g., package, easy to swallow)
39. Are any medication errors, e.g., with respect to dose mistakes, studied?
40. Are clear instructions for older persons present in the Patient Information leaflet?

Conclusion

Older persons have a significantly higher disease burden compared with younger adults, and they consume almost half of total drug expenditures. Because of the aging process, the changes in pharmacokinetics and pharmacodynamics with aging, and the increase risk for ADRs, there is a need for more clinical and observational studies in the elderly. By improving the information in the pre-authorization phase and, if the information is not present, to get it as soon as possible in the post-authorization phase, prescribers get the opportunity to prescribe more appropriate to older patients.

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Comprehensive Geriatric Assessment

Jacob Blumenthal and Steven R. Gambert

Abstract Caring for the older person is perhaps one of the most challenging tasks in clinical medicine. In addition to normal age-related changes that affect function and physiological response, certain age-prevalent diseases also accumulate. This may lead to even the most experienced clinician being surprised by the often atypical and nonspecific presentation of illness. Although a comprehensive geriatric assessment may be time- and labor-intensive, thoughtful screening is nonetheless crucial to assess an elderly person's functional ability, physical health, cognitive and mental health, and socio-environmental situation.

Keywords Geriatric · Assessment · Screening · Function

Geriatric care is perhaps one of the most challenging tasks we face in clinical medicine. Not only do older persons have normal age-related changes that affect function and physiological response but also they are more likely to have certain age-prevalent diseases that increase in incidence with each passing year. Of particular concern is the often atypical and nonspecific presentation of illness confounding even the most astute clinician when a specific diagnosis is made, given the paucity of suggestive symptoms and signs of a particular illness.

Never is it more essential for the clinician to recognize the importance of multidimensional assessment that includes not only medical issues but also areas of mental health and cognition, functional status, social support, environment, and economics. While geriatric care has long involved the use of a team of experts to assess individual aspects of the older person's health and function, due to lack of financial support for ancillary services to aid in multidimensional assessment, physicians have increasingly been faced with doing Geriatric Assessments as a way to screen for a variety of key factors that help determine the older person's ability to

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S. Stegemann (ed.), *Developing Drug Products in an Aging Society*,
AAPS Advances in the Pharmaceutical Sciences Series 24,
DOI 10.1007/978-3-319-43099-7_6

function independently and maintain as high a quality of life as possible. Problems identified on screening can then be further evaluated in more depth by specific testing or referral to specialists.

It is beyond the scope of this chapter to include all available assessment instruments and areas possible for testing. The authors have chosen those methods they believe are most useful and practical to the clinician and topics of major concern.

A Comprehensive Geriatric Assessment can be quite time-consuming; therefore the clinician needs to determinate whether a screening test is sufficient in the absence of a particular problem or concern that is raised in history-taking (or diagnostic test) or if a more in-depth evaluation is necessary. Depending on the goal of the assessment, one might be willing to accept a test with a relatively high sensitivity even if the specificity is not that high. Additional testing will rule in or out the diagnosis once the clinician is aware that a problem may exist through initial screening.

In order for the Comprehensive Geriatric Assessment to be worth the effort, it is important to first determine which individuals are most in need and thus exclude persons who are either too ill or too well to benefit from this often time-intensive process. A Comprehensive Geriatric Assessment is a **multidimensional process** done by either an experienced clinician or a team of multidisciplinary professionals. It is designed to assess an elderly person's functional ability, physical health, cognitive and mental health, and socio-environmental situation.

The following factors increase the likelihood of benefit from a Comprehensive Geriatric Assessment:
Advanced age

- Medical comorbidities including cancer, arthritis, neurological disorders, and cardiac disease among others.
- Use of four or more medications or use of antipsychotic/antianxiety, anticholinergic, or sedative/sleeping medications.
- Psychosocial problems including depression, past history of mental health issues, and/or isolation.
- Geriatric Syndromes including Dementia, Frailty, Urinary Incontinence, Falls, Dependency in Activities of Daily Living.
- Multiple recent admissions to the hospital, or frequent use of the Emergency Room.
- Identified need for more assistance and potential for relocation to a nursing home/assisted living situation.
- The following is a list of potential areas that can usually be assessed by taking a comprehensive history. A variety of clinical tools and standardized assessment instruments are also available to assist in information gathering.
- History of current symptoms and illnesses and their impact on daily function.
- Use of Medications, both prescribed and over-the-counter including vitamins, supplements, and nutritional aids.
- Past medical history including any surgeries.

- Recent and impending life changes including occupation, social network, family.
- Overall functional status including use of walking aids and driving history.
- Living situation and environment and appropriateness to function and future needs.
- Family situation and available on-going or periodic support.
- Caregiver status and need if applicable.
- Measure of cognition and emotional health.
- Assessment of mobility/gait, balance and fall history/risk.
- Rehabilitation needs and potential.
- Social habits including use of alcohol, tobacco, illicit drugs and sexual practices.
- Nutritional status and needs.
- Use of health promotion measures, including on-going medical care, health screening, and immunization history.

Ten Target Areas for Geriatric Screening[1]

Recognizing the need to limit what is done in a routine Geriatric Screening, the American College of Physicians identified the following 10 areas that yield the most benefit when assessing the older individual:

1. Vision
2. Hearing
3. Upper extremity function
4. Lower extremity function
5. Continence
6. Mental function
7. Instrumental activities of daily living
8. Basic activities of daily living
9. Environmental hazards
10. Social Supports

Perhaps nowhere in medicine is a focus on function more important. While various distinct disease states may exist, each with their own impact on health and quality of life, specific functional loss in the elderly is not always determined by a specific disease state or system that the disease resides in. Urinary incontinence, for example, may not indicate disease confined to the urinary tract. In certain circumstances, this single factor may overwhelm the ability of caretakers to provide a safe environment and lead to placement in a nursing facility. With better functional ability or support services, however, that same person might be able to remain at

[1]American College of Physicians Subcommittee on Aging; each area to be evaluated by direct questioning or by requesting the person to perform a simple task [1].

home. Functional assessment can help the clinician focus on capabilities and services that can be provided to maximize function and quality of life. Considering medical illnesses in isolation is not enough; it is essential to determine how one or more medical problems affect the older person's function and ability to be as independent as possible. Medical, social, and psychological problems need to be considered. While every problem that is identified may not be "curable," the goal is to provide treatment and support as necessary to enhance the older person's quality of life and to allow them to live as independently as possible within the constraints of their illness and limitations. Whether it involves providing a specific medication or helping to arrange for additional support, adaptive device, or additional diagnostic test, a geriatric assessment is a logical starting point.

A clear, complete problem-oriented problem list is essential. This should include not only signs and symptoms as based on history and medical diagnoses that are known, but also functional categories that will guide treatment and future planning. Not all persons with the same medical diagnosis, for example, are affected similarly. Arthritis may be present in two individuals; one cannot ambulate and has problems feeding oneself while the other is able to lead an independent existence.

A multitude of assessment instruments have been developed and validated for use. While each attempts to provide information upon which to categorize a specific disorder, it is important to know their reliability. The sensitivity and specificity of each instrument may help determine its usefulness in ruling in or out a specific problem. In general, a test with a high sensitivity but a lower specificity will cause the clinician to not overlook patients with problems though will rely on additional testing to better define if a specific problem actually exists. The latter test will need to have a high specificity. Some instruments require a significant degree of training in their use, making them less acceptable in practice. Longer assessment instruments are not necessarily better. The best assessment instrument is one that can be easily used, completed by the patient him/herself, and if possible, completed before seeing the clinician.

While an exhaustive review of all assessment modalities and instruments is beyond the scope of this chapter, we will discuss major functional domains common to the older person that play a key role in quality of life and discuss assessment instruments that may provide a useful starting point in individualized assessment.

Functional Assessment

It is important to determine just how well an older person is able to function in their environment. While studies have shown that chronic diseases are common in older persons with over two-thirds reporting at least one chronic health condition, only one-third of older persons report significant limitation in their daily activities. It is important to take into account the older person's expectations and lifestyle as not

everyone has the same goals. In order to begin to categorize function, two areas have been identified, **Activities of Daily Living** (ADL's) and **Instrumental Activities of Daily Living** (IADL's). The four basic ADL's include mobility, toileting, transferring, and feeding and are usually classified in one of the following ways: "independent," "requires some assistance," or "dependent." These functions are key to independent living. IADL's are those aspects of care that represent more complex activities. These are more easily assisted with and while important, not as essential to basic health needs. These include bathing, dressing, shopping, using a telephone, preparing meals, and managing money [2].

There are a number of other aspects of function that can be categorized.

Events of Daily Living: additional information regarding significant factors in a person's life or family that may influence their health status or environment.
Demands of Daily Living: essential activities that an older person must do either because of an inner wish to do so or because of a family or societal requirement.
Environment of Daily Living: describes one's physical environment, whether stairs must be climbed or other difficult factors that may play a role in future independence.
Values and Beliefs in Daily Living: refers to those factors that may influence one's choices, such as acceptance of transfusions, wishes concerning resuscitation, intubation, etc.

As stated previously, chronic illness is common in the elderly and, by definition, not curable. A focus on functional ability provides a framework upon which to demonstrate a change in status, whether better or worse and brings to bear resources to help promote a more independent and high quality living situation. One's ability to conduct their ADL's independently has been inversely correlated with mortality. The ability to independently conduct one's IADL's also has been inversely correlated with mortality and also has been used as a prognostic sign for the development of dementia. Whereas older persons who were able to do all five IADL's of traveling, shopping, meal preparation, housework and handling of money had a mortality rate of only 2 % within the next year, those persons who were incapable of doing any of these activities independently had a mortality rate of 27 %.

While ADL's classically include feeding, transferring, mobility and toileting, **The Katz Index of ADL** [3] includes aspects of both IADL and ADL function including one's ability to bath, dress, toilet, and transfer from bed or chair, as well as level of continence, and ability to feed. The Katz Index of ADL was first published in 1963 and provided a framework for assessing one's ability to live independently and to define what areas may need assistance with. Individuals are scored along a three-point scale as "independent," "semi-independent" (needs part-time assistance) or "dependent."

The Barthel Index [4] is another assessment instrument that can be used to assess an individual's ability to conduct self-care and has been modified to simplify ease of use. There are 15 measures on the Modified Barthel Index form. Items include ability to drink from a cup/feed from a dish; dress upper body; dress lower

body; don brace or prosthesis; grooming; wash or bathe; bladder incontinence; bowel incontinence; care of perineum/clothing at toilet; transfer from chair; transfer from toilet; transfer tub or shower; walk on level ground 50 yards or more; maneuver up and down stars for one flight or more; use wheelchair for 50 yards (if not able to walk). Items are scored Independent: Intact or Limited and Dependent: Helper or Null. Persons scoring less than 60 on the modified Barthel Index were shown to be able to perform no more than 10 of the defined ADL and IADL tasks. A score of less than 60 was also associated with the need for assistance in bathing, feeding, grooming, dressing, toileting, transferring, doing housework, and preparing meals.

The Five-item Instrumental Activities of Daily Living Screening Questionnaire assesses shopping, meal preparation, housework, handling money, and travel [5]. This is in contrast to the **Hebrew Rehabilitation Center for Aged Vulnerability Index** [6]. In this latter assessment, questions focus on meal preparation; taking out garbage; performing housework; negotiating stairs; use of a walker, cane or wheelchair; time spent outside; ability to dress; and a self-rating of how significantly illness interferes with chosen activities.

Information obtained may not accurately reflect the older person's abilities. Studies have reported that patients more commonly overrate their level of functioning and families more commonly underrate them. Certain tests have been developed that use direct observation of function. **The Performance Test of ADL** [7] uses props to test the older person's ability to function in a variety of tasks including drinking from a cup, lifting food on a spoon to the mouth, making a telephone call, brushing teeth, and telling time.

The clinician should also be able to assess their older patient's ability to ambulate. Not only has walking speed been associated with mortality with 0.8 m/s being the level below which increased mortality and frailty begin to be defined, but also with increased fall risk. The **Tinetti Timed Performance Test** [8] assesses the ability to walk 10 ft out and back "as quickly as possible." A time of greater than 11 s has been associated with increased risk of falling. Three [3] **Chair Stands** in a time greater than 10 s has also been associated with reduced physical functioning. A **Functional Reach** of less than 7 in. has been associated with an increased inability to leave the neighborhood, stand on one foot and do tandem walking. The odds ratio of more than two falls within the next 6 months is 8.1 if one is unable to reach safely, 4.0 if one is able to safely reach less than or equal to 6 in. and 2.0 if one is able to reach safely is between 6 and 10 in. The **Tinetti Balance Assessment Tool** [9] is also an accepted instrument to assess fall risk. Individuals are assessed for balance and gait. The individual begins the test in a seated position on an armless chair and is observed rising from the chair and standing. Eyes are at first open and then closed and the individual is "nudged" to assess their balance. The individual must turn 360° and then sit down again. The gait section measures step length and height, foot clearance, step symmetry and step continuity. The body trunk is observed for "sway" and walking time is measured.

Fall Assessment

It is essential to recognize a person's increased risk of falling given the significant consequences that may result. One common assessment tool is the **Morse Fall Scale** [10]. This is a rapid and simple method of assessing a patient's likelihood of falling and has been widely accepted in ambulatory and well as acute and long-term care settings.

1. History of falling: immediate or within the past 3 months
2. Secondary diagnoses
3. Use of Ambulatory aid(s): Bed rest/nurse assist; crutches/cane/walker; furniture
4. IV/Heparin Lock
5. Gait/Transferring: Normal/bed rest/immobile; weak; impaired
6. Mental status: oriented to own ability; forgets limitations

Items are scored as follows:un

- History of falling: A score of 25 is assigned if the patient has fallen during the present hospital admission or if there was an immediate history of falling. If the patient has not fallen, 0 points are assigned.
- Secondary Diagnoses: Fifteen points are assigned if there is more than one medical diagnosis and 0 points if not.
- Ambulatory aids: If the individual walks without a walking aid, even if assisted by another individual, uses a wheelchair or is at bed rest, 0 points are assigned. If the individual uses crutches, a cane, or a walker, 15 points are assigned; 30 points are assigned if the patient ambulates holding onto furniture for support.
- Intravenous therapy: 20 points are assigned if there is an intravenous or heparin lock inserted and 0 if not.
- Mental Status: 15 points are assigned if an individual overestimates or forgets his/her limitations.
- Individuals with scores between 0 and 24 are deemed at low risk. Scores of 25–44 signify medium risk and scores of greater than 45 imply a High Fall Risk.

Incontinence

Although there are many causes of urinary incontinence, most classify incontinence as either being due to stress, overflow, urge or physical/psychological. Many older persons deny that there is a problem believing that incontinence is a sign of normal aging. The American Geriatrics Society suggests screening for urinary incontinence by asking if there have been more than 5 episodes of urinary incontinence in the past year. A number of more specific questionnaires have been developed to screen for various types of urinary incontinence [11].

Nutrition

Many older persons are significantly malnourished, and evaluation of nutritional status should be part of a standard evaluation. In addition to asking about weight, patients should be routinely serially weighed. In particular, (especially involuntary) weight loss has been associated with a twofold increased relative risk of mortality over 2 years [12]. The following screening tools have also been used as predictors of problems.

Weight (kg)/Height (m^2) calculates a BMI or Body Mass Index. Measurements less than 19 or greater than 30 are significantly abnormal and deserve attention.

The **Mini Nutritional Assessment** (MNA) [13] uses 6 items to assess one's risk of malnutrition and has been widely accepted for its validity and ease of use.

1. Has food intake declined over the past 3 months due to loss of appetite, digestive problems, chewing or swallowing difficulties?
   0 = severe; 1 = moderate; 2 = no decrease
2. Weight loss during the last 3 months?
   0 = weight loss greater than 3 kg; 1 = does not know; 2 weight loss between 1 and 3 kg; 3 = no weight loss
3. Mobility
   0 = bed or chair bound; 1 = able to get out of bed/chair but does not go out 3 = goes out
4. Has suffered psychological stress or acute disease in the past 3 months?
   0 = yes; 2 = no
5. Neuropsychological problems
   0 = severe dementia or depression; 1 = mild dementia; 2 = no psychological problems
6. Body Mass Index (BMI)
   0 = <19; 1 = 19–21; 2 = 21–23; 3 = >23 OR Calf circumference in cm. 0 = <31 cm; 3 = 31 cm or greater

Screening Score (maximum 14 points):

12–14: Normal nutritional status
8–11: At risk of malnutrition
0–7: Malnourished

Finally, environmental (understood broadly to include not only physical environment, but also larger psychosocial one) and personal experience factors are crucial as well. These too need to be assessed in a systematic and rigorous manner. For example: one who lives remotely may not have easy access to public transportation, or in certain social strata a man may have never learned to cook. Attempting to assess or remedy functional deficits must be done while keeping these factors in mind, simultaneously.

Cognitive Assessment

Cognitive problems are all-too-common in the elderly. Increasing in frequency with age, these problems will only grow as the proportion (and number) of the population in the older age groups increases. Furthermore, they are both significant sources of morbidity and negatively impact quality of life. Although the need for increased time/effort to learn and recall new information with advancing age is commonly recognized, and has been demonstrated in both longitudinal and cross-sectional studies of aging individuals, healthy persons are largely able to well-compensate these mild deficits, often without deliberate conscious adaptive behaviors.

When purposeful compensation is needed, a "line" is crossed, and the Diagnostic and Statistical Manual (DSM)-V categorizes these individuals as having "neurocognitive disorder" (previously "*dementia*"). Although with tremendous individual variation, *mild neurocognitive disorder* requires compensatory strategies/accommodations (noticed by the patient, a close contact or evident through objective testing), reflecting "modest" cognitive decline, but not interfering with one's "capacity for independence in everyday activities"; however, when the impairment(s) reach this threshold, and one's function is impacted, it becomes a "*major neurocognitive disorder*" (formerly referred to as "dementia"). These more general groups of neurocognitive dysfunctions may be further subdivided based on specific etiologies—Vascular, Alzheimer's Disease, frontotemporal, HIV infection, Huntington's disease, Lewy bodies, Parkinson's disease, prion disease, traumatic brain injury, or other/multiple etiologies [14]. It is important to note, that, by definition, the decline cannot be wholly due to delirium or another mental disorder. In addition, the modifier "with behavioral disturbance" may be added. These are particularly troubling (both to the patient and caregiver), and are a major reason for institutionalization.

Delirium, on the other hand, is defined by transient, global cerebral dysfunction, with clear disturbances in (either directing, focusing, sustaining or shifting) attention or orientation as well as change in another cognitive domain (language, memory, perception) not better accounted for another neurocognitive disorder, and not occurring in the context of a severely reduced level of arousal. Although occasionally more insidious/protracted in its recognition/resolution, it is usually marked by both a rapid onset (hours–days) and fluctuating course (usually during a given day).

Depression is also exceedingly common among older individuals, although its presentation may be different from the manifestations seen in younger patients [15]. All-too-frequently, older persons may minimize their feelings of sadness, instead, they voice vague complaints of memory problems, confusion or pain. Compounding this is that a variety of other medical conditions common among older individuals often are associated with symptoms such as low energy/fatigue, anorexia or sleep problems.

All of these issues are exceedingly common and have profound implications extending far beyond individual patients. It is the hope that by identifying those with cognitive problems while the symptoms are mild, earlier interventions may be made, with the potential of slowing (or preventing) progression. In fact, interventions thus far identified are only effective at earlier stages; although a number of interventions focused on behavioral manifestations have shown promise in more advanced disease. In particular, a variety of risk factors for delirium have been identified. These can be subdivided into fundamental and precipitating factors. In her seminal papers, Inouye identified a number of independent baseline risk factors which increased the relative risk for delirium: preexisting cognitive impairment, dehydration, vision impairment, and severe illness. These further allowed risk stratification for subsequent death or nursing home placement [16]. In subsequent work, she developed a predictive model including five precipitating factors: physical restraints, the addition of three or more medications, bladder catheter, any iatrogenic event or malnutrition which significantly increased the risk of delirium. Furthermore, the contributions of baseline and precipitating factors were all independent and progressively increased risk for delirium in a cumulative fashion [17]. As practitioners will readily recognize, these predisposing factors are all-too-common, and this framework has since been validated in a variety of settings. Other common precipitating factors include infections, cardiovascular events, or metabolic abnormalities.

Nonetheless, a recent United States Preventative Services Task Force systematic review found insufficient evidence to recommend either for or against screening for Cognitive Impairment in Older Adults [18]. That being said, certainly among patients with cognitive complaints, a standardized, reproducible assessment is important, and certainly (especially in the case of delirium) serial evaluations are crucial.

Screening, Evaluation, and Differential Diagnosis

As intimated, formal "screening" for cognitive impairment remains an open question. Nonetheless, remaining alert to its possibility—particularly during functional screening (that has been shown to predict not only disability, but also nursing home placement and mortality)—is crucial. Similarly, one must remain mindful that neurocognitive disorders (formerly "dementia") are persistent clinical syndromes that involve multiple areas of neurocognitive function, and when questions are raised some evaluation must be pursued.

Careful history taking, supplemented by objective cognitive assessments, are the cornerstones of effective diagnosis. Certainly, routinely asking about both memory and cognitive problems as well as functional status should be part of periodic screening among (especially older) individuals. However, most important is close observation and the presence of an informant who knows not only the patient's baseline but also has observed the patient closely over time. This is particularly

crucial when the potential of dementia exists. Other aspects of the history—in particular the family and social history—are important as well. Although the inheritance patterns of most forms of dementia remain poorly defined, there are some notable exceptions, and our understanding of the genetics constantly evolving. Similarly, reviewing exposures often yields potential contributors—some of which may be continuing and modifiable (i.e., alcohol and other medications or environmental intoxicants).

There exist a number of brief screening instruments that can detect cognitive difficulties, and a variety of objective measures are used widely. Although with some differences, and necessarily fairly crude, they are very valuable in screening (particularly at population levels), "case-finding" in the appropriate clinical scenario, as well as following patients over time. Commonly assessed areas include: orientation, concentration and memory, visual spatial as well as executive function. Instruments in widespread use include:

Folstein Mini-Mental State Examination (MMSE) is the classic screen/assessment tool including measures of Orientation, Registration, Concentration, Recall, Naming, Repetition, language, as well as visuospatial skills and ability to follow a 3-step command. Perhaps the best-studied instrument, it has very good sensitivity and specificity (on the order of 90 %) [19].

However, because of copyright issues, it has somewhat been replaced by either the **Montreal Cognitive Assessment** (http://www.mocatest.org), or **Saint Louis University Mental Status Evaluation** (http://medschool.sluedu/agingsuccessfully/pdfsurveys/slumsexam_05.pdf) [20, 21]. These instruments assess orientation, recall, attention, naming, executive function as well as (either): repetition, verbal fluency, abstraction, and visuospatial (in the case of the former); or calculation in the case of the latter. Relatedly, the **Mini-Cog** (http://geriatrics.uthscsa.edu/tools/MINICog.pdf) utilizes three-item recall and clock drawing to assess recall, executive function and visuospatial abilities. All of these measures have very good sensitivity and specificity in a variety of settings, although the relative advantages/disadvantages in particular populations is beyond the scope of this review.

Screening for delirium, in particular, has been an active area of research. Commonly used measures (many of which may be administered by nurses at the bedside) include, perhaps most notably, the **Confusion Assessment Method for the ICU [CAM-ICU]** (http://www.icudelirium.org/docs/CAM_ICU_training.pdf) which defines the presence of delirium when there is both: (1) an acute change in or fluctuating course of mental status, (2) in attention, and (3) either an altered level of consciousness *or* disorganized thinking. The **NEECHAM confusion scale** in addition to a variety of "cognitive" measures (including attention/alertness, orientation/memory, as well as verbal and motor command) also assesses two additional domains: "behavior" (focusing verbal manifestations, appearance and sensorimotor performance) and "physiologic" (examining urinary continence, vital signs, and oxygenation). Similarly, the **Intensive Care Delirium Screening Checklist (ICDSC)** (http://www.icudelirium.org/docs/2013-Tufts-ICU-Delirium-Screening-Checklist.pdf) also is a bedside scale reflecting: level of consciousness, attention, orientation, psychomotor symptoms, hallucination/delusion/psychosis,

inappropriate speech/mood, sleep/wake cycle disturbance, as well as fluctuating symptoms [22, 23].

As intimated, these two (often related) conditions frequently co-migrate. Nonetheless, distinguishing (or noting the presence of both) is very important, with implications for treatment. In particular, differentiating delirium from dementia is crucial, as the former, by definition, is transient, precipitated by an external factor, and thereby potentially modifiable). A useful mnemonic for the latter is "DELIRIOUS" (Drugs, Electrolyte disturbances, Lines/Restraints, Infection, Renal/Hepatic, Intracranial process, Urinary/fecal retention, Oxygen/Hypercarbia, Surgery—particular unplanned)

A helpful schema is depicted below.

	Onset	Course	Attention	Movements	Hallucinations
Delirium	Sudden	Fluctuating	Disordered	Involuntary ones common	Commonly visual
Dementia	Insidious	Stable	Normal until very late	Absent	Often absent

Similarly, because depression and dementia may contribute to each other and all-too-often are seen together, screening for affective problems appears reasonable when cognitive (or functional) concerns have been raised. Two well-validated screening instruments in common usage are the: **Center for Epidemiologic Studies-Depression Scale** (CES-D; http://www.depression-help-resource.com/cesd-depression-test.pdf) [24] and **Geriatric Depression Scale** (GDS; http://psychology-tools.com/geriatric-depression-scale/) [25, 26]. Both of these (existing in various forms) are self-reports of various depressive symptoms, and have been validated in a number of populations and settings [27]. For the busy clinical practice, an abbreviated five-item version has been developed [28].

"Are you basically satisfied with your life?"
"Do you often get bored?"
"Do you often feel helpless?"
"Do you prefer to stay at home rather than going out and doing new things?"
"Do you feel pretty worthless the way you are now?"

Positive answers for depression screening are "no" to the first question and "yes" to the other questions, and a cut point score of 2 or greater has very good sensitivity and specificity.

It must be noted, however, both that the validity of the GDS as a screening tool among demented individuals has been questioned, and that a recent systematic review by the USPSTF found benefit in depression screening only when it was accompanied by substantial staff assistance and support [29].

Nonetheless, neuropsychiatric symptoms are exceedingly common (particularly among those with neurocognitive disorders, and important prognostic factors. In particular, behavioral symptoms are troubling to caregivers and a major reason for nursing home placement. For these reasons, systematically assessing these does

seem reasonable. In particular, Cummings et al.'s Neuropsychiatric Inventory (NPI) is a validated instrument (administered to caregivers of dementia patients) used widely among varied groups, including cognitively intact populations (who score extremely low), suggesting that this also well-distinguishes between healthy and demented individuals [30, 31]. 12 sub-domains (agitation/aggression, anxiety, apathy, appetite/eating abnormalities, disinhibition, delusions, dysphoria, euphoria, hallucinations, irritability/lability, motor symptoms and nighttime behaviors) are assessed both for the severity of the symptoms and the degree of distress caregivers experience due to them.

Although cognitive problems are increasingly common with age, they should not be viewed as an inevitable component of so-called "normal aging" and a thorough search for contributing factors should always be pursued. The intricacy of various types/etiologies (often multiple!) of dementia, and their evaluation is beyond the scope of this work; and the interested reader is directed to Neuropsychiatric texts for discussion of this. That being said, by far the most common "type" of dementia is so-called Alzheimer's disease dementia, the diagnosis of which has been formalized (most recently by a National Institute on Aging-Alzheimer's Association workgroup). By definition, dementia is diagnosed when there are cognitive or neuropsychiatric symptoms that both *interfere with and represent a decline from previous functioning* (the former distinguishing major from minor neurocognitive disorders), and are not explained by delirium or major psychiatric disorder [32]. Thus, some assessment of functional abilities (see above) must be pursued in order to differentiate these related conditions. Nonetheless, a reasonable approach to one with neurocognitive complaints, after a history (as outlined above), physical exam (with particular attention to neurologic signs suggesting focal/characteristic deficits), includes laboratory testing (commonly: metabolic assessments—including Folate and Vitamin D—as well as those of thyroid functioning, both a CBC and urinalysis, as well as screening for other infectious etiologies—including HIV and syphilis). Some would include other markers of inflammation (CRP, homocysteine), although these are less well-validated. Similarly, the inclusion of neuroimaging is controversial. Its use should be based on the clinical scenario, and potential to modify treatment.

In this way, a rigorous, comprehensive assessment of an older individual's functional status—including both physical and mental abilities, as well as environment can help optimize quality of life.

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Patients' Clinical Characteristics, Disease Experience, and Perception

Sven Stegemann

Abstract The increasing life expectancy and longevity is gradually shifting the characteristics of the patients toward patient populations with higher age, multimorbidity, and functional impairments. While independently managed drug therapy will remain the cornerstone of healthcare provision, the challenges that patients face with the increasing complexity of their health as well as therapy need to be considered during the development of a new drug product. Understanding the clinical, as well as personal experience and needs of patient populations and integrate these into the drug product development process must be considered as an important quality aspect of a new drug product. An integrated product and patient approach in the treatment of multimorbidity aiming for reduced therapeutic complexity, patient acceptability, and product usability will further support patient safety and effectiveness.

Keywords Multimorbidity · Polypharmacy · Older patients · Disease perception · Disease experience

Introduction

The concept of an acute or chronic disease is based on the fact that an underlying physiological deviation has occurred on molecular, cellular, or organ level. Identifying this deviation in order to develop therapeutic approaches through pharmaceutical or medical interventions against the specific disease or disease condition has generated an enormous array of medicines for the treatment of the majority of diseases. Along with the early and effective diagnostic and therapeutic intervention as well as increasing wealth, human premature mortality has significantly decreased while life expectancy

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S. Stegemann (ed.), *Developing Drug Products in an Aging Society*,
AAPS Advances in the Pharmaceutical Sciences Series 24,
DOI 10.1007/978-3-319-43099-7_7

grew every year by about three additional month of lifetime. This additional lifetime gain is not accompanied by a later onset of chronic conditions [46]; the increasing longevity is rather achieved despite the occurrence of complex disease patterns and multimorbidity [77]. The increasing age of the patients is further associated with an increasing prevalence of impaired physical and sensory functioning, frailty, dementia, sarcopenia, cachexia, and other age-related health issues. Due to naturally occurring resilience, older patients are able to adjust to these age-related life conditions and maintain their independence until late life. Nevertheless, this evolution toward longevity will continue to insidious change the patient populations and lead to a variety of distinct patient characteristics. These patient characteristics will span from the clinical patterns to the personal patterns of the patient requiring a more holistic therapeutic approach to achieve the desired health outcomes as well as wellbeing of the patient. In order to reach this objective, new therapeutic interventions and medicinal products will have to be developed with the characteristics of the targeted patients in mind. This chapter intends to provide insight into the characteristics of future patient populations with regard to their clinical expressions as well as the patient's experience and perception of the clinical conditions and the respective drug therapy.

Multimorbidity

With the unchanged and even earlier occurrence of chronic diseases during lifetime, longevity is incrementally associated with an increasing number of chronic diseases and disabilities [23]. There is general consensus that the occurrence of any second or more additional chronic diseases is termed multimorbidity [38, 48]. Since there is evidence that certain chronic diseases have a high likelihood to be associated with another specific disease and form distinct disease clusters, such associations between certain diseases is termed comorbidity [70]. Multimorbidity is accompanied with a high prevalence for functional impairment [11, 67] and might further develop into disability and frailty [25].

Multimorbidity can develop across all age groups with a significantly increasing prevalence with higher age [59, 70]. In addition to age, differences in the occurrence of multimorbidity have been shown for gender, ethnicity, and socioeconomic status [59, 72]. The occurrence of multimorbidity is present in low, middle, and high-income countries in a similar way even though the prevalence for the acute and chronic diseases might differ [3, 76]. The major chronic diseases are hypertension, heart disease, arthritis, disorders of lipid metabolism, diabetes, and dementia [60].

The prevalence for multimorbidity varies from the healthcare setting. One study found the highest prevalence with 82 % in nursing homes, 56–72 % in community-dwelling individuals and 22 % in hospital settings [60]. Dependent on the methodology and definition of multimorbidity in the studies, the reported prevalence for community-dwelling people aged 65 years and older ranged from 52 to over 90 % [21, 47, 72] and more than 99 % in patients with history of hospitalization in a geriatric ward [16]. For the community-dwelling older adults, the

majority of studies found a prevalence for multimorbidity between 70 and 90 % suggesting that on average more than 4 in 5 people aged 65 years and older show patterns of multimorbidity [1, 5, 70]. Analysis have provided evidence that multimorbidity appears as distinct clusters of patients with a common set of comorbidities. The major clusters reported are the cardiovascular and metabolic cluster, the psychiatric-substance abuse cluster, and the mechanical-obesity-thyroidal cluster [16, 52, 54]. A recent study also provided evidence that the physiological aging across multiple organ systems starts to deviate already in young age. This longitudinal study identified individuals in the young population that developed already during their midlife stages declining cognitive functions, had worse perceived self-health and looked older compared to other young individuals aging much slower along the life span [8].

Further progress has been made in the past years to understand the underlying molecular disease networks that are related to the comorbidities observed [17]. Phenotypic and genotypic disease networks have been investigated based on several thousands of patient data sets revealing the association between different nodes involved in different, closely related diseases [34, 44]. Additional research will most likely provide more evidence in the coming years on the individual process of aging and multimorbidity allowing for better prevention and targeted intervention.

Multimorbidity is associated with an increasing number of functional impairment that are required for the execution of the daily tasks like getting up from a chair, climbing stairs without resting, reaching or extending arms above shoulder level, pulling or pushing large, lifting or carrying some kilogram of weight, and picking up a small coin from a table. While 60–90 year-old persons with no disease had less than one physical functioning difficulty raising only slightly after 90 years of age. In contrast to this, each additional chronic disease was associated with another physical functioning deficit. In the age group of 70–79 years physical functioning impairment were on average 0.89, 1.72, 2.57, and 3.85 for no disease, one, two, and three diseases respectively. Within the different diseases, cognitive impairments, stroke, pulmonary diseases, and arthritis showed much higher rates of physical functioning difficulties than other chronic diseases [67]. Multimorbidity has therefore been found to be the highest risk factor for the development of long-term care dependency [41].

With the increasing longevity, specific age-related diseases will continue to increase in clinical practice.

Cancer is the leading cause for death in the population aged 40–79 years and the second leading cause for death in the 80 years and older in the USA. The data showed that 1,665,540 cancer cases occurred in 2014 in the USA of which 585,720 patients died [61]. Between 1975 and 2009 the 5 years survival rate increased by 19–22 % [61]. These advances in cancer therapy increases the number of long-term cancer survivors which is expected to be 32.5 million people worldwide and 13.7 million people in the USA in 2014 [31]. Long-term cancer survivors and patients with a cancer history represent a distinct patient population with specific health needs as they suffer from the long-term effects of the cancer therapy. Long-term cancer survivors have been found to self-report fair or poor health, have

psychological disabilities, limitations in daily tasks, and issues in working and social activities [31, 33]. With the incidence declining slightly in male and remaining stable in female, the demographic change will further increase the total number of cancer cases in the coming years [61].

Dementia including Alzheimer's disease is expected to have a twofold increase every 20 years. In 2010 there were 36 million cases of dementia. With an annual increase of 7.7 million new cases every year it is expected that in 2050 we will be reaching 115.4 million cases worldwide [18, 66]. Despite intensive research investments to better understand the pathology of dementia, the development of therapeutic interventions has been disappointing until today. The Alzheimer's Association is expecting that unless break through therapies will reach the market, caregiving to dementia patients will remain the standard intervention over the coming years [2].

Impact of Age on Health and Daily Functioning

The higher age of the future patient population will also affect physical and cognitive domains that are today not directly considered or described as disease, but will have a significant impact on the individuals daily functioning and quality of life [11, 67].

Older people often show a senescence associated inflammatory process that is still poorly understood [42, 58]. Higher inflammatory markers have been found in patients with cardiovascular diseases [30], in multimorbidity and correlating with the number of morbidity conditions [20], older people with low grip strength [14, 73] and obese people with higher heart rate [43]. The chronic inflammation markers have been associated with negative effects on neuroplasticity [51] and psychomotor speed [50]. However, it remains unclear if the low-grade inflammatory markers is causing or regulating aging and disease processes or are just the response to another underlying pathological mechanism [37].

With increasing age about 7 % of older people are at risk to develop a frailty syndrome that clinically manifests in vulnerability, declining reserves, and functions of multiple physiologic systems. Frail patients suffered from sarcopenia, unintentional weight loss, low energy, grip strength, walking speed, and physical activities [24]. Even though, frailty, disability, and co-morbidity share common characteristics of increasing dependency, they are distinctive clinical conditions [25]. Drug therapy to frail patients might requires reconsideration of the pharmacotherapy and potential adaptation [28]. Sarcopenia and cachexia are important concomitant conditions in patients with chronic illnesses that are being recognized since the late 1980s as a serious health issue in older adults [24]. Sarcopenia and frailty are conditions that have an important negative effect on the quality of life of the concerned older patients associated with a rapid decline in physical functioning and an increased risk for falls and hospitalization [57]. However, until today

therapeutic interventions to treat these conditions are still limited even though several approaches have been made during the past years [12, 13, 74].

Recent findings suggested that every second older adult show signs of dehydration [9, 62]. Dehydration is mainly caused by a lack of water intake leading to reduced body water (hypertonic dehydration) or in some cases caused by salt losses due to diarrhea, vomiting, or bleeding (hypotonic water loss). There are several reasons for dehydration such as morbidity, motoric and mobility impairments, incontinence, dysphagia, poor taste as well as thirst sensation and social isolation. Similar to dehydration, older adults have a high prevalence to be malnourished. The prevalence for malnutrition is dependent of age and the healthcare setting and can affect up to every second older adult. Malnutrition can have several root causes of which dysphagia, polypharmacy, cognitive impairments, recent hospitalization, meals-on-wheels, loneliness, poor perceived health, and a general loss in appetite seem to be the most important ones [26, 36].

Older patients are affected by sensory impairments that are important for daily life activities and independent living. A steep increase is visual impairments and blindness becomes evident at an age of 70 years and older with a further significant increase after 80 years [40]. Impaired vision also occurs as a comorbidity in diabetes patients affecting 56.3 % of patients with type 1 diabetes and 25.3 % with type 2 diabetes within 12 years of the disease onset [45]. In a similar fashion hearing losses are affecting 50–80 % of people 70 years and older [35]. Age-related hearing impairments are mainly caused by age-related decline in the neuronal encoding of the acoustic stimuli and speech recognition [27, 75].

Additional health issues associated with an increasing age are the development of chronic pain affecting daily activities, mood, and cognition and is occurring in nearly two-third of the patients 65 years and older [55]. Immobility and urinary incontinence affect 89 and 80 % respectively and cognitive decline, dementia, and delirium are present in 30 % [16].

These declining functional and health conditions are counterbalance to a substantial extent by resilience. Resilience is the ability of human being to cope with and adapt to changing life and environmental conditions or traumatic situations in order to maintain the control over the personal self and life. Longitudinal studies in 70 years and older people demonstrated wellbeing as a relatively stable condition along the life span despite the increasing occurrence of morbidity and functional impairments [65]. Another longitudinal study showed that higher level of resilience was positively correlated with social and physical functioning and negatively with depressive disorders [63]. Another study showed that older individuals who lost the spouse were coping well with the situation and made the required adjustments to their life. Even though bereavement is a very stressful event, the majority of older people seem to accept the new situation and adapt rather quickly to the widowhood [10].

Patients' Perception, Self-care, and Health Care Management

From a healthcare professional's standpoint, the diagnostic and prognostic data provide the baseline for the rational prescription of medicines to the patient and the monitoring of the disease management and progression. As logic as this procedure is, it underestimates the patients' view on the disease, the symptoms, and the consequences for the personal life. Poor acceptance of the disease and the therapeutic intervention might often be caused by patients focus on disease symptoms and adverse drug reaction of the therapy that interferes with the well-being and daily functioning.

Investigation into patient perceived and self-reported chronic conditions and the medically diagnosed chronic conditions revealed substantial discrepancies [29, 32, 39, 49, 64, 68]. Patients seems to judge a disease based on the symptoms they experience like pain, activity limitations, and depression rather than the disease conditions itself [49]. Symptoms that have been found to cause significant burden to 75 years and older, multimorbid patients were pain, lack of energy, dry mouth, poor vision, and depressive symptoms [19]. Diseases with a high disease burden like Parkinson's disease, diabetes, hip fracture, thyroid dysfunction and stroke showed a better agreement between 'patients self-reporting and physicians diagnostic evaluation [29, 64]. Patients are laypersons who experience the disease, the treatment, and the impact of their daily life. As a result, they might not only judge their diseases differently than a professional healthcare provider but also remain in disagreement with the treatment goals and strategies [56]. This might be due to the fact that patients prefer goals and strategies that remain under their control and have the least impact on their daily life [32]. Especially diseases with a negative impact on physical functioning and activities were associated with self-rated poor health conditions across all age groups and especially in very young and very old patients [15].

The perception of the multimorbidity, the illness, and its consequences as well as the healthcare service and support are important factors for self-management, self-monitoring, health decision-making as well as adherence to the therapy [39]. The increasing complexity and demand of the therapeutic intervention in multimorbid patients raises significantly the difficulties in self-coordination of the own health by planning doctor visits, organizing transport, obtaining medicines and medical equipment, scheduling drugs, and administer them as intended. There is a direct correlation between the difficulties patients experience with their healthcare tasks and their declining mental and physical health as well as their reported quality of chronic illness care. For example, increasing difficulties in healthcare tasks were associated with a higher prevalence for heart failure, stroke, hypertension, and dementia. In contrast to this, reducing the healthcare task demands and activating the patients is supporting the patients to manage their healthcare [11]. The age and disease-related decrease in capabilities and functioning is another area of importance for the self-care of multimorbid patients. Physical and motoric limitations, aggravation of diseases or their symptoms, issue with medications, social and

emotional instability, lack of support, knowledge and financial concerns are considerable barriers to sufficient self-care capabilities and capacities of the patients. This might reduce self-care activities to the conditions that are emotionally most important to the patient and affect their symptoms with the highest burden as well as focus on the therapeutic interventions with the least burden in order to keep it manageable [6]. A good example is the association between handgrip strength and multimorbidity. The decreasing handgrip strength with increasing number of medicines and polypharmacy might have a direct impact on handling the packaging of medicinal products [4, 8, 7]. The increasing demand on the self-care activities and healthcare tasks in conjunction with the declining capabilities of multimorbid patients can cause a substantial psychological distress that is further pronounced by disease symptoms, the severity of the disease, and progression over time [22].

The therapeutic interventions itself can be very burdensome with a direct impact on the therapy management. In this context, the therapeutic interventions might include life-style changes such as special diet, physical activities, or disease monitoring. While oral medication administration was very much accepted by diabetes patients, the administration of insulin or blood glucose control was much less accepted. In diabetes patients, only 5.4 % of patients reported to be always adherent to diet and 39.9 % to self-monitor the blood glucose level. While there was no difference in the adherence to oral antidiabetic drugs and insulin (79.1 and 78.9 % respectively); however, 12.6 % of patients refused the insulin therapy [71]. In addition, patients tend to have an aversion to medications and perceive them mainly as something negative that need to be avoided or at least minimized, even though the patients acknowledge that the drugs are required to maintain their health [53, 69]. Three different groups of patients have been described in terms of drug usage, the passive accepters, who simply accept the therapy as prescribed, the active accepters who use the drugs symptomatically or strategically and the rejecters who have decided not to use any medicines [53]. The passive accepters build a routine and try to follow strict intervals for their medicines. The active accepters are more likely to adapt the therapeutic scheme and use flexible dosing regimen to accommodate daily changing circumstances. Adjusting the dose or leaving out certain medications to avoid adverse drug reaction when joining a social activity are common modifications to the therapy by active accepters [69].

Summary

The increasing age of the future patient population will lead to further change in patient characteristics making therapeutic intervention increasingly complex and more patient case specific. Instead of prescribing and selecting drug products based on a single disease model, future therapy will have to become an integrative process of treating multiple diseases simultaneously while at the same time considering the physiological, physical, and psychological characteristics and expectations of the patient.

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Part III
Clinical Development of Drug Products for Older Adults

Ethical Considerations in Performing Clinical Trials in and for Older People

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Abstract In Europe, the population is ageing rapidly. Older people are taking many medicinal products daily, and these may not necessarily be suitable for them. According to research studies, older patients are underrepresented in clinical trials, especially those who are over 75 years and have co-morbidities, concomitant treatments, and/or are frail. This document provides a summary of recommendations on ethical aspects of clinical trials with older people, who may in some cases be considered a vulnerable patient population. The EFGCP's Geriatric Working Party (GMWP) has developed a guidance to promote such research and to support health care professionals in their efforts.

Keywords Geriatric · Legal informed consent · Concomitant · Co-morbidity · Frailty · Good clinical practice (GCP)

Ethical principles: The definition of a geriatric patient is reviewed. Frail and vulnerable patients, who are a minority of geriatric patients, should be included in medical research projects, whenever it is relevant. The general legal context is described, as well as the 'Informed consent' process: All adults should be presumed capable to consent, until proven otherwise; informed consent must be sought for all older people who are able to consent. A simple, short, and easy-to-understand information sheet and consent form will contribute to improving the readability and understanding of the older participant. A participant guide and the use of a simple tool to ensure decision-making capacity are also recommended.

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S. Stegemann (ed.), *Developing Drug Products in an Aging Society*,
AAPS Advances in the Pharmaceutical Sciences Series 24,
DOI 10.1007/978-3-319-43099-7_8

Assent from older and vulnerable participants: Whenever older people are unable to consent, their assent should be sought systematically using appropriate information, in addition to seeking the consent of their legal or authorized representative.

In a scientific setting, there is a need to have research ethics committees with internal and/or external geriatric expertise to balance the benefits and risks of research in older people and to appreciate and recognise their autonomy.

Clinical studies (CT) design and analysis should be adapted to the research objectives with appropriate outcomes to this patient population. A comprehensive geriatric assessment could be used as a criterion for randomisation and for outcomes in designing CT with specific endpoints, such as effects on cognitive function, balance and falls, urinary incontinence, and/or weight loss, as appropriate.

The geriatric control group and use of comparators should follow specific rules adapted for this population. The inclusion of older adults in clinical trials is necessary, and such trials should not just follow the standard procedures. There should be good evidence on how to run such trials, including the benefits it would bring to elderly patients and the sponsors of the studies.

Introduction

Drug development is long and resource-intensive process that is regulated by a national and international framework, as well as by the laws and guidance of Good Clinical Practice (GCP).

This existing framework allows for the evaluation of the parameters of safe use and proven efficacy for a given targeted population. The beneficial role of treatments made available to patients is demonstrated by the steadily growing number of market authorizations of new compounds. The available treatments and their use contribute to the overall health of individuals as whole populations. The increasing life expectancy in developed countries is partially explainable by better management of diseases and the development of better medicines.

Nevertheless, as in developed countries, the population is increasingly aging, and for many of these aged people, the drugs used in daily practice, generally, have not been specifically evaluated for them.

The reasons why medicinal products need to be studied in older people have been detailed in various publications. Differences in reactions between drugs and the body, and in adverse reactions, are more common in older people compared to adults as a whole. In comparison with younger adults, older people are characterized by age-related changes in pharmacokinetics and pharmacodynamics which, in addition to multi-morbidity and polypharmacy, increase the risk of adverse drug reactions and drug interactions.

In the cases where it is advisable to include older people in a clinical trial, the choice of subsets of the geriatric population to be included should be made on the basis of the likely target population for the medicine being tested and the possibility of extrapolation. The scientific validity of research is not necessarily valid if the extrapolation is

made from the data of younger adults. All medicines, which may be used in very old, frail or patients with multi-morbidity, should be evaluated in such individuals.

The underrepresentation of older people in pharmacokinetic and pharmacodynamic studies is a well-known fact and recently a review [1] addressed the need to include older and/or frail people into PK/PD studies specific by using specific recruitment strategies. Those future studies should also include non-traditional, more patient-centred outcomes. New portable technologies and measuring devices that collect various outcomes might be a promising field to explore and to address more old age specific questions.

Ethical Principles

Ethical principles regarding the conduct of clinical studies about and for older people are not different from those applicable for any other research participant. Moreover, these principles are expressed, for example, in the Declaration of Helsinki published by the World Medical Association [2], the Charter of Fundamental Rights of the European Union [3], the Universal Declaration on Bioethics and Human Rights [4], the Universal Declaration on the Human Genome and Human Rights [5], the International Declaration on Human Genetic Data (UNESCO 2003), the Universal Declaration of Human Rights (1948), and the Council of Europe's Convention for the Protection of Human Rights and Dignity of the Human Being with regard to the Application of Biology and Medicine: Convention on Human Rights and Biomedicine (1997). All those principles are also echoed and referred to in the ICH E6 guideline on Good Clinical Practice. For the purpose of research, three ethical principles should be adhered to:

1. Autonomy of the participant
2. Beneficence
3. Justice

Within this framework, autonomy means respect for a patient's autonomy and rights of dignity and privacy; beneficence is defined as the ethical obligation to do what is good and avoid harm; and justice is a fair distribution of the burden and benefits of research. These are fully applicable to clinical trials (CT) in all patients, older or younger.

CTs are necessary and should aim at progressing the well-being, treatment, prevention, and diagnosis of ill health (WHO definition) for the population, including older patients. The 1993 E7 ICH guidance [6] from, *Studies in Support of Special Populations: Geriatrics* provides recommendations that apply to the general population with the guiding principle: "Drugs should be studied in all age groups, including the elderly, for which they will have significant utility. Patients entering CT should be reasonable representative of the population that will be later treated by the drug".

In 2010 ICH published (ICH [7] a question and answer document (Q&A) intended to clarify key issues: "With the increasing size of the geriatric population (including patients 75 years and older) and in view of the recent advance in

pharmacokinetics and pharmacodynamics since ICH E7 guidance was established in 1993, the importance of geriatric data (from the entire spectrum of the geriatric patient population) in a drug evaluation program has increased".

Certain specific diseases are unique to older people. Specific consequences of medical interventions may be seen in older participants that are not seen in younger participants. Unfortunately, these clinical effects have been demonstrated by significant incidents alongside the use of medicinal products. Because of the special protection they deserve, legally incompetent older or vulnerable people should not be the subject of CT. Research can be done in legally competent subjects (i.e. adults capable of informed consent). When research with older people proves necessary, the inclusion of the least vulnerable amongst them should therefore be encouraged.

Ethical recommendations should contribute to the promotion and protection of the dignity, the well-being and the rights of older people, who may be vulnerable and in some circumstances unable to give informed consent.

A Brussels based non-profit organization, European Forum for Good Clinical Practice (EFGCP) has been established by and for those with a professional involvement in the conduct of biomedical research, to promote good clinical practice and to encourage the practice of common, high-quality standards in all stages of biomedical research throughout Europe. Members of EFGCP Geriatric Medicine Working Party (GMWP) identified the lack of consistent ethical guidance in Europe within aspects of medical research involving older people. The organization triggered several workshops with key stakeholders from academia, investigators, patient representatives and pharmaceutical companies to discuss the issue and to develop a common ground and a consensus paper [8].

Other groups and initiatives in Europe, like the EU, founded the PREDICT partnership, a research project that conducted studies between 2006 and 2010; it concluded that there was an evident lack of clinical data for older and, in particular, frail people. The consortium also published a charter for the rights of older people in CT, including the right to access to evidence-based treatments; this action aimed to promote the inclusion of older people in CT, to prevent discrimination, to implement practical considerations for trial conducts, safety in older people, and relevant outcome measurements. [9].

Participation of the older population in CT of oncology was the subject of a recent publication; it is regarded as an exemplary study for many others and applies for trials that focus on other medical disciplines. The key hurdles for the participation of older people in CT is broken down in three categories:

1. Physician related barriers like perceptions or fear or toxicity or comorbidities interactions.
2. Patient related barriers like lack of understanding of benefits but also financial as practical and logistical concerns.
3. The third category compasses too strict inclusion criteria, poor methods to evaluate functional status.

Practical solutions are proposed as well to encourage including more, older people into CT and an improvement of the situation can only be reached through a close interaction and work of health care professionals and researchers [10].

The definitions of key elements for older geriatric patient in medical research is important and the proposal from the Geriatric Medicine Working Party of EFGCP adapts and extends an existing definition from the geriatric section of the European Union of Medical Specialists—EUGMS

- Age: "The geriatric population" is arbitrarily defined, for the purpose of this guideline, as comprising patients aged 65 years or older. It is important, however, to seek patients in the older age range, 75 and above, to the best extent possible. Protocols should not ordinarily include arbitrary upper age cut offs.
- Gender: to be representative of the geriatric general population, the proposal recommends that a majority of women should be recruited, unless there are gender specific conditions.
- Functionality/Frailty: The proposal supports the elaboration of a consensual definition of frailty, which could be used in the clinical research setting to be studied. However, additional research is needed before an operational definition of frailty can be established. The establishment of this definition is a target of an ongoing EU sponsored IMI project. The outcome of this project is expected within the year 2015/2016.
- The number of medicines prescribed: As polypharmacy may be the consequence of multiple co-morbidities and have significant interactions itself, the registration of the number of different medications taken is a good indicator. A relatively recent overview of the literature indicates that the two most useful indicators of polypharmacy were the use of inappropriate medicines or the use of 6 and more medications at the same time.
- Possible exclusion criteria: in order to reflect the applicability of a particular study to use in this population the proposal is that when an exclusion criterion is proposed it must be fully justified.

The Vulnerable Patient

This concerns a small part of geriatric patients including frail people: Vulnerability is a condition, which represents 'Those who are relatively (or absolutely) incapable of protecting their own interests' but may also reflect some more subtle issues particular to the study population [8].

Ethical principles referred to the conduct of clinical studies in and for older people are not different from those applicable for any other research participant and are expressed, for example, in the Declaration of Helsinki published by the World Medical Association [2], the Charter of Fundamental Rights of the European Union [3], the Universal Declaration on Bioethics and Human Rights [4], the Universal Declaration on the Human Genome and Human Rights [5], the International

Declaration on Human Genetic Data (UNESCO 2003), the Universal Declaration of Human Rights (1948) [11], and the Council of Europe's Convention for the Protection of Human Rights and Dignity of the Human Being with regard to the Application of Biology and Medicine: Convention on Human Rights and Biomedicine (1997). All those principles are also echoed and referred to in the ICH E6 guideline on Good Clinical Practice [12].

Where autonomy means respect for a patient's autonomy and rights of dignity and privacy, beneficence is defined, as the ethical obligation to do good and avoid harm, and justice is a fair distribution of burden and benefits of research. These are fully applicable to CT in all patients, older or younger.

Informed Consent Process

The process of informed consent is important and mandatory but should not lead to exclusion of their participation and subsequent potential benefits. In many instances, older people wish to and are fully capable of participating in research.

All adults should be presumed capable of consent, unless proven otherwise and must be sought in all older people who are able to consent. A simple, short and easy-to-understand information sheet and consent form will contribute to improving the readability and understanding of the older participant, especially if it is adapted to those with a visual or other sensory impairment and is supplemented with supportive tools such as visual and hearing aids, cartoons as applicable, and a participant guide including information such as the study conduct, tests and procedures etc. to be carried out

Where there may be doubt that the older patient has fully understood the nature, purpose and implications of involvement in a CT, it will be useful to check this matter with a simple available tool existing in different European language (e.g. UBACC scale or Newcastle +85 checklist) [13, 14].

For instance, a rapid screening test UBACC using a 10 items scale has been developed and used a schizophrenic population in the USA. Each question was scored on a scale of 0–2 points (according to the prepared answer to fit to the protocol), with 0 for an inappropriate response and 2 for a correct answer. An intermediate score of 1 could be used for a partially appropriate response or uncertainty after a new explanation. Total scores ranged from 0 to 20 [13].

Due to the current limitations of the available tools and the lack of gold-standard assessment in the older patients [15], an EFGCP team aimed to evaluate the use of this UBACC rapid screening test in an older European population with varying degrees of mental capacity and validate a French version [16].

If there is a limitation or failure of the older person to understand the CT, their assent will not be sufficient to allow participation in that research, unless it is supplemented by the assent or consent of a proxy or the legal representative, as appropriate in that jurisdiction.

Where appropriate, a cultural mediator, familiar with medical terminology, independent from the sponsor and investigator, experienced in the language, social habits, culture, traditions, religion and particular ethnic differences should be available in the process of obtaining informed consent.

If research takes place with patients/groups of patients with limited skills of the local language, the consent form should be translated into their mother tongue. For those with poor literacy, the use of pictorials and/or relevant communication support might be useful.

It is also important to be aware of potential cultural coercion either in a positive or negative direction within the consent process and to respect the participants' privacy and dignity at all times.

Definition of Assent

The notion of assent is recognised in the Declaration of Helsinki: "When a potential subject who is deemed legally incompetent, is able to give assent to decisions about participation in research, the physician must seek that assent in addition to the consent of the legally authorized representative. The potential subject's dissent should be respected."

Whenever older people are unable to consent, their assent should still be sought systematically using appropriate information, in addition to the consent of their legal or authorised representative.

The consent/assent process and assessment of capacity to consent should always be performed, even if there is any cognitive impairment, in a supportive and caring environment with respect for patients' dignity and rights.

Role of Ethic Committees

Another point is related to the research ethics committees and their need to have internal and/or external geriatric expertise to balance the benefits and risks of research in older people and to appreciate and recognise their autonomy.

All members of the research ethics committee including geriatric experts consulted on an ad hoc basis should be independent of the sponsor, the investigator and the proposed research. The qualifications and expertise of the experts used as well as the members of the research ethics committee should be documented and appended to its opinion. Such committees normally also include laypersons, some of whom may be representatives from the civil society. This geriatric expertise should be available when reviewing the initial protocol and the subsequent amendments, as well as the follow-up of the study, until submission of the final report.

Geriatric expertise goes beyond having professionally worked with older patients and could be defined on the basis of education, training and experience in the various aspects of ageing, ethics and psychosocial aspects. Therefore, this would include (i) physicians with geriatric qualifications; (ii) geriatric ethicists; (iii) geriatric pharmacologists; (iv) qualified geriatric nurses or psychologists, etc. In addition to their qualifications, it is recommended that the experts demonstrate at least some years of experience in geriatric care and direct experience of CT with older patients in similar age groups, for example as an investigator in several trials performed in the older patient of similar age groups. If this cannot be found in one individual, two or more geriatric or gerontologist experts could contribute to the expertise needed. Expertise used should be documented and recorded by the research ethics committee.

Research ethics committees specialised in geriatrics should be considered for the evaluation of trial protocols that are complex or in serious geriatric diseases.

Clinical Studies Design

Design and analysis should be adapted to the research objectives with appropriate outcomes to this patient population. A comprehensive geriatric assessment could be used as a criterion for randomisation and for outcomes in designing CT with specific endpoints, such as effects on cognitive function, balance and falls, urinary incontinence, and/or weight loss, as appropriate. Patients entering CT should be reasonably representative of the population that will be later treated by the drug.

Geriatric trials should be analysed for potential risks, including those that may not usually be of concern in younger people, as medicines or procedures may cause adverse effects in older participants that have not been identified in young adults or lead to adverse events that have more serious impact in older than in younger adults.

The CT design depends on the objective(s) of the trial and the scientific question (s) to be answered. If the trial is conducted with a view to providing data for regulatory purposes, reference should be made to scientific guidelines for drug development in older patients, including EMA guidelines. In general it is preferable to include both non-geriatric and geriatric patients in the same study(ies), which can facilitate observation of age-related differences. In some cases, a separate study in the geriatric population can be preferable.

An appropriate representation of the geriatric population, including patients with co-morbidities and concomitant therapies should be enrolled in a clinical development programme to characterise the safety and efficacy of the drugs and allow application to everyday practice.

CT involving older people should reflect the importance of specific end-points such as quality of life (QoL), functional capacities, prevention of morbidity, reduction of symptoms and clinically relevant measures.

An appropriate comprehensive geriatric assessment could be used as criteria for randomization and for outcomes in designing CT.

Research in the setting of palliative care will look at the complex QoL issue in relation with the end-points for interventions where the older population QoL becomes more important than chronological length of survival, particularly in the frail and very old with limited remaining life expectancy.

To ensure the feasibility of CT to be performed, it is recommended that the trial design be set up following consultation of the older patients to be involved in the trial, or with patient representatives. As is the case for trials in younger adults, all measures to avoid bias should be included in trials performed in the older population. For example, unblinded and/or uncontrolled trials for the demonstration of efficacy are subject to increased bias and should be avoided whenever possible.

Whenever possible (e.g., when differences in product mode of administration are impossible to mask), open trials should include provisions for blinding of assessment. Assessment, i.e., a systematic evaluation and documentation, in many cases will be based on the assessment by relatives or other carers, but in most circumstances the evaluation by the older patients themselves will be appropriate.

Trials without a control group for demonstration of efficacy should be avoided in principle. They have limited usefulness for the demonstration of safety, unless they are used prospectively for longitudinal studies or in predefined subgroups.

Alternative (less conventional) CT designs and/or analyses should be justified and it is recommended that they should be agreed with competent authorities when used with a view to provide data for regulatory purposes.

Modelling and simulation (M&S) methods can be used in place of CT in some cases (e.g. to generate appropriate data and avoid unnecessary use of older patients in CTs) and the use of such methods should be formalized in guidance.

The size of the trial conducted in the older patients should be large enough to demonstrate the appropriate efficacy with sufficient statistical power, recognizing the consideration of a higher dropout rate. In consideration of the analysis of risks and benefit, trials involving fewer older patients should be weighed against trials involving more patients but using less invasive procedures. Adaptive, Bayesian or other designs may be used to minimise the required size of the CT.

Geriatric Control Groups

The use of control groups, including the use of placebo and/or active comparator, should be based on equipoise,[1] should be appropriate to the condition(s) under investigation in the trial. It should be justified on scientific and ethical grounds, consistent with ICH GCP and the Declaration of Helsinki.

[1]Also known as the principle of equipoise, provides the ethical basis for medical research that involves assigning patients to different treatment arms of a clinical trial. The term was first used by Benjamin Freedman in 1987.

For randomised trials there should be equipoise ("genuine uncertainty within the expert medical community […] about the preferred treatment") at the beginning of the trial and no participants should receive care known to be inferior to existing treatments. This principle should guide and help research ethics committees in reviewing geriatric trials.

Use of Comparator

Use of placebo in the older adults is more restricted than in younger adults, because some older patients cannot consent, and may not understand their use and purpose.

The use of placebos should only be allowed when it does not mean withholding effective treatment, particularly for serious and life threatening conditions. The use of a placebo is often needed for scientific reasons, including in geriatric trials. The use of a placebo may be warranted when evidence for any particular treatment is lacking or when the placebo effect is known to be very variable (e.g. pain). As the level of evidence in favour of an effective treatment increases, the ethical justification for placebo use decreases.

The use of a placebo is not equivalent to the absence of treatment, for example it could be used as well as standard care. In all cases, its use should be associated with measures to minimise exposure and avoid irreversible harm, especially in serious or rapidly evolving diseases. As appropriate, rescue[2] treatment and escape procedures[3] should be set up. Other situations where the use of placebo should be scrutinised and challenged, include run-in periods where a protocol requires active treatment to be withheld.

Situations in which a placebo may be considered as a comparator, for example, might be when there is no commonly accepted therapy for the condition and the investigational medicinal product is the first one that may modify the course of the disease process, or when the commonly used therapy for the condition is of questionable efficacy or carries a high frequency of undesirable adverse reactions and the risks may be significantly greater than the benefits.

Other trial designs should be considered if appropriate. Active-control trials may be more difficult to interpret than placebo-controlled ones but may provide useful information on comparative benefit/risk balance. Therefore it is as important to discuss the exclusion of placebo, as it is to discuss its inclusion for geriatric CT.

[2]Rescue refers to treatment that may be given on top of trial medications to avoid danger or distress, for example pain treatment, as soon as the patient reaches a defined level.

[3]Escape refers to prompt removal of subjects whose clinical status worsens or fails to improve to a defined level in a trial.

Superiority Versus Non-inferiority Trials and Comparative Effectiveness Research

Equivalence and non-inferiority trials, and in particular the choice of equivalence or non-inferiority margins in relation to sample sizes feasible in the geriatric population, raise issues such as variability, and should be fully justified when used instead of superiority trials. In addition, inconsistent trial conduct may further blur differences between treatments in equivalence or non-inferiority trials. Existing guidelines on methodology issues and/or specific EMA guidelines per therapeutic area should be consulted.

The issue of comparative effectiveness study is also relevant to research in geriatric medicine and is being pursued at the European level.

Pain, Distress and Minimisation of Fear

Physical, emotional and psychological distress should be prevented as much as possible, and effectively treated when unavoidable. This requires that physical pain and distress intensity is assessed and regularly monitored according to guidelines and appropriate validated scales, particularly in older patients who cannot express it. Effective treatment in relation to the intensity of pain should be administered and reviewed regularly on the basis of the assessments performed. In addition, if sedation is needed, monitoring should be set up and the appropriate level of sedation needed for the procedure(s) should be maintained.

Painful and invasive procedures should be minimised. Population approaches and sparse sampling for pharmacokinetic data may reduce the number of blood samples in older subjects.

Special attention should be given to appropriate explanations to the older research participant/patient prior to any investigation or procedure, in order to decrease anxiety and anticipation of pain, in honest, but not frightening terms. Any procedures that might also lead to embarrassment) of the older patients (such as undressing) should be avoided or explained. In order to minimise pain, distress, and fear, facilities should be appropriate for older patients care, and the personnel should be trained to look after older patients and supervised by experienced health care professionals. Staff should be trained to communicate with legal representatives and with older patients. Older patients in a trial should be hosted in a familiar environment, including appropriate furniture, activities, where appropriate and skilled personnel should address their concerns.

The variability of response to pain, distress and fear between older patients should be taken into consideration. Different reactions may be expected, when older people are affected by a chronic or acute disease.

Summary

Inclusion of older adults in clinical trials and development programs is necessary and needed. Clinical trials including older people should not just automatically follow the standard procedures for studies in adults and might need some adaptations. Today there is good evidence and knowledge available how to run such trials allowing bringing benefit to patients, researchers and sponsors.

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Patient Reported Outcomes in Clinical Trials and Practice with Older Patients

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Abstract Patient-reported outcomes (PRO) retrieve information directly from the patient on their perception and experience with a therapeutic intervention. PRO concepts are developed case-by-case for their specific application. They are being used in clinical research and clinical practice to support a variety of different purposes like labeling claims, comparative effectiveness research, patient communication, therapeutic decision making, and health policy development. Some remaining challenges with PRO measures are being addressed and will continue to drive the implementation into research and clinical practice over the coming years. Applying and integrating PRO measures, especially in older patient populations, early on in the development of a new drug product can provide the opportunity for enhanced drug product design, including additional label claims.

Keywords Patient reported outcomes · Patient perception · Patient expectation · Older adults

Introduction

The traditional medical and pharmaceutical perspective of developing a new drug product as well as its prescription to patients later on have been focused on the medicine's potential to modify the physiological deviation underlying the disease or its symptoms [1]. This perspective assumed that, by correcting the physiological and clinical parameter, the disease and the symptoms could be sufficiently controlled to enhance the patient's health and wellbeing. With the advances in pharmaceutical and medical sciences in the past decade, the clinical parameter as the sole indicator for the clinical outcome of a therapeutic intervention has been shifted

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S. Stegemann (ed.), *Developing Drug Products in an Aging Society*,
AAPS Advances in the Pharmaceutical Sciences Series 24,
DOI 10.1007/978-3-319-43099-7_9

to a broader context by including the patient's perception of the disease conditions and the effects of the related treatment on their quality of life. This is recognizing the fact that health and wellbeing composes the objective as well as the subjective endpoints of the physical, mental and social domains. The World Health Organization Quality of Life Assessment group (WHOQOL) published a position paper in 1995 on assessing a patient's personal perception of a therapeutic intervention. This position paper considered the patient's life in the context of culture, values, goals, expectations, concerns and other personal aspects of life [2]. This concept of Health related Quality of Life (HRQoL) has further evolved into the Patient Reported Outcomes (PRO) that are defined as, "(…) any report of the status of a patient's health condition that comes directly from the patient, without interpretation of the patient's response by a clinician or anyone else." [3]. Originally targeted to investigate the therapeutic outcomes and the risk-benefit for the patient in the developmental phase of a new drug product during clinical trials or any healthcare intervention [4], PRO have been found useful for prescribing management and monitoring of individual patients as well as communicating with patients [5]. Since then, PRO have become an inevitable instrument throughout development and clinical applications; they can provide information on the impact of therapeutic interventions on an individual patient or patient population; help clinical decision-making; and predict outcomes as well as develop appropriate health policies.

Development of PRO Instruments

In the context of the continuous advances in medical sciences, the increasing availability of diagnostic tools and of therapeutic interventions—the variety of healthcare options as well as the increasing involvement of patients in their own health and hence their expectations in a therapeutic intervention, PRO have become an important measure in drug development. PRO play an important role in assessing and understanding the overall benefit of a new drug product development for the patient as a therapeutic intervention for the specific disease. PRO are derived from qualitative research, which is a methodology based on the collection, organization, and interpretation of information derived from individual accounts of personal experience [6]. Qualitative research was introduced in healthcare several years ago and served as the basis for the development of PRO methodology [7]. One of the first PRO instruments was the Medical Outcomes Study Form (SF-36), which was a comprehensive and psychometrically sound healthcare survey practical enough for large-scale studies [8]. Even though the SF-36 is still considered a useful instrument for certain purposes, several limitations have been identified in order to receive the intended information from the patients on a therapeutic intervention as targeted by PRO [7, 9].

The development of a PRO starts with the focus on the PRO field or area that will be investigated and for which a PRO concept or target of interest is being

defined. To collect the data and information about the PRO concept, PRO instruments are being developed that include PRO measures. PRO measures are specific items that retrieve the information and data of interest like questionnaires. The PRO instrument might also consider pre-specified outcomes in the form of PRO claims that can be specifically evaluated. For the evaluation process, PRO scores can be used e.g. in the form of a Likert scale to collect the necessary input from the patients concerned. As there is a huge variety of patients, indications and treatments, PRO concepts including their instruments, questionnaires, scores, or claims need to be developed and fine-tuned for each application. This also assumes that the PRO concept is being validated and proven to be capable of retrieving the full and unbiased response of the individual patient on the specific question or outcome target investigated.

For the development of a new PRO concept, it has been suggested to follow a sequence of five steps (Table 1) [10].

Determining the context requires a clear understanding of the medicinal product as well as the targeted disease of the medicinal product. The targeted disease by itself is composed of a variety of different conditions, symptoms and pathophysiological expressions that affect or are of high importance to the patient and might or might not by influenced by the medicinal product. Other challenges include predicting a patient's expectations of the new therapy, their disease history, cultural background, capability to identify and express their conditions and expectations. Based on this information, a research protocol for the qualitative elicitation and analysis will have to be developed with consideration to: the patients in the study, the methodology used to collect the information, the setting in which this will take place, and how the interview will be performed. The methodology requires flexibility and allows either a move from a hypothetic particular item to the general (inductive) or from the general to a particular item (deductive) [11]. The developed PRO concept will then be evaluated through mock interviews and focus groups to further fine-tune the instrument and practice the PRO instrument before the final study. Next, the received verbatim information will have to be analyzed and translated into a qualitative data set, which is done through the classification and coding of the data. The outcomes of the focus group and mock interviews will be further analyzed for their completeness and saturation of the targeted PRO instrument outcomes. Finally, the PRO instrument development will have to be documented together with the methodology and results being achieved to prove the validity of the PRO concept [10]. In a second stage, the newly developed PRO

Table 1 Steps to develop PRO concepts

1. Determine the context of use
2. Develop the research protocol for qualitative concept elicitation and analysis
3. Conduct the concept elicitation interviews and focus groups
4. Analyze the qualitative data
5. Document concept development and elicitation methodology and results

instrument will need to be tested in the concerned patient population to assure that the instrument including the measures are understood by the participants and that they capture the targeted aspects and items of interest within the PRO instrument [12]. This verification of the content validity can be done through cognitive interviewing of the participants regarding their interpretation of e.g. a question and subsequently their response through a different measure e.g. numeric rating scale.

To perform quantitative research by interviewing a patient population and gathering valid responses requires adopting a structured and standardized approach by skilled interviewers. The interview should be performed in a comfortable and calm environment. The interview should be inductive with ongoing adaptation to the participant response, non-biased or directed questions, allowing for spontaneous responses and inquiring for clarification, reformulation and reflection of the participants for completion of the response [13]. The interviewer should be an active listener, calm with no time pressure which is also reflected in the verbal and non-verbal communication aspects. For quantitative interviewing of older people, some important additional aspects should be considered. Older people might have hearing loss, requiring slow and loud communication [14], cognitive impairments impacting the recall of experiences, and other sensory declines, limiting the ability to provide detailed information on their experiences. Hence these participants are also more sensitive to suggestive questions and feedback from the interviewer [15].

Use of PRO in Clinical Trials

Clinical trials are the core of any new drug product development, needed to provide the clinical evidence for safety and efficacy of a new drug product. Based on the outcomes of clinical trials the risk-benefit ratio of the new drug product is established benefitting labeling and prescription. The efficacy established during the clinical trials, i.e. measuring clinical parameters and biomarkers, often do not translate into effectiveness of the new drug product due to other non-desirable effects perceived by the patient and impacting different areas of daily life. With the inclusion of PRO into clinical trials, a set of sensitive and specific measurements are being added into the clinical program. The clinical outcomes are extended by the critical direct input from the patients on the effect of the drug product and therapy on the quality of life, the symptoms and disease expressions that are relevant to the patient and perceived magnitude of benefit [16].

PRO measures have to be integrated as additional endpoints in the clinical trial design and defined in the clinical trial protocol. The clinical trial protocol is an essential part to secure the quality of the clinical trial as such and specifically the PRO items including the detailed instructions on how the PRO measures should be performed and documented during the clinical trial [17].

The PRO in clinical trials should not just focus on the clinical parameter and their related symptoms investigated in the efficacy study. Other symptoms related to the disease and the therapy might have a much higher impact and importance for

the patient. The therapeutic intervention will therefore be judged on these symptoms and the expected change. M. Parkinson patients have a variety of different symptoms affecting the motor, non-motor, cognitive and psychological as well as social domain. The perception of the severity of the symptoms can vary considerably between patients and be focused on only a very few even though the therapy has multi-dimensional benefits. The perceived severity of a symptom has been found to have a direct implication for the expectation in the therapy. For patients with M. Parkinson, the association between the expectation and severity were highest for the motor and non-motor domain and to a lesser extent for the cognitive and psychological domain, and weakest for the social domain [18].

The use of PRO can support the development of additional specific claims in the product labeling. Such claims are often derived from the patient's experience and perception on claims that cannot be measured by the typical clinical trial endpoints. The development of label claims, of meaningful patient benefits that are derived directly from the patient's experience, follow the basic principles of the PRO instrument development—starting with the definition of the desired claim, moving on to the development of the PRO concept, and through to the PRO instrument [16]. For the development of a PRO concept for label claims, a structural approach has been proposed to build a conceptual framework for the PRO concept development. The structure is based on an instrument hierarchy, classifying the PRO instruments according to their taxonomy and measurement tools. This approach will start from the "family" as a taxonomic category underneath which several subcategories exist. These subcategories are "compound concept" as the next level and several "singular concept" levels. For example, arthritis-related physical function is the "family," physical disability, the "compound concept," and walking is one of the "singular concepts" [19].

The PRO trials are increasingly used as primary or secondary outcomes within the clinical trial program to demonstrate patient-perceived and experienced benefits of a therapy. Moreover, the PRO provide scientific evidence for clinical decision-making, labeling claims as well as healthcare policy directions. However, recent research has found that PRO are not yet implemented and applied in the clinical research programs in drug product development as required [20, 21]. It has been suggested that further regulatory guidance on the development of easily accessible and consensus-driven PRO guidelines are required to improve the collection and reporting of PRO in clinical trial programs [9]. Moreover, the PRO gathered in the clinical trial should be synthesized into guidance supported by evidence and information for clinical practice [23].

With the growing prevalence for long-term multimorbidity and the increasing age of patients, the importance of using PRO to identify additional meaningful patient benefits in such patient populations will be as important as the clinical parameter itself. Perceived and experienced symptom relief (or better physical functioning) as well as the prioritization of healthcare goals can be expected to rank higher in value in the old and very old than in younger populations [24, 25].

Patient Reported Outcomes in Clinical Practice

Traditionally, clinical practice bases the patient treatment plan on disease-related clinical parameters and general symptoms. The goal is to treat or manage the disease and prolong the patient's lifetime by considering medical science. This paradigm has shifted in the past decade towards a more patient-centered approach. Understanding the perception and experience of the patient with the disease, its symptoms, and its impact on everyday life is being increasingly considered as important in the therapeutic decision process. Patient Reported Outcomes enlarge the patient-centered approach by using solid evidence of the therapeutic impact on the disease burden from a patient's perspective, allowing one to identify specific and important benefits that go beyond the traditional disease treatment.

Using PRO in clinical practice aims to increase patient understanding and satisfaction with their therapy by improving the management of the relevant symptoms and overall quality of life. This is achieved by applying PRO to a variety of situations. A PRO measure can serve as a single procedure to screen for a specific condition or symptom of the patient that is often underestimated by the physician or unexpressed by the patient. Monitoring the therapy to identify additional issues or therapy progress is another PRO measurement in improving patient centered therapy. The PRO measures and results can improve communication with the patient and involve the patient more actively in the therapeutic decision through treatment choices. Patient information and involvement in therapeutic decisions will help to increase the effectiveness of the intervention. Finally, the use of PRO will help provide a common understanding of the patient's situation across the multidisciplinary healthcare teams [26, 27].

Implementing PRO into clinical practice has been recognized as an important transformation towards a more patient centered healthcare provision and better health outcomes [28]. Because the implementation of PRO into clinical practice has had an impact on the existing healthcare provision, resistance and barriers need to be considered. As with all new tools, PRO still need to demonstrate their value for clinicians as well as for the individual patients to get their buy in and transfer into daily healthcare provision. This will include the effort and time that clinicians and patients have to spend on the PRO measure and how these disrupt their present workflow. Education and training on the PRO methodology and the selection of the goals and measures will be required. Interpretation of the data as well as the relevance and modifiability of the determined feedback needs to be considered in this context. It has been suggested that the implementation of the PRO in clinical practice requires a well-thought-out process to identify and address the existing barriers of the implementation at all stakeholder levels [29, 30].

It is not surprising that the implementation of PRO in clinical practice took place primarily in oncology, taking into account the consequences of the disease and the treatment on the patient's psychology, experience, and functioning short and long term. In a recent review, it was shown that PRO measures were done for all different cancer types and in the pre-treatment, treatment, and post treatment phases.

Table 2 User guide items to implement PRO assessments in clinical practice [31]

1. Identifying the goals for collecting PRO in clinical practice
2. Selecting the patients, setting, and timing of assessment
3. Determining which questionnaire(s) to use
4. Choosing a mode for administering and scoring the questionnaire
5. Designing processes for reporting results
6. Identifying aids to facilitate score interpretation
7. Developing strategies for responding to issues identified by the questionnaires
8. Evaluating the impact of the PRO intervention on the practice

Using different PRO instruments, positive impact was demonstrated for perceived quality of care, acceptability, patient-clinician communication, clinical decision making and symptom monitoring, while for patient satisfaction and patient health outcomes, no significant difference could be demonstrated [30]. As a result, the International Society for Quality of Life Research (ISOQOL) has developed and proposed a user guide for the implementation of PRO in clinical practice (Table 2). This guideline focuses on the methodology, process and practical use of PRO in a clinical setting [31] and helps to provide the required standardization of the PRO instruments and their use in the clinical practice [30].

Patient Reported Outcomes in Comparative Effectiveness Research

With the increasing number of available effective drug products and other therapeutic options, comparative effectiveness research became an important element for research and clinical practice. The objective of comparative effectiveness research is to compare the efficacy and effectiveness of different therapies. To achieve this objective, the traditional concept of comparing the clinical outcomes and health care utilization costs has to be extended to include the patient reported outcomes. Beside the PRO, comparative effectiveness research makes use of a variety of different measures and data sources like clinical data, electronic health records, and administrative healthcare data, that allow determining which intervention is most beneficial for an individual patient [32].

Selecting the right PRO measures to support the patient centered outcome research and comparative effectiveness research is essential for gathering the important clinical and patient perspective data of a therapeutic intervention. Building on the principles of a PRO development [10, 12] the ISOQOL initiated a consensus paper on the recommendations for the minimal standards that should be met by patient-reported outcome measures in comparative effectiveness trials [33]. Similar initiatives have been reported for patient reported outcome measures in comparative effectiveness research in cancer therapy for adults. The recommendations were built using

multi-stakeholder feedback, working groups, and public comments. These recommendations take into account the specific impact of cancer and how the treatment affects the patients' health perception, functioning, and quality of life [34].

Recent advances in information and communication technology (ICT) has enabled electronic health care recording and its integration into patient portals in a variety of different ways. Serving a number of different purposes, comparative effectiveness research through electronic health records needs to take into consideration the needs of the different stakeholders that will benefit from the outcomes. In order to achieve this, standardization of the patient-reported outcome measures have been proposed [35].

Conclusion

Patient-reported outcomes have evolved from its basic idea, to collect information on the patients' perspective and experience with therapeutic intervention, into a sound methodology for research purposes and clinical practice. Since the FDA guidance about PRO was published in 2009, substantial progress has been achieved through various multidisciplinary expert groups to translate the report's guidelines into practical and valid methodology applicable for research, clinical and health policy purposes. PRO measures, not only support the pharmaceutical industry in product development and the clinicians in therapeutic decision making, but most importantly, they can facilitate communication with the patient and encourage their active involvement in therapeutic decisions. Due to the variety of opportunities in using PRO instruments and the multidisciplinary nature of applying PRO in clinical research and practice, there are still some challenges to be resolved to leverage the full potential benefits of PRO for the pharmaceutical industry, the physicians, the health care system and ultimately the patients. Several initiatives have been taken by different expert groups to work on: PRO instrument development protocols; implementation processes into research and clinical practice; the use and application of electronic health records; as well as standards for the selection through to the interpretation of relevant PRO measures. PRO can be expected to become an increasingly important instrument to provide evidence on the benefits of a therapeutic intervention for drug product research and therapeutic decision making in geriatric-based clinical practice.

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Pharmacokinetic and Pharmacodynamic Considerations in Elderly Population

Jatinder Kaur Mukker, Ravi Shankar Prasad Singh and Hartmut Derendorf

Abstract Physiological changes with age may alter absorption, distribution, metabolism, and excretion of drugs in the elderly population. Reduced elimination and prolonged half-life are most commonly observed pharmacokinetic changes in older patients whereas altered sensitivity to drugs and change in receptor affinity are major pharmacodynamic changes. These potential changes should be considered in designing dosage regimen to elderly population during clinical and pharmaceutical development as well as prescription. Understanding and managing these age-related pharmacokinetic and pharmacodynamics changes is an important factor for the benefit to risk ratio of a new drug product. The physiological changes affecting pharmacokinetics and Pharmacodynamics of drugs and their clinical implications are discussed here.

Keywords Pharmacokinetics · Pharmacodynamics · Elderly · Age-dependency · Geriatrics

Introduction

Elderly people who are 65 years of age or older is the fastest growing drug consumer population in the United States (US). According to US Department of Health and Human Services, population age 65 years or older numbered 45 million in 2013 which is an increase of 25 % since 2003 [1]. About every one in seven Americans is an older adult. The definition of older or elderly adult is arbitrary; however from clinical pharmacology perspective, individuals of 65 years or older are considered 'elderly population'. Elderly population contributes to approximately 26 % of the drug expenditures in US [2].

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S. Stegemann (ed.), *Developing Drug Products in an Aging Society*,
AAPS Advances in the Pharmaceutical Sciences Series 24,
DOI 10.1007/978-3-319-43099-7_10

The pharmacology and pharmacokinetics of a drug in the elderly population may be very different than in the adult below 65 years of age. Age related changes in physiology, chronic disease conditions, and poly-pharmacy may make elderly people to respond differently than expected [3, 4]. Not only the frequency, also severity of adverse effects increases with age, which is the most common cause of hospitalizations and high drug expenditure in case of elderly population. In 2013, patients 65 years of age or older represented 40 % of hospitalized adults [2].

Altered drug response in elderly population is mostly suggested due to changes in drug pharmacokinetics and pharmacodynamics with age [4]. Major pharmacokinetic changes include decrease in drug clearance with age which may lead to greater drug exposure and prolonged half-life in elderly population compared to healthy young adult [5]. Major pharmacodynamic changes include altered drug sensitivity (greater or lesser) especially in central nervous system (CNS) and cardiovascular (CVD) drugs [4], and these changes in drug sensitivity may lead to altered drug response and may potentiate adverse drug effects.

In this chapter, changes in pharmacokinetics and pharmacodynamics with age and its impact on pharmacotherapy in elderly population will be discussed.

Pharmacokinetic Considerations in Elderly Population

Absorption

Absorption of drugs usually remains unchanged in healthy elderly population although changes are reported in gastrointestinal physiology with age. Conceptually, gastric pH increases with age and capacity to secrete gastric acid decreases [3, 6]. Elevated gastric pH and reduced acidity may affect the ionization and solubility of drugs. Altered ionization and solubility of drug molecules will impact the permeability and thus absorption across gastrointestinal membranes [7]. Gastric motility gets reduced with age which leads to faster stomach emptiness [8]. Reduced gastric surface area and lower gastrointestinal blood flow with age also contributes to reduced absorption of drugs across gastrointestinal membranes [9, 10]. In elderly population, tissue perfusion is slower compared to young adults. This may affect the absorption of drugs administered by subcutaneous, intramuscular and transdermal route [3]. Theoretically, all these physiological changes with age may impact the absorption of drugs in elderly; however clinical implications of these changes are not very apparent.

Although drug absorption remains relatively unchanged in healthy elderly population, certain disease conditions and administration of concomitant medications may alter the specific drug absorption in elderly. Use of anticholinergic drugs reduces saliva secretion and impedes the rate but not the extent of drug absorption by oral mucosa, e.g., buccal midazolam and sublingual nitrates [3]. Reduction in gastrointestinal transporter mechanisms with age can decrease the absorption of

vitamin B_{12} and iron [6]. Conversely, prokinetic agents, such as erythromycin and domperidone may increase the rate of absorption of orally delivered drugs [3, 6].

Distribution

Distribution of lipid soluble drugs increases and water soluble drugs decreases in elderly population. As people age, there is reduction in total body water content and muscle mass and increase in content of body fat [4, 11, 12]. These changes affect the volume of distribution (V_d) of drugs in elderly population. Low body water content leads to lower V_d for water soluble drugs and high body fat contributes to higher V_d for lipid soluble drugs [10]. Since volume of distribution is a proportionality constant between plasma concentration (C_p) and dose of the drug, C_p will be different for water and lipid soluble drugs as age progresses compared to healthy adult when same dose will be prescribed to old and young adult. Lipophilic drugs will have higher V_d and prolonged half-life in elderly [5]. Diazepam is a lipid soluble drug and has two fold higher volume of distribution in elderly population. If the same dose as that of young adult will be administered to elderly person, it could prolong its half-life by two folds in elderly person [13]. Thus 50 % of adult dose is generally recommended in elderly populations. Conversely, V_d decreases for hydrophilic drugs and equal doses as in young individuals would results in higher plasma C_p of drugs. Major examples include aspirin, famotidine, and tubocurarine [10, 14]. Additionally, reduced cardiac output, decreased renal and hepatic blood flow, and increased peripheral vascular resistance in elderly population significantly affect distribution of drugs [3].

Plasma protein binding does not change significantly in healthy elderly individuals. Most of drugs bind to plasma proteins such as albumin and α-acid glycoprotein, when circulating in the blood. In general, acidic drugs bind to albumin and basic drugs bind to α-acid glycoprotein [15]. Binding of drugs to plasma proteins leads to change in free fraction of drugs, which is primarily responsible for the therapeutic action. Age does not contribute much to change in plasma protein levels [4]. Thus in healthy elderly population, free fraction of drugs changes minimally to exhibit their therapeutic actions.

Although in healthy elderly population, there is minimal change in plasma protein levels; chronic illnesses may cause alteration in their plasma protein levels. In frail and hospitalized elderly person, serum albumin levels can be significantly reduced, leading to low plasma protein binding and higher free fraction of the administered drugs. Most common drugs whose plasma protein binding is decreased include sodium valproate [16] and warfarin [17]. High free plasma levels of drugs may increase the potential of drug toxicity, adverse effects and drug-drug interactions. Similar to albumin, binding of lipophilic drugs to α-acid glycoprotein increases with acute illness such as myocardial infarction. For example, propranolol and lignocaine may bind to α-acid glycoprotein to a greater extent and lead to decrease in its free fraction in plasma [18, 19]. However, higher binding to α-acid

glycoprotein is temporary and goes away as elderly people recover from acute illness [20].

In addition, gender is also known to be a determining factor of plasma protein binding of drugs in elderly patients. Harry et al. reported 50 % decrease in total plasma clearance of alfentanil in elderly women compared to men, and these differences are believed to be due to difference in alfentanil's plasma protein binding in both genders in elderly population [4, 21]. Since alfentanil is an intermediate extraction ratio drug, liver blood flow or intrinsic clearance could not explain the large differences (50 %) in total plasma clearance in women.

Metabolism

Metabolic ability of the liver declines with age and affects significantly Phase-I enzyme metabolism compared to Phase-II enzyme metabolism [3]. Number of structural and functional changes occurs in liver with age that can impact the metabolism of the drugs including decline in hepatic mass (30 %) and perfusion rate (40 %) of the liver [22, 23]. These changes lower the metabolic elimination of drugs and leads to prolonged half-life of drugs. Phase-I metabolizing enzymes (oxidation, reduction, and hydrolysis) such as microsomal mixed function oxidases are more affected than the Phase-II conjugating enzymes such as glutathione transferase and UDP glucuronyltransferase [4]. However, literature also report inconsistency between age and Phase-I enzymatic reactions. No consistent relationship was found between age and the activity of various microsomal cytochrome P450 (CYPs) in in vitro system [24]. Schmucker et al. [25] also reported no significant age dependent differences in activity of mixed functional oxidases using an in vitro enzymatic setup.

Contradictory evidences in age dependent changes in hepatic enzymes activities in elderly can be attributed to multiple factors. First, inter-individual variability increases with age [26]. Second, in vitro experimental result may not always be reflective of clinical observations. For example, clinical studies suggest decrease in metabolic clearances (20–40 %) with age for theophylline [27] and imipramine [28] but in vitro experiments show no changes in metabolic clearances using mixed functional oxidase systems [25].

Clinical studies suggest altered metabolic clearances of many drugs in elderly population. In elderly patients, demethylation of desipramine is slower, which leads to reduced clearance and prolonged elimination half-life [29, 30]. Similarly, decarboxylation of levodopa is a major metabolic pathway in its first pass metabolism and the enzyme responsible for decarboxylation decreases with age. In a clinical study, area under the curve (AUC) of levodopa was 54 % greater in elderly subjects compared to young subjects [31]. Other drugs including verapamil, amitriptyline, and morphine also have higher bioavailability in elderly subjects than in young adults [32, 33].

Higher bioavailability and reduced metabolic clearance in elderly population may necessitate dose adjustment to avoid any adverse events. The use of

antihypertensive agents (with high extraction ratio) in elderly are associated with hypotension as a potential adverse effect if dose normalization is not done in elderly population. Reduced metabolic clearance with age leads to higher bioavailability and prolonged actions in antihypertensive therapy and subsequently causes hypotension in elderly population [4]. Therefore, dose and administration time normalization should be considered before starting antihypertensive therapy in elderly population. For example, ramipril (antihypertensive drug) is administered as 1.25 mg (initial dose) to elderly compared to 2.5 mg (initial dose) to young adults and gradual dose titrations are performed due to higher risk of hypotension as adverse reactions in elderly population [34–36].

Increase in enzyme induction with age may lead to higher metabolic clearance and affect therapeutic outcomes of drugs. Enzyme induction usually takes longer time to occur and may causes therapeutic failure if drug is to be administered for multiple days. For example, decline in antipyrine clearance is reported with time in elderly individuals who smoke [37]. It is suggested that smoking may have induced the microsomal enzyme activity. However, role of enzyme induction in therapeutic effects of the drugs in elderly is still controversial. For example, rifampicin is a known potent inducer of microsomal activity but failed to have any induction effects on elimination half-life of antipyrine [38].

Excretion

Major changes occur in renal size, function and perfusion with age causing decreased renal clearance of drugs. Glomerular filtration rate (GFR) and renal plasma flow (RPF) gradually declines with age. There is a greater decrease in RPF ($\sim$50 %) than GFR, causing significant increase in filtration fraction in elderly population [39]. In renal physiology, filtration fraction is the ratio of GFR to RPF. In addition, diminished reabsorbing capacity and loss of tubular function is also observed in elderly population [40]. All these factors may lead to reduced overall renal elimination of administered drugs.

Other factors including coexisting medical conditions, poly-pharmacy, and increased inter-individual variability with age can significantly impact the renal clearance of the drugs [3]. A population pharmacokinetic model predicts high risk of digoxin toxicity if the same adult dose is administered to elderly population with co-existing medical conditions as renal impairment and heart failure [41]. The study analysis suggested a limited daily dose to 0.125 mg or less per day and reported significant reduction in digoxin clearance (43 %) with covariates such as body weight, congestive heart failure, and concomitant use of medications such as calcium channel blockers, spironolactone, etc. [41]. Non-steroidal anti-inflammatory drugs (NSAIDs) use causes renal adverse effects in elderly population such as acute kidney injury, acute interstitial nephritis, proteinuria and acute tubular necrosis [42]. Concomitant use of diuretics and other hypertensive medicines with NSAIDs potentiates these adverse effects [43–47].

Measuring endogenous creatinine levels is a better way to assess renal function in elderly population. Serum creatinine is the most common evaluation used to test renal functions; however, changes in body muscle mass with age make this evaluation misleading. Corsonello et al. [48] reported that 50 % of elderly people with normal serum creatinine have reduced GFR. Measurement of endogenous creatinine clearance would be a more precise way to assess renal function and is helpful to adjust dose of renally excreted drugs. However, compromised tubular secretion of creatinine with age may lead to altered GFR and need to be considered while selecting and adjusting the dose in elderly population. Additionally, GFR should be estimated using well established formulas such as Cockcroft and Gault [49] and modification of diet in renal diseases [50].

Figure 1 represents major pharmacokinetic changes with age including changes in absorption, distribution, metabolism, and excretion. Pharmacokinetic changes with age may increase the potential of adverse effects or sub therapeutic plasma levels of drugs, if dose normalization is not done in elderly population. Therefore, above-mentioned important factors need to be evaluated during the drug development phase to provide accurate information for prescribing the drugs to the older patients.

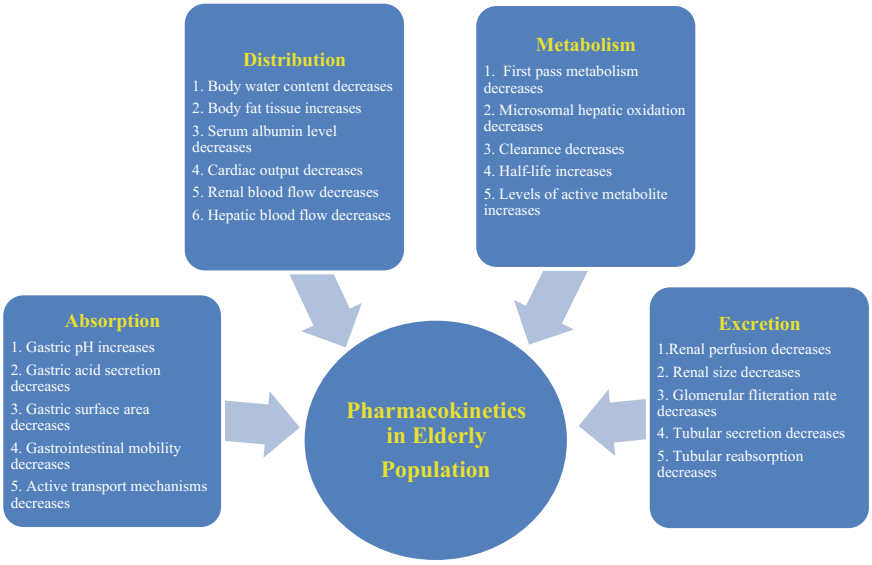

Fig. 1 Diagrammatic representation of major pharmacokinetic changes (changes in absorption, distribution, metabolism, and excretion) in elderly population

Pharmacodynamic Considerations in Elderly Population

Pharmacodynamic changes are less studied and known compared to pharmacokinetic changes. It is relatively easy to understand the change in pharmacokinetics by measuring blood/biometrics drug concentrations over time; however, it is difficult to measure the drug response due to number of reasons. First, it is very challenging to develop and validate appropriate measures of drug response especially at the site of action. Pharmacodynamic changes may occur at variety of sites in the body using various drug-receptor interfaces and through number of mechanisms. Most of the time, it is difficult to measure drug response at site of action especially when the mechanism of action is not known. Second, pharmacodynamic response depends on receptor number and affinity, signal transduction mechanisms, cellular responses, and homeostatic mechanisms along with inter-individual variability [4]. Thus, it is difficult to understand and measure the complex cascade of events between drug administration and drug response. Third, human body is a complex system and it is difficult to investigate abnormality with a good precision. It is possible to conduct in vitro and animal experiments to differentiate and address various scientific issues between receptors and/or post receptor changes (second messenger mechanisms); however, extrapolation from animal data to human data further complicates the situation [4, 51].

In general, pharmacodynamic response declines with age and may be explained by number of factors. These factors include changes in receptor number and affinity [52], changes in CNS [53], changes in reflux responses [54], and alterations in fluid and electrolyte balance [55]. In the following paragraphs, we will discuss these factors in details.

Generally, age causes change in receptor density, affinity, and the ability to activate second messengers in signal cascades impacting the pharmacodynamics response in elderly population. Lippa et al. [56] observed cholinergic dysfunction and memory loss in aged rats due to decreased number of muscarinic acetylcholine receptors with aging. With age, decrease in number of μ opioid receptors, as well as, decrease in opioid peptide content is reported. Specific drugs binding to these receptors lead to increased impotence, hypodipsia, anorexia like behavioral changes in elderly population [57, 58]. Age causes diminished calcium responsiveness and changes in calcium mobilization, which is required for different functions including secretion, neurotransmission, muscle contraction, and cell division. Thus diminished calcium responsiveness could affect all these processes requiring calcium [4, 59].

The sensitivity of CNS acting drugs get altered with age, e.g., benzodiazepines, tricyclic antidepressants, barbiturates, opiates etc. Albrecht et al. suggested 50 % reduction of dose of midazolam in elderly population to obtain comparable pharmacodynamic outcomes to that in young adults. Significant reduction in the half maximal effective concentration (EC_{50}) was observed in elderly population due to increased sensitivity of midazolam in older patients [60]. Besides age, blood supply to the brain may get compromised by atherosclerotic narrowing of vertebral and

carotid systems in elderly population. Decrease in blood supply could lead to neuronal loss and altered drug sensitivity [4].

Sensitivity to anticoagulant drugs also increases with age. Although there were no significant age dependent pharmacokinetic differences reported in case of warfarin, increased effect, and risk of bleeding is reported in elderly subjects when same dose of warfarin is administered to elderly and young adults likely due to increased intrinsic sensitivity of warfarin with age [17]. Therefore, lower initial and standard doses are recommended in elderly patients. Similarly, increased sensitivity to anticoagulant effects of dabigatran was observed in elderly patients, and lower doses of dabigatran are recommended in patients 80 years of age or above [61].

Elderly population is less sensitive to baroreceptor reflex and responsiveness. Because of these changes, they are more prone to postural hypotension and bradycardia when they take nitroglycerin, diuretics, phenothiazines, and peripheral α-blockers [54]. It is suggested that these symptoms are due to increased vascular smooth muscle action of nitrates.

In conclusion the pharmacodynamics changes occurring with age have to be considered in development and prescription. This might not only relate to the prescribed dose but also to the risk-benefit assessment of specific drugs for older patients due to the declining homeostasis, increasing vulnerability and adverse drug reactions severity. For example, the increased risk for hypotension with antihypertensive drugs or the increased sensitivity for CNS drugs increases the risk for falls, which are a major factor for mobility loss [62].

Population Pharmacokinetics/Pharmacodynamics (PK/PD): Dose Selection and Regimen in Elderly Population

Population PK/PD modeling approach enables to account inter-individual variability by identification of covariates and to correlate the drug concentration with drug response in a modeling framework to allow prediction of concentrations and response in individuals in whom the drug has not been tested [63]. PK/PD approach uses a mathematical relationship to relate dose to plasma concentration and subsequently plasma concentration is related with pharmacodynamic response. Population PK/PD is not only able to determine the population parameters and covariate effects (fixed effects) but also estimate inter- and intra-individual variabilities (random effects) in the population. These covariates may include intrinsic and extrinsic patient related factors such as body weight, age, sex, renal and hepatic functions, genetic markers, biological markers etc. and non-patient related covariates [64]. Estimation of parameters and identification of the right set of covariate relationship in PK/PD modeling framework allows prediction of

concentration and response; therefore, enables design of individualized dosing regimen. Mostly, these models are used for the dosing regimen design in the population in which the model has been developed. In certain situations (based on reasonable assumptions), these models may be used for dosing regimen design in other special populations in which the availability of the data is very limited due to practical and ethical considerations [65]. Most examples include extrapolation of the model into pediatric population, pregnant women population, where the data is very limited; however, similar approach may be applied for geriatric population, wherever applicable.

In geriatric population the pharmacokinetics, efficacy and safety data is still very limited and therefore, the PK/PD modeling framework developed for young adult population may be used for the prediction of the dosing regimen in elderly patients. Ideally, the drug should be studied in geriatric population owing to the physiological changes those could affect pharmacokinetics and pharmacodynamic response in elderly patients. Taking into account the recent update of the ICH E7 guideline it can be expected that more studies including relevant older patient populations in clinical trials will become available [66, 67].

Saeed et al. [68] proposed a framework for PK/PD modeling and simulations in elderly populations for prediction of dosing regimen (Fig. 2). This framework describes the scenario when clinical safety, efficacy, pharmacokinetics, and population pharmacokinetics studies in elderly population is needed and the scenario when this can be avoided. In most cases, a combination of safety, efficacy, pharmacokinetics, and population pharmacokinetic studies are needed for appropriate dosing regimen design. In a case the indication, disease stage, pathophysiology, dose-response relationship, treatment outcome and PK/PD relationship is similar to young adults, a modeling and simulation approach can be used for dosing predictions in elderly population. Elderly patients are seldom included in most of the pharmacokinetic, safety, and efficacy studies; however, more studies on elderly population is needed to understand the differences in pharmacokinetic and pharmacodynamics in elderly patients [67].

Given that most elderly patients use multiple drugs, the prediction of drug-drug interaction (DDI) is challenging. The study of all possible combination of drugs used in elderly population is difficult. However, a new and emerging physiology-based pharmacokinetic (PBPK) approach may be used for DDI predictions in elderly populations [69]. PBPK is currently being extensively used for drug-drug interaction predictions in young adults, children, and pregnant women [70]; however, it has not been used extensively in elderly population. PBPK can incorporate the physiological differences from young adults into the model to predict the pharmacokinetics of drugs in elderly population.

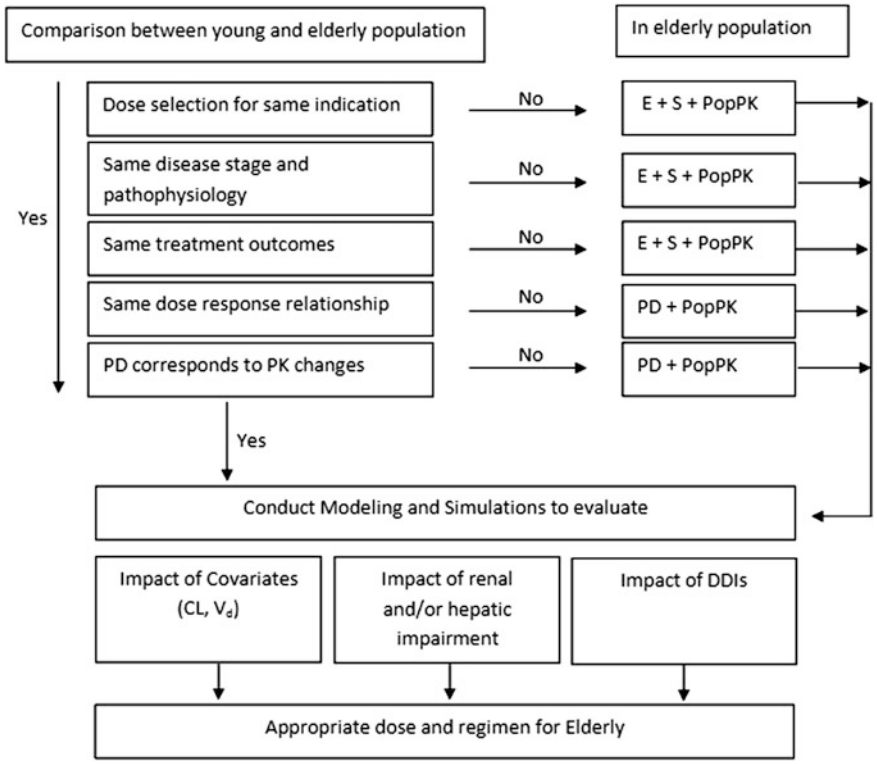

Fig. 2 Proposed framework for pharmacokinetic/pharmacodynamic (PK/PD) modeling and simulations in appropriate dose and regimen recommendations for elderly population. This framework describes need for clinical safety (S), efficacy (E), pharmacokinetics (PK), and population pharmacokinetics (PopPK) studies or utility of modeling and simulations in elderly population based on comparison between young and elderly population [63]

Conclusion

Pharmacokinetic and pharmacodynamic considerations are important for dosage recommendations in elderly population. Physiological changes with age are well known but their impact on pharmacokinetics and pharmacodynamics of drugs are less studied and less understood in elderly patients, and this limited knowledge often poses challenges in dosing elderly patients. Furthermore, the prevalent practice of poly-pharmacy in elderly patients complicates the dosing recommendations in elderly patients. Therefore, more pharmacokinetic and pharmacodynamic studies are required in elderly patients to assess the benefits/risks of administered drugs. Newer approaches such as population PK/PD and PBPK approaches may be used in designing dosing regimen and estimate the risk-benefit of drugs in elderly patients.

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The Expectation to Treatment Model: A Framework for Adherence and Effectiveness

Sven Stegemann

Abstract The decision to visit and seek help from a doctor is often derived from changes in perceived health conditions that affect the Quality of Life (QoL) and are judged as threatening. The disease diagnosis is a stressful event for an individual and might represent an important step in one's life history. Healthcare professionals use a set of diagnostic tools to identify the reason for the health condition as well as propose a therapeutic intervention. The prescription of medicines is the most used intervention to interfere with the disease target, to manage or cure the disease according to the medical expectations. Once a person has accepted to be affected by a disease, one will deliberately or saliently form expectations in the proposed proceedings of the healthcare professional. If the expectations seem to be, the health care strategy will be evaluated and judged by the patient's own bodily sensations, functioning, and wellbeing, as well as by the perceptions and beliefs about the type of coping strategy. If these evaluation confirms that the expectations are met, the patient will temporarily accept the therapy. During the course of drug therapy, the patient is exposed to the tangible disease as well as drug therapy-related effects. These can affect the patient's perception of the therapy during its time and become inconsistent with one's expectations and beliefs. Through the evaluation and constant reevaluation process of whether the drug therapy meets the patient's personal expectations, the patient may consider modifications or apply changes to the drug therapy or coping strategy. The execution of the drug therapy is a goal-directed behavior that is initiated by the intention or a set of intentions by forming a plan (medication schedule and implementation plan) and the subsequent performance on following through the medication plan. The Expectation to Treatment Model acknowledges that with any coping strategy, intention and behavior remain a moving and dynamic interaction with the perceived risk-benefit balance and is centered on the patients' (temporal) expectations, perceptions, and beliefs. Meeting patients' expectations will be key in bridging the efficacy-effectiveness gap.

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S. Stegemann (ed.), *Developing Drug Products in an Aging Society*,
AAPS Advances in the Pharmaceutical Sciences Series 24,
DOI 10.1007/978-3-319-43099-7_11

Keywords Patient expectation · Expectation to treatment model · Disease perception · Disease experience · Health beliefs

Introduction

The prescription of drug products in order to treat a diagnosed chronic disease remains the major therapeutic intervention in healthcare. Despite the fact that the drug products have been thoroughly investigated in clinical trials and provided sufficient evidence to be effective in the targeted disease, the final therapeutic outcomes in real world settings are often disappointing. However, a "disease" is not an abstract construct that someone figuratively possesses. A disease is an individually tangible condition and part of someone's entire life experience; it might affect the everyday quality of life, functioning, and wellbeing of a person. Moreover, being diagnosed with a disease and becoming responsible for managing one's own disease in everyday life is associated with substantial distress to the individual. The meaning and perception of disease include significant social, emotional, and cultural elements that cannot be solely addressed by professional, rational, or strategic proceedings.

It is not surprising that there is a significant discrepancy between clinically proven "efficacy" and all-day observable "effectiveness". The variety of different reasons like variability of drug response, perceived severity of adverse drug reactions, poor adherence and general medication problems or errors, which were not identified during the clinical trials, were recently well summarized by Eichler et al. [1]. Due to potential age related changes in physiology, metabolism, reserves, homeostasis but also disease stage, multimorbidity and polypharmacy, the risk-benefit profile of a drug might be shifting in older patients, away from that which characterizes the adult population, as investigated in the clinical trials [2, 3]. While the aspects above are increasingly being recognized and considered in effectiveness research of drug therapy to older adults, the psychosocial aspects of a disease diagnosis for a patient and the resulting prescription of its drug treatment do not receive much attention in research and practice as a potential source of poor effectiveness.

This chapter will focus on the impact of the psychosocial aspects of a patient in the context of being diagnosed with a disease and prescribed to a drug therapy.

The Different Dimensions of Disease Acceptance and Old Age

The theory of Darwin [4] that evolution is driven by natural selection, whereby individuals and species gain reproductive advantages when they are most capable to adapt to a changing environment to maintain or increase their fitness is termed as

"survival of the fittest". From this evolutionary perspective, the avoidance of a disease and old age was a survival tactic and strategy for the individual as well as the population. In some animal species, the sick or old leave the population to die on their own. There is evidence that disease or old age is perceived instinctively followed by ritualistic or stereotypic avoidance reaction [5, 6]. The avoidance of disease has been in the absence of effective treatment options a survival strategy for humankind and has helped to prevent serious infective disease from spreading across the entire population (e.g. Black Death, cholera, influenza etc.). The possible devastating nature of diseases remain valid until today. With the recent Ebola outbreak the seriousness of a disease on individuals and entire populations have been brought back to public and raised concerns to spread even into USA [7] and Europe [8]. Despite the availability of effective treatments for acute and chronic diseases as well as increasing life expectancy the avoidance of disease or old age is still preserved as an attitude in modern societies. Often the occurrence of chronic diseases might trigger a fatalistic resignation in an individual, which is supported by the subliminal stigmatization of chronic disease that marks the patient as different or not normal. This might devaluate or destroy the patient's life value and social integrity [9].

For the individual being diagnosed and "labeled" with a disease, the acceptance of the disease is an important initial step to enter into the complex and active process to deal with the disease. This includes that the patient will be directly confronted with the stressful event requiring life-style changes and/or drug therapy [10, 11]. Especially chronic diseases are characterized by its long-term and inevitable condition, which contains uncontrollability, unpredictability and un-changeability aspects. The acceptance of the disease is influenced by somatic factors and most importantly by a variety of psychological, social and spiritual factors that acknowledge the complex etiology of the chronic disease and the active and intensive therapeutic process. The personal process of disease acceptance occurs on two interconnected levels, a rational (cognitive) acceptance based on education and self-management and an emotional acceptance that is guided by feelings of anger, guilt and integration of disease as a part of the self-concept. Limitations to the emotional acceptance due to denial, guilt, fighting against or escape is a risk factor to non-acceptance even if the rational acceptance remains [10]. Due to the complex nature of chronic diseases and the multiple implications it presents for the patient, the emotional state remains unstable and can shift during the course of the disease [12]. Remaining in control of the disease is an important appraisal for disease acceptance and active coping strategy. When increasing morbidity and co-morbidity is occurring with age the distress will further increase. This might lead to a negative appraisal with loss in self-confidence, the perception of the un-changeability of the disease progression and the distancing or avoidance of disease acceptance.

In order to cope with the aversive meaning of the disease, three different generic "Illness Cognition Model" that patients use to evaluate the aversive nature of the disease have been suggested. The expression of helplessness as a way to stress the refusal of the disease and hence non-acceptance, the acceptance of the disease to

reduce the aversive meaning of the disease as well as the association of benefits the disease provides to achieve a positive meaning [13]. The underlying mechanism by which patients try to structure, understand and perceive their disease seem to follow a similar pathway. This pathway includes different aspects of the disease especially the name of the disease, the symptoms that are perceived to be associated with the disease, believes in why the disease occurred, how long it will last, what the consequences will be and to which extend the disease can be personally controlled or controlled by the treatment. However, uncertainties and concerns about the disease might persist or being reinforced by a laypersons interpretation of diagnostic results. Simply the performance of a diagnostic test to exclude a severe disease can create believes about vulnerability and severity of the patients health condition [14].

In addition to the stereotypic perception of disease as being something infectious and therefore to be avoided, chronological "old" age is often being regarded as the principle cause of chronic diseases. This implies that chronic diseases are a natural process with increasing age and therefore neither changeable nor controllable or treatable by life-style changes or therapeutic intervention [15]. As these stereotypes are reinforced over the lifetime [16], older people perceive symptoms as age related but not as health related issue that could be addressed by diagnose and treatment [17]. With the misperception of increasing age as the sole root cause of chronic diseases and multimorbidity, people are less likely to engage in health maintenance behaviors. They tend to develop negative emotions and self-perception leading to faster progression of disease, functional declines and finally increased mortality [15].

It is evident that acceptance of the disease is not automatically derived from the results of diagnose or clinical parameter shared with the patient. The confrontation with the event of having a disease initiates a multidimensional reflection process in the person that might or might not lead to disease acceptance. Neglecting the disease in the first instance will prevent people from considering any interventions to manage the disease. As symptoms might remain or reappear, acceptance of the disease might occur later providing patients with a favorable attitude to consider interventions.

Patient Experience and Living with Disease

Maintaining good health is the natural objective of self-care activity that individuals execute during their daily life. According to the WHO, health is defined as "a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity". This emphasizes the fact that health is perceived across the rational and emotional domain. When bodily sensations are no longer perceived as "normal" people start to reflect about disease as a potential root cause. This reflection might lead to the assumption of having some kind of illness whereby this perception is based on the bodily sensation itself, prior experience with diseases or similar symptoms as well as information received from external sources like relatives, friends and media [18]. According to the "Common Sense Model", the

individuals will interpret the experienced conditions by organizing and analyzing the information to build a representation of the potential illness. This representation serves as the basis to identify and initiate coping strategies as a response to the representation. The coping activities, which can be rational and cognitive as well as emotional driven, will be constantly monitored for appraisal. The perception and intensity of bodily sensations and symptoms varies greatly between individuals as well as their interpretation. Individuals with a tendency to avoid negative feelings and emotional distress about illness are more likely to suppress bodily sensations and symptoms. With increasing age, occurring ambiguous symptoms and functional impairments are more likely to be perceived as associated to the normal aging process and judged as not preventable, evitable or treatable [17]. This also implies that older patients attributing their symptoms to aging are more focused in their coping strategies to compensate for the symptoms and maintain their actual functioning rather than to seek support and treatment from a physician.

When symptoms are experienced and perceived as a deviation from normal health, they incrementally affect wellbeing. The extent to which the symptoms and bodily sensations affect patients' life depends on how threatening, serious and distressing these symptoms are perceived as well as on how these interfere with the daily functioning and QoL of the patient [19]. The objective and subjective measures and hence patient perception of the disease impact measured by QoL tools can differ substantially [20]. In the same way, the perception of the QoL remains a moving target with the adaptive and coping strategies, emotional and rational disease appraisal, uncertainty of disease and disease progression, self-control, self-efficacy and optimism/pessimism ([20, 12]). Thus, the perception of the disease and symptoms is a dynamic and individual experience that vary within the entire and actual context of the individual situation. For example, relieve from a headache related to a flu infection might be most important expectation for a patient, but in relation to a brain tumor, headache might become a much less important treatment expectation. Consequently, patients respond to the symptoms with a careful observation of their changes over time and remain vigilant on the interference with their physical, psychological and social functioning [21].

The symptoms and bodily sensations experienced with a chronic disease represent stressful events that can have significant effects on employment and work, relationships and social activities as well as future life plans. In order to cope with the disease burden adaptive strategies are initiated. Acceptance of being ill, defining new challenges, adapting to the new social identity, giving up ordinary activities, dealing with the physical impairments, finding new ways in social relationships, depending on others as well as recognizing the own needs are major themes that people diagnosed with chronic diseases are dealing with. The importance and the objectives of these themes are disease specific and can vary completely from one disease to the other. For example, adapting to the social identity is important for patients with Parkinson's Disease and Chronic Fatigue Syndrome, however, while Parkinson's Disease patients want to be treated like normal people, Chronic Fatigue Syndrome patients struggle to be perceived as being ill [22]. It should be noted that physical functioning, independence and self-efficacy remain the most important

aspects in the QoL of patients with chronic diseases, multimorbidity as well as frailty. This represents the important expectations of remaining energized, being free of pain, maintaining the ability to do activities of daily living and mobility [23].

The prevalence of living with disease and functional impairments is expected to increase in the coming years due to therapeutic interventions in the early phases of the diseases that prevent and delay the fatal consequences of the disease. Recent research also provided evidence of the earlier onset of chronic diseases like cardiovascular diseases because of life style factors. An increase in functional impairments related to the cardiovascular disease conditions like heart disease, stroke, diabetes, arthritis, musculoskeletal problems and obesity were also prevalent [24, 25]. The results of these trends will further increase the number of patients with multiple diseases conditions, experiences as well as complex associations and perceptions on symptoms and bodily sensations. Adapting and coping with the disease as well as appraisal will become more challenging in multimorbid patients as well as the level of predictability, certainty and controllability will be scrutinized.

Self-rated Health (SRH) is a measure that consists of only one question that is: Overall, how would you rate your health? Despite its simplicity, it has demonstrated to be a very useful predictor for mortality and functional declines especially in older persons. It has been suggested that this is due to the person's conscious or unconscious perception of health and wellbeing that reflects preclinical conditions, recently changing health, health behaviors and self-perception of health [26]. The predictive strength of SRH for the health projection is further increased by including a comparative past and future time perspective [27, 28]. In predicting mortality and functioning, the SRH provides evidence that older people have a very good sense about their future health trajectory and time orientation. As the SRH has a strong temporal dimension and remains dynamic, older people constantly reevaluating their goals and future opportunities in the light of their perceived remaining lifetime. This also includes that health behaviors and personal goals will change with changing SRH and time horizon [29, 30]. Interestingly the change in priorities from a goal directed to more emotional directed when the time horizon gets limited, is independent of age and similar in young and old people with the same time horizon [31]. Even though no studies could be found investigating the relationship between SRH and the influence on the coping strategy with chronic diseases, we can hypothesize that patients will adapt their expectations in the coping strategy to more short-term achievable wellbeing.

The constant experience and interpretation of the disease is a continuous personal assessment and evaluation across the different domains by which a person tries to understand and get control of the disease. It is important to notice that patients have a very good sense on their health and wellbeing and modify the coping strategies based on their expectations.

Health Literacy and Information Retrieval

In order to take conscious decisions about the coping strategy with a disease, a certain level of knowledge on the disease itself as well as the therapeutic interventions are required. The extent to which people are able to make judgements and informed decisions with regard to healthcare, disease prevention and health promotion is described by health literacy. Health literacy is defined by the Institute of Medicine of the National Academies of Sciences, Engineering and Medicine in the USA as "the degree to which individuals have the capacity to obtain, process and understand basic health information and services needed to make appropriate health decisions". Studies on the general health literacy in Europe have shown that health literacy is being considered inadequate or problematic ranging from 27 % in the Netherlands to up to 61 % in Bulgaria [32]. Similar data have been obtained in the USA considering about 30 % of the population having poor or basic health literacy, whereby much higher poor to basic health literacy was determined in people 65 years and older [33].

Health, disease and medicines are an important public topic that are addressed by a variety of different media like TV, radio, newspapers, magazines, internet and others. TV, radio, magazine and newspapers were the major information sources on disease specific information used by adult diabetic type 2 patients and to a lesser extent healthcare providers and patient education brochures [34]. Much concern has been raised about the validity and accurateness of health information delivered through public media, which may lead to misconceptions about health and diseases [35]. In addition, it should be taken into consideration that the public media are more likely to report on negative drug outcomes like unforeseen adverse reactions and product withdrawals rather than on the positive health outcomes achieved by the medicines. This explains a rather negative than positive public perception of medicines.

As part of the healthcare system in primary care, healthcare professionals provide information about disease, therapy and recommendations on life style change to the individual patients. It is assumed that the patient possesses sufficient health literacy and is proficient enough to independently manage the disease and use the drugs accordingly. While significant research has been done in the past decades to understand, why patients do not comply and adhere to the proposed therapeutic proceedings [36], it is important to acknowledge that the decision remains a personal choice of the patient and as such has to be respected. According to the "Health Belief Model", which proposes that patients weigh up a health-related behavior (e.g. compliance) by considering illness and benefits [37]. The weigh up process considers the patients' perspective on perceived susceptibility, perceived seriousness, perceived benefits, perceived barriers, cues to action and self-efficacy [38, 39]. Additional patterns from the "Illness Cognition Model" include personality aspects like positive or negative thinking [13], impact on identity, cause of illness, personal consequences, personal control or control by treatment [14]. Low mood, somatizing tendency [40] and perception of disease progression and long-term effects [41]

further contribute to the patient perception and disease construct. Moreover, it is important to notice in the context of patient information retrieval about a disease the behavior of avoiding information that are threatening. Two types of avoidance behaviors have been identified called the "monitors" seeking for information that reduce the risk and the "blunters" that try to avoid finding threatening information [42, 43].

The depth of understanding of medical and pharmaceutical information described by health literacy. Health literacy and health beliefs further determines the patient perspective on (the own) health and is the result of patients knowledge, perception, meaning and perspective of the disease and its treatment. As a result, patients will form expectations deliberately or saliently in their health and coping strategy.

Expectations, Beliefs and Experience of the Drug Therapy

It is worth to recognize that people decide to visit a physician only when they experience symptoms or changes in wellbeing, which raise concerns about their health. The intention in seeking help from the healthcare professional is the restoration of the health and wellbeing of the previous times. In the ideal case, patients expect that the condition is just temporal, can be clearly diagnosed by the physician and being resolved with a minimal intervention in short time. When this is not the case and the health concerns turn out to be a chronic, eventually a life threatening disease, the situation represents a significant disruption and crossroad in a person's life.

On the other side, when doctors diagnose a chronic disease in a patient, they will apply their professional knowledge and experience in conjunction with the therapeutic and medical standards in order to restore functioning and reduce risk of mortality. The physician, based on clinical data and labeling information, sees drug therapy as the most powerful intervention in the context of chronic diseases and tends to prescribe medicines as the primary coping approach. Life style changes might also be proposed in support of the drug therapy like stop smoking, do some exercise or reduce calorie intake.

While healthcare professionals are often convinced that the patient expectation is best addressed by drug therapy to cope with the chronic disease, patients develop their own expectations in what the coping strategy should achieve. The drug therapy is only one coping strategy, which does not necessarily include the persons' coping process with a problem-focused and an emotion-focused decision. As rational prescribing relates to problem-focused coping strategy, the patient might use the drug therapy only in the first place and will adapt potentially with continuous appraisal and reappraisal in relation to the expectations. Drug therapy as the sole coping proposal, might be perceived by patients as being imposed and out of one person's control. Having choices of coping with the disease is important as it includes the possibility of one's own expectation. When choices exist, more than

half of the patients would chose alternative coping approaches in the first instance [44] or actually use complementary and alternative medicines on a routine base [45, 46]. In addition to this, a positive or negative attitude on the coping strategy (e.g. drug therapy) to meet the expectation in pain relief significantly influenced the therapeutic outcome [47].

As stated above, the people seeks help from a professional once she or he experience symptoms and bodily sensations that are perceived as being threatening and important to investigate. When a disease is being diagnosed and accepted by the patient, a drug therapy will be one of the coping strategies to remove the symptoms and treat or manage the underlying disease mechanism. The patient will make the appraisal of the effectivity of the coping strategy within short time-frames by observing the changes of the symptoms and other bodily sensation. This self-monitoring includes disease symptoms as well as drug effects that will have to match with expectations. The perception of the symptoms as being disease or therapy related are often misinterpreted by lay persons leading to a negative judgement of the therapy and modification or omission of the medicine as a response [48]. Even if the therapy as such will not be questioned by the patient as the primary coping strategy, adjustments to the therapy in terms of dose, frequency, time of administration, modification of the dosage form for easy swallowing are common results of the appraisal and reappraisal process [48]. In order to adjust the drug therapy to the daily routine and social activities drugs can be taken symptomatically or strategically. For example, the use of anti-hypertensives as an acute treatment in case relevant symptoms occur or omission of diuretics in case of planned social activities.

Taking into account the expectation of the patient to restore the status of perceived health and wellbeing, the constant appraisal and reappraisal of the benefit as well as the risks and concerns of the disease and its coping strategy, the patients' attitude towards the drug therapy can change over time. When the disease burden is low or negligible and the benefit is long term (e.g. preventive medicine), the perceived benefit of the therapy can decline over the course of treatment [49] and with the perceived time horizon [31, 29, 30].

Acceptance of the disease is normally followed by expectations in a specific coping strategy. Keeping in mind that the objective of a patient might be to restore the health conditions prior to the occurrence of the symptoms, they will monitor carefully their bodily sensations and symptoms with regard to their expected outcomes.

Behavioral Approach to Drug Therapy

Human behavior is mainly driven by volitional activities to organize and manage daily obligations and undertakings. That behaviors differ substantially between individuals is caused by the variety of expectations in life, goals, wishes and life fulfillments. This is also related to behaviors that include risks and unhealthy life

styles like smoking, excessive alcohol, speeding or even wingsuit flying that are done under full consciousness of the person. In other words, some people are willing to take higher risks then others to achieve goals that are perceived as reasonable for satisfaction they provide. People also tend to prefer the immediate rewards compared to the ones that will occur with a delay and that are probabilistic rather than sure like it is the case with the majority of preventive drug therapies [50]. In contrast to this, the objectives of healthcare professionals as well as of the prescription of drugs are directed towards the main goals of increasing health, reducing risks and maximize the life span. Healthcare professionals judge an absolute risk reduction for a major cardiovascular event of 1 % and less over a 5 years treatment period with statins as a higher benefit for the patient than the risks and consequences of the drug therapy [51]. It is further assumed that this is the major goal of the patients for which the responsibility is with the healthcare professional to achieve this objective. It is obvious that their might be a discrepancy between the individual's risk acceptance to achieve a certain level of life satisfaction and the assumption that as a patient individuals would automatically aim for the greatest risk reduction and maximal life time at all costs. As a minimal consensus we can say that a common objective of an appropriate coping strategy with the disease is to restore patients' perceived wellbeing and health. The patient will compare the health with the status before occurrence of the symptoms and will monitor bodily sensation carefully during the course of treatment. In the context of multimorbidity, older patients are aware that certain compromises with regard to their expectations need to be made [52]. Research have provided evidence that remaining their functional ability is a major expectation as it is essential for doing things that they value, satisfy their basic needs and enables them to continue to learn, grow, make decisions, move around, build and maintain relationships and contribute to the society [53].

To follow the prescribed drug therapy is a volitional action taken by the patient that is best described through the 'Theory of Planned Behavior' [54]. The basic principle of the 'Theory of Planned Behavior' proceed on the assumption that human behaviors are goal-directed behaviors in which an intention towards a certain behavior is being formulated followed by an action to carry out the intention. As tasks are often complex they require a set of intentions that forms a plan to perform the task. The smallest plan unit is the set of actions required to use a medicine as prescribed. Under polypharmacy conditions a number of plan units need to be combined and aligned to follow the complex medication schedule. The individual is setting an intention from an attitude towards the behavior that is generated through personal evaluation of the behavior. The attitude towards a behavior is generated through the rational examination based on the personal values and beliefs (e.g. perception or experience of a drug effect) and subjective norms perceived e.g. from the social environment, hence the emotional values and beliefs (e.g. opinions and suggestions from relatives, friends or referents). The intention will most likely lead to the behavior if it is immediate, but the intention can change if too much time passes by before the behavior can be executed or the execution is prevented by product usability limitations (e.g. inaccessibility of the packaging,

administration barriers like swallowability issues). The intention and behavior is subject of constant appraisal and reappraisal of the individual and as such at risk for subtle or disruptive changes. The change can either affect the direction or the strength of the intention modifying the original intention and behavior (e.g. to follow through the therapeutic schedule). For example with time, the distance to diagnose might reduce the perceived seriousness of the disease or a raise in the concerns regarding the drugs due to new information can lead to an unfavorable risk-benefit assumption. It should be recognized that a rational based decision making on the risk-benefit assessment require substantial medical and pharmaceutical knowledge in a broader context.

As every intended behavior has some degree of uncertainty of the control that one person has over the behavior, the person is exposed to the risk to fail on the behavior. The internal factors that impact on volitional control are the self-confidence of the individual to be capable to perform the behavior, the level of skills, information and abilities the individual has to perform, the will-power put into the performance as well as emotions and compulsions that occur during behavior performance. In addition, external factors can have an influence on the performance of the behavior like time, lack of opportunity and dependence on others. Therefore, despite formulating the intention to follow through a therapeutic regimen personal and external factors can interfere with the intention and behavior.

This is especially true in case of increasing therapeutic complexity due to polypharmacy and age or morbidity related functional impairments [55]. Complex tasks as the handling and management of multiple drug products in a therapeutic regimen consists of a number of different intentions and activities that together form and execute the plan. Each intentional plan remains specific for a drug, the appraisal and reappraisal of the expectation towards each drug and its specific disease condition remains sensitive to patients weigh up of risk-benefit and the potential modification of use [56].

In the case of drug therapy and especially complex therapeutic regimen, intentions and behaviors of patients remain a moving target along the time course of the therapy. The key two domains involved in this process are the attitudes towards the behavior and the subjective norms. The attitudes towards the behavior is the set of patients personal acceptance or perception of the disease, its severity, experience with therapy, impact on daily life, concerns, personal goals, self-efficacy, knowledge etc., whereby the subjective norms represent the opinions and expectations from relatives, friends and important referents, social and cultural norms, the reaction of the environment etc. As it is a dynamic process, patients remain in control of the therapy through a variety of ‘planned behaviors’ to evaluate the potential success of the drug therapy, adapt the therapy if needed to better comply with their expectations based on personal objectives and beliefs and align with the subjective norms [57].

The Expectation to Treatment Model

The development of medicines for the treatment and management of diseases is a fundamental achievement of medical and pharmaceutical sciences. Prescribing is done according to rational guidelines focusing on restoring the health by risk reduction, disease symptom relief and extension of the survival time. These rational medical goals cannot be seen as separated from the patient health experiences and beliefs, which includes a substantial emotional domain. The individual health and wellbeing underlies the same principles of goal direction towards an expected outcome. On these grounds, the expectations of the patient in the therapeutic intervention are guiding principles for acceptance and implementation.

The patient decision process to follow a prescribed medication after accepting the diagnose and the disease is a first essential step of therapy acceptance and implementation. The decision process orientates towards the personal expectations in the treatment formed by objective and subjective aspects.

The expectations are associated with certain health beliefs in the therapy (coping strategy) and the therapy with positive effects on the subjective and objective bodily sensations and symptoms, restoring the health conditions prior to the disease. Through this evaluation cycle a personal assessment of the effects and adverse effects of the medicine(s) on the perceived health is being performed (patients' risk-benefit assessment). During this patients' evaluation process, the medication schedule might be modified several times by reducing the dose, omission, and shift in administration time etc. until the expectations are being sufficiently met. The more realistic the expectations are in a medicine the more likely it is that expectations can be matched and the therapy will be accepted. In the simplest case, the expectation of a patient is to receive a clear diagnose and drug prescription as the doctor is regarded as the authority to decide on the coping strategy. In contrast to this, patients who are medication adverse might already reject a medicine based on the patient information leaflet or information received from other sources.

The temporal acceptance of a therapy is the initial entry point into the implementation of the treatment, which is the second step into drug adherence and effectiveness. Each drug product has specific requirements for its use and administration in addition to use instructions received from the doctor and/or pharmacist. These information need to be translated into a specific set of intentions needed to perform on the therapeutic plan according to the requirements. With the prescription of additional medicines to be used, the intentional plans for any new drug will have to be incorporated into the existing therapeutic schedule increasing the complexity and demand on the plan performance. Because of the different administration times and long term use of medicines, the intentions are set long ahead of actual execution of this intention. Unexpected things can occur that prevent patients from performing on the intention. These can be due to a poor routine like a lack of structure in the day [58] or issues with handling or administrating the drug product or dosage forms ([59, 60]). Especially when additional new medicines

are being implemented drug-drug interaction might occur that can lead to an appraisal that does no longer match the expectations of the patient.

The "Expectation to Treatment" Model (Fig. 1) combines the evaluation phase of the treatment by the patient and the subsequent implementation phase after principle acceptance. The patient expectation in the treatment remains in the center of the medication process as the reference point for acceptance. Deviations from the therapeutic schedule will most likely occur, when patient trajectory and patterns change over time leading to a mismatch between the established therapy and the expectation. In a similar way, the process of the constant appraisal of the therapy can significantly be influenced by perceptional changes on the therapy or in the medicines, which may no longer be in accordance with the expectations. The "Expectation to Treatment" Model also recognizes that the experience of bodily sensations and symptoms, thus how the patient feels in terms of physical, mental and social wellbeing plays a dominant role in the expectations and hence the appraisal and reappraisal process of the treatment.

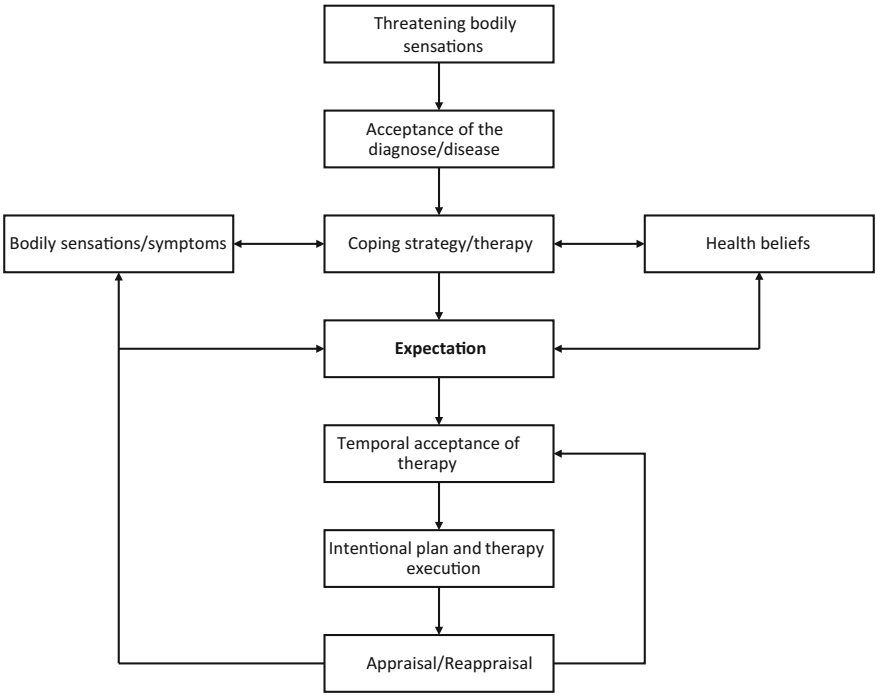

Fig. 1 The schematic flow chart of the "Expectation to Treatment Model"

Conclusion

The concept of developing drugs and treating patients for a single disease is still widespread in the healthcare provision. The success of decades of sound medical and pharmaceutical sciences have removed the life threatening and devastating effects of the majority of acute and chronic diseases tremendously contributing to the increasing life expectancy and longevity of humans. The effective treatment and longevity comes along with an increasing rate of multimorbidity and polypharmacy creating a new challenge in drug prescription and achievable therapeutic goals. This might be one reason why the progress has not received unanimous approval by the public. Another reason might be that suffering from a disease or being old still follows the defensive and negative stereotype reactions as well as medicines and the pharmaceutical industry per se maintains a negative connotation.

Bodily sensations or symptoms judged as threatening are normally the reason for seeking support from healthcare professionals. For example, a headache occurring after a night of too much alcohol will not be perceived as threatening, while the same headache suddenly or repeatedly occurring might cause a threatening perception. From the healthcare professional it is expected that (s)he is able to provide a clear diagnose and propose a coping strategy that will remove the symptoms and restore the health conditions.

The first step towards an effective treatment is the acceptance of the diagnoses and the disease. The acceptance of a disease or additional illness represents a disruptive incidence for the patient and can cause substantial distress. Non-acceptance (avoiding to be confronted with the illness) as such can already be a coping strategy that will nearly exclude the consideration for any kind of therapy. When the principle diagnoses and disease is accepted, the potential coping strategy will be requested. The most evident expectation of the coping strategy will be to restore the health as to the state prior to occurrence of bodily sensation. According to the WHO, health is defined as "a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity." In the context of disease morbidity, multimorbitity and high age but also health beliefs and cultural norms the expectations in physical, mental and social well-being may vary considerably within and in-between patients.

For the temporal acceptance of the drug therapy as a future coping strategy, the patient will evaluate the intervention with regard to the conformity with his or her expectations. The expectations are associated with health beliefs in the coping strategy and the coping strategy with restoring effects on the bodily sensations and symptoms. This risk-benefit assessment of the patient can be accompanied by consciously or unconsciously modifications to the proposed medications and medication schedule. When the therapy sufficiently meet the expectations, the patient will provide temporal acceptance and decide to implement the therapeutic schedule into daily life. The implementation and execution of the therapy requires a set of intentions (building a plan) and behaviors (taking the medicines). With any additional drug product, additional intentional plans and behaviors need to be integrated

into an overall medication schedule. Under polypharmacy conditions, the medication schedules become very complex and demanding increasing the risk for intended or unintended modifications. Especially as medications for chronic diseases are long term treatments and intentions are long ahead of the actual behavior performance they bear the risk for unexpected interferences preventing execution. For example, even though the intention was to take the medicines at 6.00 pm with the dinner, unexpected changes in the day plan might prevent the patient from taking the drugs. Even though the patient has temporal accepted the coping strategy and set a plan to manage the medication, salient appraisal and re-appraisal of the health and coping strategy will occur. As for the expectations and beliefs, the appraisal remains subject of personal changes across time. For example, when the time horizon gets shorter, long-term therapy benefits get less important or when negative information on drug occur the risk might now be perceived higher than the benefit.

The "Expectation to Treatment" Model provides a framework for medication adherence and its underlying process. It recognizes patient expectation as the central point for temporal therapy acceptance and implementation. The evaluation of the conformity with the expectations is based on subjective and objective bodily sensations and symptoms. In the initial phase of a new drug prescription salient or deliberate evaluation cycles will verify congruence with the expectations. The execution phase is accomplished by intentional plans and plan performance. As expectations, disease and therapy perception are temporal phenomena the adherence to an established therapeutic plan remain dynamic and can fluctuate, change gradually or disruptively. In essence, adherence to a treatment is achieved, when expectations of the patients are fulfilled, the intentional plan can be executed and the constant reappraisal confirms consistent conformity with the expectations.

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Pharmacoepidemiology and Pharmacovigilance for Safety and Efficacy in Older People

Sarah N. Hilmer and Danijela Gnjidic

Abstract At the time of drug product approval, there is limited data on drug safety and efficacy in older patients. In old age there is an increased prevalence of chronic disease and of medication utilization resulting in multimorbidity and polypharmacy. While older people have potential for significant benefit from medicines, they are also susceptible to adverse drug events. Pharmacoepidemiology and pharmacovigilance studies provide real-world evidence on drug utilization and safety, and limited information on efficacy and effectiveness of drugs in older people. The reliability and validity of pharmacoepidemiologic studies have improved with advances in and standardization of study design and reporting, as well as development of objective measures to capture key aspects of geriatric medicine. Pharmacoepidemiologic studies now inform both clinical practice and medicines policy.

Keywords Pharmacoepidemiology · Pharmacovigilance · Elderly · Adverse drug events

Role of Pharmacoepidemiology and Pharmacovigilance in Establishing Safety and Efficacy of Drugs in Older People

At the time of drug product approval, there is limited data on drug safety and efficacy in older patients. Older people have high drug utilization and great potential for benefit from medicines due to high prevalence of disease. They are also very susceptible to adverse drug events. Pharmacoepidemiologic and pharmacovigilance studies provide real-world data on drug utilization and drug safety, as well as some

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S. Stegemann (ed.), *Developing Drug Products in an Aging Society*,
AAPS Advances in the Pharmaceutical Sciences Series 24,
DOI 10.1007/978-3-319-43099-7_12

degree of information on efficacy and effectiveness of drugs in older people that can inform clinical practice and medicines policy [1].

Pharmacoepidemiology is the study of the utilization and effects of medicines in large numbers of people, bridging the sciences of clinical pharmacology and epidemiology [2]. Rigor in both clinical pharmacology and epidemiology principles are essential to generate valid, meaningful studies that inform practice and policy.

Pharmacoepidemiologic methods include descriptive studies of drug utilization and analytic studies that compare groups by pharmacological exposure, and may be observational or experimental in design. Pharmacovigilance is monitoring for safety outcomes in drugs that are already on the market, and relies predominantly on spontaneous reports of adverse events to a central agency.

Preclinical and clinical trials conducted before marketing often do not give adequate information on the effects of drugs in older adults [1]. Preclinical studies are rarely conducted in aged animals, despite emerging evidence that pharmacokinetics, efficacy, and toxicity differ in old age. Older people are typically excluded from Phase I and II studies because they have higher risks of unanticipated toxicity. International guidelines suggest that Phase III studies include people aged 65 years and older, not unnecessarily exclude patients with concomitant illness, and include patients who are representative of the population that will be treated if the drug is licenced. However, there is a growing body of research demonstrating that compared to participants in clinical trials, the people who use drugs in practice are older, with a higher prevalence of multimorbidity, disability, and polypharmacy. This was recently demonstrated for acetylcholinesterase inhibitors [3], and has been well documented in many other areas of therapeutics including oncology [4] and cardiology [5].

Furthermore, premarketing trials are rarely designed to address outcomes that are important to older adults. Most clinical trials aim to improve a surrogate marker, a single disease, or even a global clinical outcome such as hospitalization or death. In old age, surrogates may not correlate as well with clinical outcomes as in middle age, and single disease outcomes are less relevant in the presence of multiple competing causes of morbidity and mortality. A key outcome of medical therapy in older adults is ‘successful ageing’ [6]. This refers to the absence of chronic disease and risk factors for disease, maintenance of physical and cognitive functioning and active engagement with life (maintenance of autonomy and social support) [7]; as well as satisfaction with one’s past and present life [8]. There is a large and growing body of pharmacoepidemiologic data on the associations of pharmacological exposures with adverse outcomes in the geriatric patient population, such as falls, frailty and impaired physical, and cognitive function [9]. Clinical trials rarely address functional and psychosocial outcomes, and thus do not provide adequate evidence to guide therapy to help older patients achieve their goals. Data from pharmacoepidemiological studies currently fill this evidence gap.

Role of Drug Utilization Studies in Older People

Despite the paucity of data from older people at the time of marketing, older adults are the major users of medicines in the developed world, with 50 % taking five and more medicines. Pharmacoepidemiology is able to document patterns of drug utilization in terms of age, and with respect to other characteristics of users such as sociodemographics (e.g., race disparities in prescription drug use [10]), comorbidities (e.g., influence of comorbidities on therapeutic progression of diabetes treatment [11]), and place in life-course (e.g., the last year of life).

Drug utilization studies can estimate adherence to prescribing guidelines for a condition in a population, as well as adherence to prescribed medicines, although this often relies on the suboptimal surrogate of dispensing data. For example, the prevalence of 'optimal medical therapy' for secondary prevention in coronary heart disease in a cohort of community-dwelling older men was 16 % and did not differ between men with and men without a geriatric syndrome [12]. Patient adherence is likely to influence assessment of effectiveness, and this is often different in clinical practice than in clinical trials. For example, overall adherence to prescribed statins over one year is only 49 % in observational studies but 93 % in clinical trials [13].

Drug utilization studies can also document clinically relevant details of the pharmacologic exposure. Examples include pattern of uptake of high risk or new drugs, such as the new oral anticoagulants [14] and dose used, including prevalence and appropriateness of dose adjustment [15]. Drug utilization studies describe duration of therapy including cessation or deprescribing [16] of medicines, for instance the prevalence of discontinuation of statins in older adults after receiving a diagnosis of cancer [17].

Drug utilization studies also describe the use of medicines that are taken concurrently with a study drug in practice. This is critical to understanding drug effects, since the majority of older people are treated in the setting of polypharmacy and potentially interacting drugs are common exclusion criteria in clinical trials. Drug utilization studies can describe the prevalence of measures of multiple concurrent drug exposures, such as polypharmacy or hyperpolypharmacy [18], drug-drug interactions [19], prescribing cascades [20], anticholinergic and/or sedative burdens [21, 22] and potentially inappropriate medicines [23].

Role of Pharmacoepidemiologic Studies of Safety of Medicines for Older People

A major role of pharmacoepidemiology and pharmacovigilance studies is to provide data on the safety of medicines. This methodology is important for all age groups because clinical trials are not large enough to detect rare adverse drug events [24]. However, it is particularly important for older adults, due to their increased risk of and from adverse drug events. The risk of adverse drug events is increased in old age by changes in pharmacokinetics and pharmacodynamics, reduced

physiologic reserve; as well as multiple concurrent medicines, comorbidities and health care providers. Pharmacoepidemiologic analytic observational studies are an excellent methodology to determine the prevalence of adverse drug events and associated risk factors in populations. For example, the risk of hospitalization for a haemorrhagic event with warfarin is particularly increased with concurrent administration of interacting drugs [25].

Pharmacovigilance studies are particularly useful for detecting new unanticipated signals of adverse events, and may raise the scientific questions for subsequent pharmacoepidemiolgic analytic observational studies. The association of the 'triple whammy' of concurrent use of diuretics, angiotensin converting enzyme inhibitors, or angiotensin receptor blockers with nonsteroidal anti-inflammatory drugs (NSAIDs), with acute impairment of renal function was first documented through pharmacovigilance of cases that predominantly occurred in older patients [26]. The risk was subsequently further defined through a case-control study [27]. Pharmacoepidemiologic and pharamcovigilance studies are able to investigate adverse drug reactions that may not be routinely collected in clinical trials but are highly relevant to older adults, such as falls, delirium, dementia, incontinence, and frailty.

Role of Pharmacoepidemiologic Studies of Efficacy and Effectiveness of Medicines for Older People

There is a great potential for benefit from medicines in older people, which, in the absence of high-quality clinical trials, can be partly assessed using pharmacoepidemiologic analytic studies. Observational studies of efficacy, such as cohort and case-control studies, are considered at best hypothesis generating. However, a recent systematic review did find that healthcare outcomes assessed using observational study designs were similar to those from randomized trials [28]. Pharmacoepidemiologic experimental studies (clinical trials) are needed to obtain high quality evidence on benefits of medicines already in the drug development phase in older adults, and these studies are the subject of Sect. 3.1 of this book. Advances in methodology, the 'practical clinical trial' [29] or 'randomized database study' [30], uses a randomized trial design to administer an intervention, and monitors outcomes from routinely collected administrative or clinical data. This may be a feasible and cost-effective way to obtain efficacy data in older adults, as well as patients in other age groups, in the setting of routine care.

Methodological Considerations in Pharmacoepidemiology and Pharmacovigilance Studies of Older People

There are a number of methodological challenges that are present in pharmacoepidemiology and pharmacovigilance research, in particular challenges related to the choice of study design, use of routinely collected administrative health data in

pharmacoepidemiologic studies, approaches used to define medication exposure and outcomes, validity, bias, and confounding. In pharmacoepidemiologic studies, two primary information sources can be used to obtain the data including data from ongoing cohort studies and large population-based administrative databases. Much progress has been made to encourage the best use of the available data in pharmacoepidemiology safety studies with including guidelines for good database selection to address the specific research question [31].

Study Types

The choice of study design to answer a specific scientific question requires consideration of issues related to the definitions of pharmacological exposure, outcomes, internal and external validity, as well as methods to control for confounding. Broadly, pharmacovigilance studies can include many study types from spontaneous adverse event reporting and analytical studies such as cohort, case-control studies, and clinical trials (Table 1).

While clinical trials are essential to establish evidence on the benefits of medical therapies, they are quite complex, costly, and can be especially challenging for recruiting older people with poor functioning, frailty, and dementia. Pharmacoepidemiologic observational studies have a major role in estimating the 'real-world' risks associated with medicines in older people.

Before interpreting real-world evidence from observational studies of older people, it is critical to understand the quality of the data used across studies, how participants were identified, strategies employed to assess exposures, endpoints, confounders, and the analytic approach used. Choice of observational study design and methods used to control for confounding can be critical in estimating the effects of medications on outcomes in older people. For instance, the results from studies assessing the effects of antipsychotic medications on cerebrovascular events, stroke and mortality in older people vary significantly across study designs and approaches used to control for important confounders. Overall, cohort studies are more likely to generate similar estimates for mortality risk with antipsychotics to those reported in longer clinical trials, while case-control studies tend to provide a higher estimate [32].

Exposure, Outcome, and Covariate Assessments

Exposure Definition

Accurate assessment of medication exposures is essential in studies of older people. The availability and accuracy of medication data is highly variable, and is a major determinant of the quality of pharmacoepidemiologic studies. Cohort studies collect

Table 1 The application and advantages and disadvantages of different observational study types (adapted from Table 1 [1])

Study type	Purpose	Sensitivity	Complexity	Limitations	Cost
Spontaneous case reports and case series (passive surveillance)	Initial signal	±	+	Incomplete reporting	+
	Rare events	−	–	Biased reporting	–
Cross-sectional studies (active surveillance)	Initial signal	+	++	Methods in development confounding	++
	Signal confirmation	++	–	Selection bias	–
	More common events	+	–	–	–
	Rare events	−	–	Recall bias	–
Case-control studies	Signal confirmation	++	+++	Confounding	+++
	More common events	++	–	Selection bias	–
	Rare events	++	–	Recall bias	–
Prospective cohort/randomized studies	Signal confirmation	+++	–	Cost	+++ +
	Common events	+++	++++	Loss to follow-up	–
Practical clinical trial	Signal confirmation	+++	+++	Cost	+++
	Common events	+++	–	Limited outcomes	–

± Indicate the degree of suitability

data from sources ranging from unprompted or prompted self-report to observed medication 'brown bag' histories, with varying periods and recall, and do not consistently collect information about dose or duration of use [33]. Administrative databases are usually limited to drugs dispensed or subsidies which results in omission of over the counter, complementary, and alternative medicines or unfunded medicines. Medication use can be coded to allow analysis by pharmacological class, using taxonomies such as the Anatomical Therapeutic Chemical (ATC) classification system (http://www.whocc.no/).

A number of explicit and implicit criteria and pharmacological risk assessment tools have been developed to standardize assessment of drug exposure in older people. When investigating the effects of medications in older people, it is important to consider basic pharmacological principles including drug class effects, dose response, and cumulative effect parameters. Medication exposures defined

using risk assessment tools that incorporate pharmacological parameters are more strongly and consistently associated with outcomes in older people than tools that do not take into account pharmacological parameters [34].

However, the application of explicit and implicit criteria has been limited or inconsistent across pharmacoepidemiological studies of older people, which may be in part due to data sources used across studies. For example, Beers Criteria to define inappropriate drug use in older people was originally developed in 1991, and was designed to be applied in frail older people living in nursing homes in the USA. However, over the last 20 years, the Beers Criteria have been applied in a range of populations of older people internationally [34]. Not surprisingly, the findings across studies have been inconsistent. This may have been due to modifications used to define exposure to the Beers Criteria, particularly restriction to the lists of potentially inappropriate drugs only, rather than including dose or drugs that may be inappropriate in particular conditions, due to limited availability of this data. Furthermore, studies of Beers Criteria have been conducted across various settings, testing the criteria against clinical outcomes, for which they were not originally developed.

Another approach to capture medication exposure is to use pharmacological risk assessment tools to measure the impact of cumulative medication load on clinically relevant outcomes in older people. For instance, a number of tools to categorize anticholinergic and/or sedative burden have been developed. Commonly used measures include Anticholinergic Risk Scale (ARS), Anticholinergic Drug Scale (ADS), Anticholinergic Cognitive Burden Scale (ACB), Sedative Load, and Drug Burden Index (DBI). However, a major challenge with applying anticholinergic scales is lack of international consensus in terms of defining drugs with anticholinergic effects. For instance, recent studies have found that there is poor agreement between common anticholinergic scales in terms of defining drug exposure [22]. This will have significant implications for studies on association with outcomes as the method chosen to measure anticholinergic drug exposure can have a significant effect on the results in terms of studying specific outcome, as can the method chosen to measure the outcome [35]. Interestingly, while there are substantial differences in the estimation of anticholinergic burden between the scales, all scales are associated with adverse clinical outcomes such as falls, GP visits, and mortality in older people [22].

Outcome Definition

Assessment of study endpoints in observational studies has advanced from measuring global outcomes such as hospitalization and mortality to capturing other critical outcomes for older people including geriatric syndromes such as falls, frailty, cognitive function, physical function, global self-reported health, and quality of life measures. Standardized and validated measures are available to capture data on falls (e.g., falls diaries) in cohort studies, while administrative data base studies often rely on hospitalisations for fall-related injuries.

Objective measures of physical functioning can be tested as outcomes of medication exposure. The Short Physical Performance Battery (SPPB), which predicts clinically meaningful outcomes such as disability, nursing home admission, and death is one of the most common objective measures of function used in studies of older people [36].

The association of medicines with cognitive function can also be assessed using pharmacoepidemiologic studies, although interpretation of these studies is very complex. There are a wide range of cognitive outcomes available, which can all be assessed with varying quality, from clinical diagnoses, to any number of cognitive screening or neuropsychiatric tests. Drug effects on cognition may occur almost immediately or over decades, making it important to define the appropriate timeframe for the study. Drugs tend to affect specific domains of cognition, with different domains detected by different tests, and pharmacoepidemiology studies need to investigate cognitive outcomes appropriate to the pharmacological exposure.

While there is no universal definition to define "frailty" at present, two frailty definitions commonly used for research purposes include the Fried Phenotype and Frailty Index. Recent evidence suggests that increasing medication loads, in particular polypharmacy and Drug Burden Index (anticholinergic and sedative exposure), is associated with development of frailty in community-dwelling men measured using the Fried Phenotype [37]. This has been confirmed in other studies of older people internationally [38, 39]. Other studies have shown no association between exposure to statins [40] or ACE inhibitors [41] and incident frailty. However, there is a lack of consistent evidence that associates medication measures with outcomes in frail older people.

Some pharmacoepidemiological studies of nursing home residents, who are often frail, have reported associations of inappropriate drug use with hospitalization and death, while others have not. It may be that measures developed to optimize pharmacological therapies in older robust people may not apply to frail people. Studies are required to provide a better understanding of the clinical benefits and harms of medicines in older adults with established frailty status as well as other geriatric syndromes, and of the impact of medicines on 'successful ageing.'

Covariate Data

In pharmacoepidemiological studies it is critical to capture correct data on potential confounders to ensure the internal validity. One of the main challenges is capturing data on disease or disease severity, particularly problematic for studies relying on large health databases. Efforts have been made to develop metrics based on medication data to indicate the presence of diseases. Examples include the Chronic Disease Score and Rx-Risk Score to estimate medical comorbidities [42]. The latter score has been widely used in large health datasets to identify comorbidities in studies of older people. Moreover, unmeasured confounders can also affect the study validity. This is harder to account for and is of particular challenge in studies

using large health datasets, as detailed information on clinical parameters, lifestyle, and over the counter medications are rarely captured [43].

Validity

Internal validity, defined as the extent to which the results accurately represent the study population, can be accomplished by using accurate and objective tools to assess study exposures and outcomes, as discussed in sections on 'Exposure Definition' and 'Outcome Definition.' In studies of older people, in terms of defining medication exposure, medication inventory taken by a trained investigator from a patient with their medicines is generally considered as a gold standard, although others have argued that dispensing databases may represent the gold standard [44].

External validity or generalizability to other populations can be difficult to accomplish in pharmacoepidemiological studies of older people. A number of factors can compromise the external validity including available data in terms of participant characteristics and place of residence. In a study of community-dwelling men, frail men were more likely to be institutionalized and die than non-frail men, independent of their statin exposure, suggesting no additional risks or benefits with statin treatment in either subgroup [45]. Therefore, one approach to achieve external validity is to stratify study populations according to geriatric syndrome such as frailty or multimorbidity status, provided that these individuals are included in the study.

Study setting such as community versus residential care is another important determinant of the applicability of study findings in terms of drug utilization and effects on clinical outcomes. Studies have shown that the prevalence of psychotropic medication use is consistently higher among people with dementia living in nursing homes compared with those living in the community setting [46]. The factors that contribute to continued high use of psychotropics in older people living in nursing homes are complex and require multifaceted interventions [47]. Likewise, in terms of studying the outcomes of medicines in older people, while some studies have shown beneficial effects of statins among older frail people living in nursing homes [48, 49], this has not been observed in studies conducted in the community setting [45].

Bias

Biases that are inadequately addressed can compromise the validity of pharmacoepidemiologic studies. Different types of bias may occur in pharmacoepidemiologic studies, including selection bias, information bias, and confounding. Selection bias, or bias related to how the study population is being selected is often

hard to address. This is of particular problem for studies of older people as many studies will readily exclude individuals based on their age, comorbidity or presence of cognitive impairment.

Information or misclassification bias which refers to the assessment of the exposure, outcome, and covariates is of particular challenge in older people, especially those with poor cognitive function in studies that rely on self-reported data. This can be minimized by using accurate and objective instruments to define exposure and outcomes.

Channeling and confounding by indication are major challenges for observational studies [2]. Channeling refers to the condition where medications are prescribed to patients differently due to the presence or absence of factors predictive of patient outcomes. Confounding by indication occurs when the indication, which is associated with the drug exposure, is an independent risk factor for the outcome. While many indices have been developed to capture the presence of diseases likely to predict the outcome of interest, in population-based studies, data on disease severity or severity of chronic conditions are rarely available. There are indices that can be used to capture disease severity, such as the Cumulative Illness Rating Scale (CIRS) [50, 51], but these can be rather time consuming and often require administration by trained personnel, so are not often collected. Moreover, confounding by indication is of particular concern in studies using administrative health data as these data do not routinely capture the indication for drug use. Recent efforts have been proposed to capture frailty status in pharmacoepidemiological studies using databases (Kim and Schneeweiss [52], which is important as frailty may be a major source of channeling. Frailty may also modify the effects of medicines in older people, and this can be tested using interaction terms.

Advances in Pharmacoepidemiology to Address Bias and Confounding

New-User Design and Propensity Score Modeling

Recent advances in the pharmacoepidemiology field including the use of new-user design and propensity scores have led to better control of bias and confounding in observational studies. In most observational studies, prevalent users, defined as those taking a therapy before study follow-up began, are commonly included. To eliminate the presence of prevalent users termed as ‘survivors’ in observational studies, the new-user design restricts the analysis to individuals under observation at the start of the current course of treatment. The inclusion of prevalent users can introduce substantial bias if risks vary with time, and covariates for drug users at study entry often are plausibly affected by the drug itself.

Propensity score modeling is another approach used to control for confounding by estimating the conditional probability of exposure to a treatment given observed

covariates. Matching or stratifying treated and control subjects on propensity score tends to balance all of the observed covariates. Propensity score modeling is particularly important in studies of older people as many outcomes are multifactorial.

To account for changes in medication exposures over time and time-varying covariates, pharmacoepidemiologic studies are increasingly employing statistical methods including mixed-effects modeling and multiple imputation methods to more accurately estimate the impact of medications. There is also growing interest in applying novel techniques to perform drug prescription data analysis using the network sciences approach. This methodology can be applied in large administrative datasets to monitor for the complexity of drug utilization patterns at participant and population level in particular to assess point prevalence, point incidence, duration of use, as well as other parameters [53].

Application

Impact on Clinical Practice

Pharmacoepidemiology and pharmacovigilance data on drug utilization and drug safety has a major influence on prescribing for older people, with growing impact from pharmacoepidemiologic studies of efficacy.

Pharmacoepidemiologic data on drug utilization in older people can demonstrate variability in prescribing and the determinants of that variability. This can identify opportunities and strategies to improve quality use of medicines. For example, a study of variation in antipsychotic treatment choice across US nursing homes found that individually, patient characteristics accounted for 36 % of the explained variation, facility characteristics for 23 %, and nursing home prescribing tendency for 81 % [54]. These findings point to the culture of the nursing home itself as a potential target for interventions to improve antipsychotic utilization. Duration of antibiotic prescribing in nursing homes has been shown to be strongly influenced by physician preference [55], suggesting a role for antimicrobial stewardship programs that target the individual prescriber.

Drug utilization studies are also helpful in detecting patterns of concurrent drug use which may be targets for prescribing improvement interventions. Prescribing cascades, when a new drug is prescribed to treat the unrecognized adverse effects of another drug, have been well documented through pharmacoepidemiology, initially with users of nonsteroidal anti-inflammatory drugs being at risk of starting antihypertensive therapy [56], and more recently for users of cholinesterase inhibitors commencing anticholinergic medicines [20]. The results of these studies inform prescribers of the risks of a prescribing a new drug to treat unrecognized side effects in specific settings, which should help clinicians recognize side effects and minimize prescribing cascades.

Pharmacoepidemiology studies have been the main source of information on the safety of drugs in older adults, and have identified clinically relevant drug interactions and adverse drug reactions not detected by clinical trials. For example, a population-based case-control study found that people taking alprazolam, lorazepam, or zolpidem had an increased risk of hip fracture if they also took an interacting medicine that increased exposure to these sedative hypnotics or resulted in cumulative central nervous system depression [57], demonstrating the clinical relevance of these interactions to clinicians. The increased mortality from antipsychotic medicines in people with dementia was discovered through pharmacovigilance and pharmacoepidemiology studies [58], and has led to labeling, policy, and legislation changes around prescribing antipsychotics for behavioral and psychological symptoms of dementia. Subsequent drug utilization studies have shown that the FDA black box warning for increased mortality from antipsychotics in treatment of older people with behavioral and psychological symptoms of dementia reduced their utilization in people with dementia [59].

Clinical prescribing and deprescribing practices are informed by knowledge of the effects of medicines on increasing the risk of geriatric syndromes. This knowledge comes predominantly from pharmacovigilance and pharmacoepidemiology studies. Data on geriatric syndromes are not collected in most clinical trials of pharmacologic therapy and patients at risk of these events rarely participate in clinical trials. For example, data on drug-induced delirium come from case reports, case series, and population-based studies [60], and have been translated into clinical practice guidelines (American Geriatrics Society Expert Panel on Postoperative Delirium in Older, [61].

Similarly, our understanding of the role of medicines in the pathogenesis of degenerative diseases often comes from pharmacoepidemiologic studies. Diseases like dementia can take decades to develop, which is beyond the timeframe of most clinical trials. Epidemiologic studies have demonstrated associations of increasing benzodiazepine use with incident Alzheimer's disease [62], and of increasing exposure to medicines with strong anticholinergic effects with incident dementia and Alzheimer's disease [63]. It remains to be seen whether these findings will influence practice by strengthening the rationale for minimizing use of benzodiazepines and anticholinergic drugs throughout life.

Furthermore, pharmacoepidemiology studies allow clinicians to assess the effects of medicines in patient subgroups similar to the individual they are treating, helping prescribers to apply the evidence to the patient in front of them. Clinical trials frequently exclude patients with a wide range of comorbidities, co-medications, or functional impairments. Observational studies allow evaluation of subgroups with these features, which may be relevant to patients in practice. For example, a recent study of haemorrhagic rates with warfarin and dabigatran in older people with atrial fibrillation documented real-world incidence of adverse events and to compare outcomes with treatment, by subgroup. The observed adjusted incidence of major bleeding was 9.0 % (95 % CI, 7.8–10.2 %) for the dabigatran group and 5.9 % (95 % CI, 5.1–6.6 %) for the warfarin group. Overall, the study found that compared with warfarin, the hazard ratios associated with dabigatran

were 1.58 (95 % CI, 1.36–1.83) for major bleeding, 1.30 (95 % CI, 1.20–1.41) for any bleeding, and 0.32 (95 % CI, 0.20–0.50) for intracranial bleeding. The age-stratified results for intracranial bleeding indicated that warfarin increased the risk of intracranial hemorrhage for patients older than 75 years (HR 0.10, 95 % CI, 0.04–0.24) but the hazard rates of intracranial bleeding for patients younger than 75 were not different between the treatment groups. This could help clinicians provide accurate estimates of risk and guide treatment selection for older patients with atrial fibrillation by age group [64].

Pharmacoepidemiologic studies can specifically inform clinicians of the risks of medicines in populations of older people with polypharmacy, frailty or dementia, who are almost never studied in clinical trials. For example, in community-dwelling older men, statins are used less often by frail than by non-frail men, and do not independently increase the risk of institutionalization or mortality in non-frail or frail [45]. Amongst older people in Finland, increasing exposure to anticholinergic and sedative medicines, measured using Drug Burden Index, is more prevalent amongst those with Alzheimer's disease than in those without, and an increase in Drug Burden Index of one unit increases the risk of mortality in those with Alzheimer's disease (HR = 1.21; 95 % confidence intervals [CI]: 1.09–1.33) and in those without (HR 1.37; 95 % CI: 1.20–1.56) [65].

When evaluating efficacy, pharmacoepidemiologic studies are generally considered hypothesis generating. However, this study type can provide estimates of effectiveness in different population subgroups that may be relevant to the individual patient. For example, a population-based study of the effects of statins in older people [66] found that restriction of the population to people similar to those in randomized controlled trials gave similar results to the trials, while the effects differed in populations with different baseline characteristics.

Therefore, in clinical practice, pharmacoepidemiologic drug utilization studies inform clinicians and healthcare providers of patterns of utilization, which can be used to target interventions to improve quality use of medicines. Pharmacoepidemiologic studies of drug safety inform practice and guidelines. Real-world observational studies of drug safety and efficacy allow physicians and patients to discuss the likely risks and benefits of medicines in comparable patients to make informed clinical prescribing decisions. There is potential for pharmacoepidemiologic studies in older people to further define the older population studied, in terms of multimorbidity, polypharmacy, falls history, or frailty, to help clinicians estimate drug effects in our patients.

Implications for Drug Development and Regulation

There are many opportunities in drug development to use pharmacovigilance and pharmacoepidemiologic data. Planned pharmacovigilance programs in older patients are important to assess safety and efficacy of these medicines in frail older people who may respond differently to the younger more robust participants in

clinical trials performed prior to marketing. There are increasing efforts to combine large data sets across multiple regions to monitor for adverse drug events, for example, the EU-ADR project (http://euadr-project.org).

Results of such studies can result in changes to licenced/registered prescribing information. Limitations may be made to the population treated, or to changes to recommended dosing regimens. For example, dabigatran is available at 150 and 110 mg strengths (dose reduced for older people and those with renal impairment) in Europe, Canada, Australia, and New Zealand, but the FDA approved only the 150 mg strength of dabigatran. Pharmacovigilance reports of excessive bleeding with the 150 mg strength and pharmacoepidemiologic observational studies of the safety and efficacy of the 110 mg strength in older people have resulted in calls for licencing of the 110 mg strength by the FDA [67]. Other pharmacoepidemiologic data has resulted in new black box warnings. For example, the addition of warnings about the risk of diabetes and cognitive impairment to the prescribing information for statins was based on pharmacovigilance and pharmacoepidemiologic data (http://www.fda.gov/Drugs/DrugSafety/ucm293101.htm).

Drug utilization studies can also be used to assess the impact of policies and interventions that aim to improve drug use in a population. A good example in the USA is studies investigating the impact of the omnibus reforms on antipsychotic utilization in nursing home residents [68]. Examples from Australia include the Veteran's Mates program, which audits relevant aspects of practitioners prescribing before and after specific educational interventions and benchmarks them to their peers [69]. The Australian NPS MedicinesWise program evaluates the impact of national educational programs on prescribing [70].

Drug utilization studies have also been used to encourage adherence to prescribing guidelines. For example, in the UK, government funding to local doctors is linked to measures of prevalence of adherence to guidelines through the pay for performance Quality and Outcomes Framework. This funding incentive may create a conflict of interest for practitioners managing older adults with multimorbidity, in whom following disease-specific guidelines is likely to result in polypharmacy, drug-drug interactions, drug-disease interactions, and enormous treatment burden. This complexity needs to be considered when performing pharmacoepidemiologic measures to evaluate treatment in older populations and when designing such policies.

Conclusions and Future Directions

Optimizing medication development and utilization for older people is a challenging and important task for scientists, regulators, and clinicians. Pharmacoepidemiologic studies provide critical information in terms of drug utilization, safety, and efficacy, which informs regulators, clinicians, and patients. Advances in pharmacoepidemiologic methods can tackle some of the challenges of bias and validity inherent to the methodology, as well as tackle the complex

systems and networks that drive medication utilization. Advances in gerontology research, such as objective definitions of frailty, can improve characterization of observed populations and of patients to allow clinicians to use data from populations that are directly comparable to the patients they treat.

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Part IV
Product Development for Older Adults

Defining Patient Centric Drug Product Design and Its Impact on Improving Safety and Effectiveness

Sven Stegemann

Abstract Drug therapy is being recognized as the most preferred intervention in the cure or management of acute and chronic diseases. Progress in medical and pharmaceutical sciences coupled with the increasing life expectancy in aging societies has constantly increased the sophistication of the drug products as well as the complexity of the patients and their therapeutic regimen. Despite the fact that acute and chronic diseases can be treated with several drugs very effectively, poor adherence and medication errors often lead to poor therapeutic outcomes. Patient centricity has been identified as the way forward to improve the therapeutic outcomes by including the patient in a variety of different ways in drug product development and the therapy process. This review focus on the critical patient–product interface taking into account the increasing complexity of the micro- and macro-ergonomic context of the drug product and its use within therapeutic schemes and regimen of the patient. A definition for "patient centric drug product design" is proposed and the impact on drug product safety and effectiveness is discussed.

Keywords Patient centricity · Patient centric design adherence medication · Errors effectiveness

Introduction

In a recent paper Carnes and Witten investigated the intrinsic biological lifespan of humans taking into account the theory of Darwin for the time required to maintain our species, referred to as Darwinian fitness [1]. Compared to other animals the approximate time to mortality for humans was calculated with 50–55 years. That humans have successfully reduced extrinsic and intrinsic mortality is because of the

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S. Stegemann (ed.), *Developing Drug Products in an Aging Society*,
AAPS Advances in the Pharmaceutical Sciences Series 24,
DOI 10.1007/978-3-319-43099-7_13

continuous progress in technology and recently the ability to intervene into the biology to modify health-threatening physiological deviations or defend from external infectious diseases.

Medical and pharmaceutical sciences are traditionally oriented toward establishing efficacy, safety, and quality of pharmaceutical products independent of whether if it is a new chemical entity or a generic molecule. Substantial scientific and technical knowledge as well as regulatory guidance have been developed over the years to provide pharmaceutical products and drug therapies to patients with a favorable risk–benefit profile. Each new medicinal product is developed and tested in a series of clinical trials in randomized patient population in a double blind trial design, in comparison to placebo as well as the established first line treatment. Even so the efficacy is proven in a large and statistically relevant patient sample size, the expected and estimated therapeutic outcomes in the real world, called effectiveness, often remain disappointing [2].

The main use and perceived advantage of drug therapy is the prescription and provision of the drug products to the patients for independent administration and management. The transfer of the responsibility for the execution of the therapy to the patients is supported by patient information leaflet containing all information about the drug, drug product, the adverse drug reaction, contraindications, mode of use, and other therapy and product-related information. In case the patient still has questions or is missing some important information, additional advice is provided by physicians or pharmacists. It is assumed that this enables the patient to take each drug in the right dose, at the right time, and in the intended way. That compliance and even the more collaborative efforts between physicians and patients adherence and concordance are still considered to be poor and a major concern in achieving the therapeutic goals, little is being done to involve the true patients more into the drug product and dosage form development process or to understand their laypersons perception, conclusion, and decision when interfacing with and using the drug product.

Patient centricity has recently become a frequently used word in drug delivery research and product development. Patient centricity is referred to as appropriateness, meeting patient needs, personalized medicine, patient convenience, ease of use, direct communication as well as empowerment of patients and delivering services to patients beyond the product and used in a variety of different contexts and from different perspectives. For patients, patient centricity means personal consultation, medical advice, education and explanation on the disease, drug therapy and potential adverse drug reactions [3] as well as the use of IT-based healthcare solutions and access to information through media [4], while payers and the healthcare insurance companies see patient centricity as part of the therapeutic solution to the patient as they move to a pay-for-performance model [5]. Regulators have started to focus their regulatory guidance and evaluation on individual patient populations like pediatrics and start to require evidence on product effectiveness in addition to the efficacy [2]. The pharmaceutical industry is recognizing the increasing patient demand and involvement in their personal health and defines patient centricity as a tool to communicate with the patient and develop a longer term relationship and brand loyalty. In addition, technology providers and companies are increasingly trying to

enter into healthcare introducing their technologies at the interface of healthcare providers and patients or physicians under the umbrella of patient-centric solutions like telemedicine or electronic patient healthcare cards. What is common in all the different perspectives of "patient centricity" is the fact that the patients are recognized as an important part of their own health and therapy that needs to be considered from the early stage of drug product development through to the treatment or management of the disease by the patient or caregiver. The objective of this article is to review the recent trends in drug discovery, drug development, patient populations, and their impact on drug therapy over the past decades. A definition for "patient centricity" related to the drug product development including drug product design and manufacturing is being proposed to contribute to further discussions on patient centricity in the development and design of drug products.

Evolution in Drug Discovery

In the nineteenth century drugs were discovered by chance and mainly derived by extraction from plants like digitalis from foxglove, Quinine from Cinchona tree, ipecacuanha from Cephaelis plant, and salicylic acid from the bark of the willow tree. At the beginning of the twentieth century a series of chemical structures were characterized and found to be effective treatments for infectious diseases. In the mid 1950s the first structure of the human DNA was proposed [6] and pharmacology and synthetic organic chemistry progressed into scientific rational drug discovery tools. Since then, drug discovery entered into a constant innovation path introducing high throughput screening (HTS), recombinatorial chemistry, pharmacogenomic technologies, and systems biology [7]. This led to the introduction of many new drug classes for the treatment of the major chronic diseases followed by a series of molecules with distinct different properties within each class. During the past 70 years the FDA approved 1496 new chemical entities with the majority of products launched during the past 30 years (775 products) with the highest number launched between 1992 and 2001 accounting for 309 new chemical entities as summarized in Table 1.

The application of HTS methods started 1990 and was coupled with combinatorial chemistry a few years later to become the new paradigm in drug discovery [9]. Combinatorial chemistry allowed the chemical synthesis and rational design of

Table 1 Number of new chemical entities launched by the FDA between 1942 and 2011 [8]

Time frame [years]	Number of New Chemical Entities
1942–1951	203
1952–1961	202
1962–1971	134
1972–1981	182
1982–1991	231
1992–2001	309
2002–2011	235
total 1942–2011	1496

drug molecules in an automated manner creating hundreds of different molecules in a single day. This rational drug design focused on the in vitro receptor binding capacity by optimizing the coverage of the three-dimensional receptor structures. This is normally achieved by more lipophilic groups that occupy the receptor pockets and increase the receptor affinity. Due to the fact that for the HTS the compounds were dissolved in dimethyl sulfoxide (DSMO) rather than in aqueous media, aqueous drug solubility became less important in drug discovery [10]. As a result the drug compounds derived from HTS and combinatorial chemistry increased in molecular weight, lipophilicity and higher H-bonding properties which directly impacted aqueous solubility and permeability [11]. This advances in medicinal chemistry and drug discovery led to an increasing number of molecules with challenging absorption, distribution, metabolism, and excretion (ADME) characteristics that entered into the drug product development phases. Sophisticated drug delivery technologies as well as more restricted and specific administration procedures are required for the administration of the resulting oral drug products.

With the discovery of the Polymer Chain Reaction (PCR) in the mid-1980s by Kary Mullis and the genome sequencing biotechnology tools, pharmacogenomic technologies started to make inroads into the drug discovery as well as led to the introduction of biopharmaceuticals into drug therapy. With the sequencing of the human genome and its publication in 2001 [12] and 2004 [13] the era of the single nucleotide polymorphism and the—omics created a new hype in drug discovery. Even so several of the expectations could not be met until today there is constant progress and success that will continue to advance clinical medicine, understanding disease networks, and identify new diagnostics and therapeutics [14–16].

As a result from the 451 new drug launches between 1996 and 2010, 67 products were biopharmaceuticals representing 17.5 % of the total new drug launches [17]. These drugs also referred to as “large molecules” cover a wide range of different therapeutics, such as proteins, monoclonal antibodies, vaccines, biosimilars, nucleic acids, glycol engineered products, and reformulations of existing biopharmaceuticals [18]. These molecules differ from small molecules in the sense of molecular size, heterogeneity in structure, manufacturing, characterizability, and immunogenicity [19] as well as in their respective drug delivery and dosage form which is mainly by the parenteral route [20]. In the past years the first generic versions of biopharmaceuticals so called “biosimilars” have been launched in Europe and lately also the FDA put respective guideline in place [21] and accepted the first application of a filgrastim generic [22]. Due to the biologically derived nature of these products, biosimilars are not exact copies of existing products and could not necessarily be used interchangeably like generics of small molecules [23]. Similar types of products that have reached the market in the past years are molecules that do not have a homo-molecular structure, cannot be completely characterized by analytical means and are highly dependent from the manufacturing process. These non-biological complex drugs (NBCD) share the same challenge and limitation of interchangeability of its generic versions like the biopharmaceuticals [24].

Modern drug discovery starts evolving less than 50 years ago and progressed rapidly with several disruptive innovations in science and technology. These

advances have not only provided hundreds of new compounds and drug classes but also came along with increasingly challenging chemical properties as well as biological compounds requiring sophisticated formulation and drug delivery technologies to convert them into administrable drug products.

Progress in Drug Therapy

Modern drug therapy started with the implementation of rational drug discovery and the introduction of chemically synthetized drugs in the 1950s. Acute and chronic diseases could now be treated effectively with single pharmaceutical products that were made available to an increasing number of patients. With time, different therapeutic targets for the chronic diseases were identified and drugs were developed [25, 26]. The possibility of intervening a chronic disease through different clinical targets and the availability of respective drugs has been found in practice to achieve the best possible therapeutic outcomes. To assure high treatment quality, therapy schemes for the specific chronic disease expressions have been formalized by healthcare professionals through establishing therapeutic guidelines [27, 28]. The therapeutic guidelines are considered as the standards in prescribing even so deviations from the prescribing guidelines are possible and sometime recommended [29]. With the increasing progress in understanding the disease cascades and networks as part of the drug discovery process respective diagnostic tools will provide further evidence for the co-prescription of several drugs in the treatment of a chronic disease condition.

Pharmacogenomic research has identified disease- and treatment-specific biomarkers as well as individual metabolic pathways that are associated with the safety and efficacy of the therapy that increasingly lead to the personalization of the therapy by validated diagnostics. One of the first products that were launched along with a companion diagnostic device was the product trastuzumab (Herceptin®) for the treatment of HER2 overexpressing breast cancer. This companion diagnostics will evolve further in validated tools applied in the selection and prescription process of the drug for the specific patient, the exclusion of drugs in certain patient populations as well as to determine the precise dose required for an individual patient to achieve the targeted plasma levels or concentrations at the receptor site [30]. Despite some drawbacks in developing and implementing validated genome sequencing methods [31] the FDA has recently approved a first high throughput genomic sequencer that is expected to stimulate the development of several new genome-based diagnostic tests [32] as well as lead to its implementation into routine practice in drug therapy and prescribing [33, 34].

Despite the insufficient involvement of older adults in clinical trials [35, 36] older people benefit from drug therapy even though the therapeutic decisions are moving more toward individual, patient-specific treatment decisions [37, 38]. Different approaches have been developed for individual prescribing tools for older adults such as the Beers List [39], the Priscus List [40], or the STOPP and START

criteria [41], which are not expected to reduce the overall number of drugs prescribed to older patients as over- and under-prescribing have been identified in older adults [42]. Individual therapeutic decisions and prescribing to older adults will remain a moving target throughout the lifetime and may change considerably toward the end life stage, when the therapeutic goals change significantly as well as should be aligned much closer with the patients' goals [43–45]. As a matter of fact polypharmacy especially in multimorbid and frail patients can therefore be expected to remain the rule rather than the exception, but will become more individualized taking into account the specific patient disease patterns, needs, and wishes.

The availability of drugs to treat more and more disease conditions effectively also increased awareness of the different patient populations receiving such treatments or could benefit from the drugs. In the year 2000 the International Conference for Harmonization (ICH) published the E 11 guideline [46] to stimulate the development of medicinal products for pediatric patients early on in new drug development which was followed by several guidelines of the FDA and European Medicines Agency (EMA) on pediatric regulations [47]. This guidance was further extended by a reflection paper of the EMA to emphasize on the formulation and medicinal product design as an important part of the pediatric drug product and to include such considerations early on into the product development for pediatric products [48, 49]. A similar initiative has been taken recently by the ICH with the E 7 guideline [50, 51] and the EMA for the geriatric patient population as well by defining their Geriatric Medicines Strategy in 2011 [52] followed by the decision to develop a reflection paper on appropriate product design and quality [53].

Over the past decades drug therapy has evolved into the major and broadly applied intervention to treat or manage acute and chronic diseases. Based on evidence and increasingly on the understanding of the underlying genetic variation and their interplay in disease networks modern drug therapy intervenes simultaneously at different stages of the cascade through the use of different drugs. With the increasing life expectancy the prevalence for multimorbidity and very high age of the future patient populations will continue to drive polypharmacy. The growing use of pharmacogenomics and biomarkers in standard practice will lead to personalized dosing regimens especially in vulnerable patient populations like pediatric and geriatric patients. This has and will continue to enlarge the sophistication in drug therapy and drug therapy management for healthcare professionals as well as patients.

Advances in Drug Delivery

Traditionally pharmaceutical products were derived from natural sources and supplied to the patients as extracts, encapsulated in gelatin or as "pills" using glucose syrup as a binder to form round balls on a pill board. Little was known at that time regarding the impact of excipients and processing until the year 1937, when a sulfanilamide medicine was prepared and sold as an Elexir that caused massive poisoning and the deaths of more than 100 people [54]. The main excipient

used in this formulation was diethylene glycol, an antifreezing agent that leads to liver and kidney failures. In 1967 another incidence occurred when a manufacturer exchange calcium sulphate dehydrate by lactose in a phenytoin capsule formulation, which led to 3–4 times higher plasma levels and intoxication of several patients [55] As a result of this latter incidence, the FDA started an initiative to understand bioavailability (BA) and bioequivalence (BE) for drug products in 1970 and formulated its first regulation for BA data in product submissions [56]. From 1986 to 1989 the FDA put a BE task force in place to develop its first BE guidelines for new and generic drug product developments that was followed by additional Scaling Up and Post Approval Changes (SUPAC) guidelines for Immediate Release (IR), Modified Release (MR), and Nonsterile Semi solid (SS) formulations in 1995 and 1997 respectively. These regulations also required to study BA and BE in the fed and fasted stage [57].

Around the same time, pharmaceutical scientists start to explore drug formulation and dosage forms as a way to deliver the drugs to targeted tissues and with a controlled time release. The development of controlled release oral products started around 1950 with around 180 different prolonged release products on the market in the USA in 1961. However this early attempts were not necessarily well understood or evaluated but has progressed constantly over the past decades using polymer coating, matrix systems, ion-exchange resin complexes, or osmatic pump systems as well as inhalation aerosols, transdermal delivery and intramuscular or subcutaneous injections [58]. As reviewed by Hoffman, the area of controlled drug delivery devices started with ophthalmic inserts, intrauterine device, and skin patches that released the drugs by a zero-order kinetic. Biodegradable microparticles were developed as im, sc, or iv controlled drug delivery systems, as well as polymer drug conjugates and release of drugs from surface coatings that were mainly used as implants [59]. Today there are a variety of drug delivery systems that provide different release kinetics, routes of administration, and formulation types. Table 2 provides an overview of the major drug delivery systems and their route of administration.

Table 2 Major dosage forms and routes of administration

Oral	Non-oral	Injectable
• Tablets • Capsules • Soft capsules • Sprinkles • Orodispersible tablets • Wafer/films/strips • Mucoadhesive tablets • Buccal tablets • Sublingual tablets • Chewable • Liquids (ready to use or for reconstitution) • Oral gels • Gum • Sachets • Dose sipping straw	• Nasal • Orally inhaled products (DPI, MDI, Nebulizer) • Transdermal patches • Ointments/creams • Suppositories • Intrauterine rings • Eye drops/creams • Eye inserts • Ear drops	• Intravenous • Intramuscular • Subcutaneous • Implant • Autoinjector/pen • Prefilled syringes

To optimize the clinical outcomes a variety of drug delivery technologies and dosage forms have been applied systematically in drug product development since. The products brought to the market are able to target the release in the intestine or to the receptor site, achieve a specific plasma profile or provide an alternative route of drug administration. Along with the continuously growing number of drug classes, new therapeutic molecule options and drug products introduced each year in the market, the available multitude of drug products and therapies is reaching a level that is starting to create a challenge by its own. This has been recognized by various healthcare professionals in the recent years especially when dealing with older patients with multiple chronic diseases. Geriatricians are trying to establish prescription guidelines to prevent drug–drug interactions or to adjust the risk–benefit profile of a medicine based on the severity of a potential adverse drug reaction for this patient population. There is an increasing awareness of a growing risk for medication errors occurring at the prescription stage [60] as well as administration stage by professional caregivers [61] and patients themselves [62].

Stimulated by the regulatory guidelines [63] specific attention is drawn to pediatric formulation in the past years. The challenges identified since are ranging from sufficient safety data on the excipients for drug product formulation [64] to palatability of the dosage form [65]. The traditional concept on suitable pediatric formulations were the use of oral solution [66] until recently a study demonstrated the higher acceptability and safe administration of orally disintegrating mini-tablets to infants and preschool children aged 6 months to 6 years [67, 68]. This study clearly provided evidence that patient-centric drug delivery systems cannot solely rely on a theoretic concept, but need to be tested in the concerned patient population taking into account various other aspects of the patient population specific conditions that might affect the use, safety, and effectiveness of the drug product.

Modern drug delivery technologies have enabled the development of drug therapies by improving the BA of the drug, maintaining a therapeutic plasma level as well as the targeting of the drug to a specific tissue. In order to achieve these clinical objectives, the drug delivery technologies came along with specific administration instructions and restrictions; different from the other pharmaceutical drug products even though they look similar to these other products and as such are familiar to the patient. Each specific requirement or need for a preparative step or administration procedures increase significantly the complexity and level of demand for the patient bearing the risk for medication errors to occur more frequently [69].

Patient Characteristics and Demographics

During lifetime the human physiology is in constant change starting from the impregnation through to death. The human physiology is in a dynamic developmental process with a growth and maturation time frame until early adulthood [70]

followed by a slowly starting decay and aging phase that is differential and individual [71, 72].

During the life course different patient population can be identified based on their physiological state, pharmacokinetics, pharmacodynamics, and abilities/disabilities related to drug therapy. Major patient populations are summarized under pediatrics (newborn infants, infants and toddlers, preschool children, school children and adolescents) and geriatrics (e.g. high age, multimorbid, and frail). Common in these patient populations is the need for flexible dose adjustment according to the age of the patient [70, 73], disease conditions [74], or co-administered drugs [75, 76]. This is especially true for drugs with a narrow therapeutic window and metabolic variability based on genomic differences [33, 34, 77].

According to the Gallup–Healthways Well–Being-Index [78] the onset of chronic diseases today starts at an age of 35 years and peaks at 75–80 years in Americans. The most recent generations tend to develop chronic diseases earlier in life [79] with 90 % of the people 70 years and older with at least one chronic disease and even 30 % with five or more diseases [80]. Due to significant progress of medical interventions and drugs developed in the past 50 years, multimorbidity can be treated very effective providing humans with a constant growing life expectancy which is reaching in the western world 80 years and more. At the same time multimorbidity will inevitably lead to polypharmacy, normally defined as the concomitant use of five drugs and more and the needs for the patient to be followed through the medication on a daily base [81].

The changing demographics and shift toward older and very old people also changes the average age of the user groups of medicinal products as well as raise the prevalence for diseases which are correlated with higher age like M. Alzheimer and cancer [82, 83]. As this demographic change is evolving "silently" over time but yet rapidly for drug product development which takes about 10–15 years to get to the market, this actual and future patient population is not represented sufficiently in the drug development program [35, 36, 84]. The prevalence for multimorbidity will also further increase with the associated additional complexity in drug therapy [85] and increasing risk for polypharmacy [86]. Recent investigations into specific morbidity and co-morbidity patterns of multimorbid patients identified certain disease clusters with common morbidities [87] of which clusters with two chronic diseases already lead to a drug therapy consisting of more than 8 drugs [88]. This development and evolution of the major patient population away from a patient with a middle aged, single disease and single drug treated patient to patients with several disease conditions, disabilities and a complex drug therapy is not only a challenge for prescription [81] but also questions the dosage form and dose strength of the pharmaceutical products that still follow the same standards that are to a certain extent responsible for medication errors on various levels of the process [89] including drug administration [90] as well as related to the drug product design [91].

Managing and administering medicines is a task that has to be performed by the patients or their caregivers. To perform a task information need to be processed and the respective actions need to be taken to achieve the goal of the task. Information processing in task performance requires different levels of demand. Skill-based

tasks are executions of highly practiced actions which does not require much attention and that is done in an automatic and nonconscious manner. Rule-based tasks are tasks that deal with certain uncertainties that are resolved by applying some rules or procedures to perform the task. This rules and procedures can be based on previous empirical problem solving or by learned and stored rule. A task becomes knowledge based when the task or situation is unfamiliar and no rules or previous experience exists. In such a case the task and the goal can only be achieved through an effortful cognitive process and additional know how [92]. With regard to drug therapy, the administration of a single drug per day might be considered a skill-based task as it can easily be transferred in a routine practice. In contrast to this polypharmacy means the use of multiple drug products per day that differ in the administration time, dose, dosage form, route of administration, pre- or postprandial intake, handling of devices and other specific administration instructions that require much more consciousness and attention and will increasingly include knowledge-based tasks, especially when the dosage form cannot be administered as intended (e.g., too big to be swallowed), adverse drug reactions or drug–drug interactions occur or additional OTC medications are used. For example, to overcome oral medicines administration issues the modification of the dosage form by crushing the tablet or opening the capsules is a frequently used practice by patients and caregivers [93]. Reported incidences showed that this is not only a concern for the geriatric patient population but also in pediatrics [94]. Investigation into the root cause of this practice provided evidence that the decision is a truly knowledge-based task requiring a high degree of expertise [95].

Even so the medicinal products are accompanied with intense patient information the language used is often highly medicinal and technical, medical and pharmaceutical terms are used with the consequences that such information are misread [96]. It is accepted today that many people do not have sufficient health literacy and have limited ability to read and understand healthcare information and to take the appropriate decisions [97, 98]. Moreover it has been shown that there is an age relationship in information processing of prescription drug labels that have an impact on drug product understanding of the patient [99].

Patients are normally laypersons with their own ‘knowledge’ and beliefs [100] and concerns about taking medicines [101]. Patients may do their own clinical trials for adverse drug reactions, reject medicines or actively adjust and modify their therapy [101]. Patients do not want necessarily to be involved in drug therapy decision as they feel to lack knowledge, have low self-efficacy, have fears, or simply do not trust the prescribing physician [102]. Patient not necessarily develop medication administration routine, confusion with generic names and therapeutic duplication, hoarding medication including expired drugs as well as continuing using medications that were discontinued. Multiple storage locations, especially kitchen and bathroom have been identified as common practices in patients with poor adherence and therapeutic outcomes. Further to this, patients often take out the medication from the original package due to the need of tablet splitting or because of issues related to the original packaging without proper labeling or respect of the storage conditions [103, 104].

Patients may not only suffer from the symptoms of a disease but also have functional impairments or disabilities due to the disease or advanced age that directly impact the ability to everyday activities including to manage the medication. One of the prerequisites to handle and administer pharmaceutical products is sufficient hand functioning in terms of muscle strength, dexterity, and fine motoric functions. These elementary functions are impacted by age and disease [105–107]. Another important factor in independent medication management is sufficient visual capability and performance to find and identify the drug products, retrieve written information wherever necessary as well as follow the time of administration. Various studies have demonstrated the age relationship of visual impairments [108], the increased prevalence for Macular degeneration [109], and the high ratio of undiagnosed case of correctable visual impairments [110]. It is well accepted today that communication plays a key role in patient acceptance and understanding of the disease and therapy. Age- or disease-related loss in hearing function, speech recognition, and word recall and ordering starts to decline in adulthood and is becoming prominent in higher age [111–113].

Patients do not represent a homogeneous population with a common set of needs and capabilities. Aging is a dynamic process that is different from person to person. With the increasing life expectancy the prevalence for diseases, impairments and disabilities is growing, leading to the progressive use of more drug products. The demand for the management of the medications constantly increases but the patient remains a layperson who has to take decisions and perform medication administration tasks that require substantial knowledge and experience. While the level of demand is growing with each additional drug to take the patient capacity to manage the drug therapy is negatively impacted by the progression of age and disease related impairments.

Environmental Conditions in Drug Therapy

In primary care settings the drug therapy is generally organized and managed by the patients in their own home. Drug therapy is a dynamic process occurring at all different life stages. In acute situations drug therapy might involve one or two drugs and will span only from days to weeks while in chronic conditions drug therapy and the number of drugs will build up over time, change in between and continue for several years up to decades. Following through the drug therapy at home the patient encompasses a large number and different types of interactions. The patient has to interface with the drug product, with the home environment as well as the "workplace" at home. Moreover, the patient needs to organize the medication and build a process for its management and administration according to the objectives of the health goal. It is well known that these micro- and macro-ergonomics are important factors in generating or preventing human errors throughout the provision of healthcare [114]. A human error is defined by the Quality Interagency Coordination Task Force of the Agency for Healthcare Research and Quality

(AHRQ) as "*the failure of a planned action to be completed as intended, or the use of a wrong plan to achieve the aim. Errors can include problems in practice, products, procedures, and systems.*" [115]. In professional healthcare environments and systems, special attention is given to the design of organizational structure, workspace, technology ergonomics, and the constant monitoring of its efficiency in preventing human errors. In contrast to these professional healthcare environments, a traditional household is neither optimized nor even set up for the management and administration of complex medication schedules nor do the patients and their caregivers receive appropriate training on managing the drug products. In reality the medications are often stored altogether in one carton or on the cupboard eventually together with the medication of another family members, discontinued drugs are not removed, medicines might have been taken out from the blister or box prior by a caregiver, stored in unlabeled cups or other containers [116] as well as the remaining halves of split tablets. The medications are prepared in poor lightening and on tables covered already with many different things, television and relatives might interrupt and distract during medication preparation and intake or even drugs being shared with other family members that have a direct impact on safe medication management [117, 118]. In such a patient context, the design of the pharmaceutical product as the direct interface with the patients play an important role in overcoming limitations caused by the environmental conditions of home settings. The required product design features will follow the same principles as applied in human factored design, which is already applied in drug-device combination products [119].

The environmental circumstances also include the living standards and the social as well as economic situation in the region creating patient population with specific or additional needs [120]. When developing and distributing drug products to countries with limited traceability of the supply chain eventually coupled with high temperature and high humidity conditions, anti-counterfeiting measures as well as drug product stability becomes a critical and important challenge [121]. It should also be considered that even so between 1990 and 2012, 1.6 billion people on earth gained access to clean and piped water, there are still 748 million people that do not have access to an improved water supply and continue to rely on surface water sources, especially in the sub-Saharan African region [122].

In such cases the priorities in patient centricity of the drug therapy might change to supply chain security, transport and storage conditions, anti-counterfeiting as well as the limitations of clean drinking water and will supersede the other drug product factors that are important for safe and effective drug administration. These environmental factors are specifically important for drugs that are developed for the tropical and neglected diseases in conjunction with the targeted patient populations that might include newborn and young children to a large extent.

Safe and effective medication scheduling and intake require an environment that maintains the focus on the task and supports the safe and effective task execution. The environmental circumstances in outpatients, are normally not designed for medication management and use; however, the demand and complexity is growing. For patients in emerging and poor economies drug therapy is additionally impacted

by issues in the supply of the product and the intake modalities, which might be of higher priority to solve than issues occurring in the mature markets to secure safe and effective drug therapy.

Medication Errors and Non-adherence

The importance of the patient following through the medication on the outcomes of drug therapy and drug safety is known since the beginning of modern drug therapy about 45 years ago [123]. In the early days the term "compliance" was used describing a very directive top-down approach, whereby the patient was supposed to follow all the instructions given by the physician. This has moved toward "adherence," an expression that considers the importance of involving the patient in the decision process and getting her or his principle agreement on the therapy. Some authors lately suggested an even more intense involvement of the patient in the therapeutic decision process referred to as "concordance," whereby the medication schedule is aimed to be compatible with the patients day structure and routine [124, 125]. Despite all efforts done, adherence to drug therapy remains insufficient as it is caused by a variety of factors, mainly social/economic, therapy related, patient related, condition related, or health system factors [126]. Several studies have been performed to evaluate the impact of specific interventions on adherence improvement with mixed outcomes or limited positive effect [127–130]. The reason might be the fact of the variety of different reasons for poor adherence that cannot be resolved with one kind intervention, rather require an individual approach and incremental improvements on the various factors including drug product design [131].

So far the dosage form and the product design have only gained limited attention as a contributing factor to adherence even so it has been shown that inappropriate product design could lead to a high level of drug omission [132–134]. Another way to deal with drug products that cause issues for the patient in handling and administration is a problem solving approach by the patient. For example, tablet crushing or crushing combined with mixing under food has been identified as a standard practice to overcome swallowing issues [135]. Thus, "adherence" is often established by inappropriate alteration of the drug product, which can be considered as a medication error with the potential consequence on safety and efficacy.

The impact of medication errors on safety, efficacy, and effectiveness has recently received substantial attention [136]. As a consequence medication errors have been included as a reportable safety concerns in the pharmacovigilance process by the Directive 2010/84 (EC) and the EMA Guidelines on good pharmacovigilance practices (GVP) [137–139] whereby "*Medication error refers to any unintentional error in the prescribing, dispensing, or administration [including preparation for administration] of a medicinal product while in control of the healthcare professional, patient or consumer*." [139]. Further guidance has been provided on the drug product design specifically through additional guideline of the EMA [140] and the FDA [141]. These latter guidelines urge patient-centered

product development by considering potential medication errors by the patients and take away any confusion or need for patient education and important labeling. These guidelines follow several reports on medication administration issues in long-term care facilities [142], transdermal patches [143–145], swallowing of products still in the blister [146–148], and intravenous preparations [149–151].

The patient interface with the product needs to be considered as an important factor for non-adherence and medication errors. Intended or unintended medication errors or non-adherence are closely related to poor drug product design and can occur at healthcare professional level [152, 153] however only limited studies have been done to understand medication errors on the patient level [154, 155]. It should be noted that adherence and medication errors are related to the complexity of the therapy [153, 156] and drug product design needs to be viewed within such a polypharmacy context and not just on the individual product basis.

Definition of Patient-Centric Drug Product Design

Modern drug therapy has significantly improved treatment and management of the major acute and chronic diseases to the benefit of the patients and society. Increasing age, multimorbidity, polypharmacy as well as combinatorial chemistry, drug delivery technology, and routes of administration have substantially increased the complexity of the patients, the drug therapy, and its management. This level of complexity is transferred to the patient responsibility for independent scheduling and implementation of the entire drug therapy into daily practice at home. Patient-centric drug product development builds on human factored design within the patient context (Fig. 1) and on a user interface that is guided by simplicity and intuition.

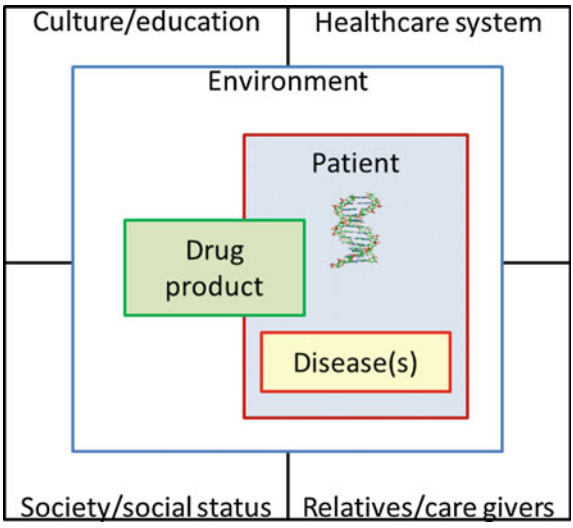

Fig. 1 Framework of patient-centric drug product development

Patient-centric drug products are based on the following principles:

- Are tailored in terms of dose strength and drug combinations to the clinical need of the patient
- Anticipation and prediction of the behavioral and physiological characteristics of the targeted patient population
- Identification and elimination of product features or handling requirements that could lead to medication errors or administration issues
- Design principles that clearly identify the product, have contextual cues and lay outs that intuitively provoke the intended use.

Patient-centric drug product development aims to enhance safety and effectiveness by

- Simplification of the product, therapy, and therapeutic schedule
- Elimination or reduction of sources for medication errors
- Triggering or improving adherence.

Patient-centric drug products might additionally make use of integrated innovative technology to monitor disease markers and adherence. For very critical and complex patients, patient-centric drug products might require manufacturing and delivering on an individual basis using innovative and flexible manufacturing platforms, distribution channels, and healthcare support systems.

Discussion

The past 50 years in medical and pharmaceutical sciences have been characterized by substantial progress that contributed to the longevity and health of the people in the society. These advancements came along with an increasing sophistication, complexity, and level of demand in the drug products and therapy. In contrast to this, with the higher age and multimorbidity of the patients but also the increasing use of effective drug therapies in certain patient populations like pediatrics the management and administration of such drug products is becoming a real challenge due to the characteristics of these patients and their limited capabilities. This discrepancy between product design and characteristics of the user groups needs to be resolved to secure a patient–product interface that supports safety and effectiveness.

Drug therapy is the major intervention used in primary care settings. Following the prescription and dispensing of the drug products, the responsibility for the appropriate management of these drug products is transferred to the patients within their micro- and macro-ergonomic framework. Patients are laypersons with different level of understanding about their disease and interventions with medicinal products. Drug therapy and medication is often being used by the patients from their own logic based on their understanding and prior experience with medicines generated through the use of OTC drugs or short-term treatments of acute diseases with strong

symptoms in earlier lifetime. Over several years polypharmacy is built up by changes and additions of new drug products or generic versions of drug products to the medication schedule relying on the patient capacity to implement this in the right medicinal and pharmaceutical schedule. Especially after hospitalization and discharge of the patients the medications are changed or modified creating significant challenges for patients to follow through the new regimen [157–159].

Each drug products is very specific in terms of its clinical profile, adverse drug reactions, mode of use, and administration. This information is provided through the package insert and healthcare professional consultation. The amount of information per drug product is quite substantial and often must be interpreted in the entire medical and pharmaceutical context. The medicinal and technical language used requires more or less prior knowledge or education and sufficient health literacy, time and interest of the patient to acquire the relevant information. It is important to acknowledge that drug products especially the oral forms look very similar to each other in terms of appearance and packaging. Different modes of use, administration procedures, warnings, or other restriction are not obvious for laypersons and even professional caregivers [90, 142]. In this aspect, patient-centric product design is also referring to caregivers, nurses, and healthcare professionals' who are responsible for prescribing, medication management, administration and medication preparation for their patients and face similar issues [160, 161]. However, when reviewing the literature for scientific evidence on studies being done to demonstrate the appropriateness of drug products in older adults no studies with the concerned patient population could be identified that would substantiate the claims being derived from theory [162].

The disease or multiple diseases as well as age-related impairments have an important impact on patients and patient's daily lives especially when the disease burden is high resulting in poor quality of life and psychological stress in managing daily tasks [163–165]. This also affects the ability to handle, administer, and manage the drug products and drug therapy [166, 167] and stay adherent [168, 169]. Consequently, increasingly demanding drug products and complex therapeutic regimen are being handled by patients with disease or age-related declining capabilities to deal with such demanding products and complex schedules.

To deal with this complexity, positively and self-engaged patients using their own strategy to simplify the drug therapy, build the therapy into their day structure and convert it into a routine practice [170] whereby medication administration errors might be implemented as well as are resistant to potential changes in the therapeutic schedule later due to the developed routine. Similar results have been found by Pound et al. who identified three different groups of people, the ones rejecting the therapy, passive and active accepters. Even the active accepters tend to modify their regimen symptomatically or strategically to minimize unwanted effects or to make the therapy more acceptable for them [101]. In this context it is important to note that medicines-related problems often occur due to poor comprehension of the patients on the drug products like dose, specific use requirements as well as changes due to generic substitution that can be prevented in the majority of cases by intensive counseling, monitoring, and more meaningful instructions to

the patients [171]. It is important to recognize that any changes to the drug therapy for example by substitution with other generics are a disruption for the patient and will shift the skill or rule-based process of an established therapy toward a knowledge base process as the patient has to understand the principles of "interchangeability" and generic substitution. This has been shown in a recent study demonstrating that the generic substitution related change in color and shape of essential medicines prescribed to cardiovascular disease patients after a myocardial infarction increased the odds ratio for non-persistence by 34 % for a change in color and 66 % for a change in shape [172]. This has been recognized by the FDA [173] despite the persisting legal implication on the U.S. intellectual-property law [174]. It should be noted that color and shape in contrary might play an important role in patient-centric drug product design for the identification of the drug product and as a contextual cue [175, 176]. As such the drugs, drug therapy as well as the coping strategies developed by patients remain a source of potential non-adherence and medication errors that can impact the safety and effectiveness of the therapy.

Patient-centric drug product design focuses on the product and the product–user interface as an important part of the safe and as intended use of the drug product within a drug therapy by the targeted patient and patient population. The definition of patient-centric drug product design adds the second dimension to the product quality according to the ICH guideline Q 8 requirement that "In all case the product should be designed to meet patients' needs and the intended product performance." As such, patient-centric drug product design has to be included early on in the Targeted Quality Product Profile (TQPP). Patient-centric drug product design is based on four key principles of (1) tailoring the product to the patient needs, (2) anticipating patients interface with the product, (3) eliminating potential sources of errors, and (4) a self-explaining product design. This requires a thorough understanding of the targeted patient population and their specific morbidity and co-morbidity as well as co-medication profile. This understanding will also include the anticipation and prediction of the behavioral and physiological dimension of the patient when interacting with the drug product. Potential areas of errors can be identified and solved through the product design and tested within the targeted patient population in order to find solutions. In an ideal case this will lead to a product design that is self-explaining to the patient and trigger intuitively the right sequence of patient interactions with the product to administer it in the right and intended way. Even so not all potential issues and sources of errors can be overcome by the product design the development should first prioritize and focus on the most important issues with the highest impact on safety and effectiveness. Patient-centric drug product design can also include integrated adherence monitoring systems or alert functions to support the patient in following through the medication and time schedule. This might be specifically important for drugs with a narrow therapeutic window for which the administration time is critical.

The safe and effective use of the drug therapy by the patient is the result of the patients' acceptance of the disease, acceptance of the therapy, the receipt of sufficient information about the therapy, the willingness and capability to adhere to the therapy and drug products that are appropriate for the specific patient. As such,

patient-centric drug product design importantly contributes to the safety and effectiveness by reducing the complexity of the therapy and therapeutic schedule and the level of demand for the patient as well as by the provision of a product tailored to the clinical and personal needs of the patient. In contrast to this, poor drug product design, the need for manipulation or preparation of the drug product before administration (e.g., tablet splitting), poor differentiation to other concomitantly administered drug products and issues in handling and administration leads to poor beliefs and a low perception in the therapy and can create substantial frustration promoting medication errors and non-adherence.

The limitations today in the development of patient-centric drug products is the lag of validated methodology for the evaluation of patient-centric drug product design, the limited knowledge on the patients and their interface with the drug products and the persisting science, technology and data focus in drug product development. The ongoing discussions on introducing guidelines on human factor design and usability engineering for the development of medical devices [177] is expected to create more awareness on the patient as one of the most important stakeholders in achieving the goals of the drug therapy to initiate the required research in this area.

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Dosing Considerations in Older Adults

Gregory J. Hughes and Judith L. Beizer

Abstract Drug and dose selection in older adults is a complex process. Ensuring an optimal regimen may involve considerations beyond those that are immediately obvious. Factors affecting dosing in older adults vary across a wide spectrum and include changes to pharmacokinetics, pharmacodynamics, cognitive abilities, financial constraints, functional deficits, varying treatment-specific endpoints, and availability of evidence-based medicine. This chapter reviews these concepts and outlines the thought processes that clinicians should consider while making their dosing decisions. Recommendations to address these issues often include a combination of interventions and may require some creativity on behalf of the family, caregiver, and health care professionals. These factors should be considered during product development and could result in improved care of older adults.

Keywords Dose selection · Drug intolerance · Drug metabolism · Sustained-release · Inhaled medication · Adherence aids

Introduction

Selecting an appropriate dose of medication for older adults can be a complex process for a clinician. Many factors come into play including those that are patient-related, drug product-related, and literature-related. This chapter will deal with the various issues that should be considered when selecting or adjusting medication doses and some management options to reduce the risk of adverse drug events, over-, or under-treating geriatric patients.

The dosing of medications in older adults requires careful diligence on behalf of the prescriber. As patients age, multiple chronic medical and psychiatric conditions accrue, affecting functional status, increasing risk of adverse drug events, increasing risk of drug interactions, creating adherence issues, and altering goals of therapy.

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S. Stegemann (ed.), *Developing Drug Products in an Aging Society*,
AAPS Advances in the Pharmaceutical Sciences Series 24,
DOI 10.1007/978-3-319-43099-7_14

Senescence alone involves certain pharmacokinetic and pharmacodynamic changes that can drive preference toward certain drug dosing or product selection. Functional deficits such as decreased dexterity, swallowing issues, complex timing requirements, or cognitive deficits also make some drug dosing regimens more desirable than others. Older adults vary across a spectrum from the highly functioning and robustly health to the severely debilitated and frail end-of-life patient. As with many aspects of care for these patients, drug dosing requires an individualized comprehensive management plan that considers the above factors in addition to a deliberate plan for follow up and monitoring [1].

Recommended initial and maintenance doses of medications are listed in the package inserts approved by regulatory authorities such as the Food and Drug Administration in the United States. Both the prescribing information in the United States and the patient information leaflet in Europe have sections designated for special populations which can include the geriatric population. Unfortunately, the vast majority of clinical trials did not stratify populations by age a priori, specifically study, or even include the older population. The result is that studies of the general adult population usually only include a small number of older adults which are analyzed post hoc. This paucity of robust information in combination with generalized knowledge of changes to a drug's pharmacokinetic and pharmacodynamic behavior typically results in broad statements in package inserts. These statements will often simply advise to "prescribe with caution," "monitor frequently," or "use the low end of dosing range" without providing specific recommendations. This leaves clinicians with only vague guidance on how to create a safe dosing strategy for their patients. Studies are more recently being conducted that target older adults and give advice more specific than that just mentioned, but their number is limited. In the context of the growing number of older and multimorbid patients, more clinical data and guidance for the prescribing in such patient populations by an appropriate clinical trial program during development will be essential for implementing new therapeutics quickly into clinical practice.

The old adage to "start low, and go slow" remains true for initiating and titrating dosing in older adults for a variety of reasons. Physiologic changes affecting a medication's pharmacokinetic and pharmacodynamic profile can result in over- or under-exposure of medication. These changes are briefly reviewed below and a more in-depth review can be found in Chapter 10 "Pharmacokinetic and Pharmacodynamic Considerations in Elderly Population". Another problem stems from the sheer number of medications older adults take for their chronic conditions. Patients are often on multiple medications that share similar side effect profiles and their aggregate negative effects may leave little room for tolerating an additional agent with the same undesirable characteristics. This commonly occurs with medications that share anticholinergic properties because this trait persists in a wide range of drug classes such as antidepressants, antihistamines, antipsychotics, muscle relaxants, antispasmodics, and anti-vertigo agents. Tools have been developed to attempt to quantify the anticholinergic burden because of its commonality [2, 3].

In older adults, drug intolerances frequently manifest with nonspecific complaints such as confusion, falls, dizziness, or gastrointestinal complaints, making

identification of the culpable agent difficult. For these reasons, initial dosing of medication should generally be conservative, with the lowest dose or even half of the lowest dose selected. Careful monitoring and a thorough review of systems should be performed each time a medication is started or titrated to identify adverse drug effects. If the medication seems to be tolerated well, upward titration of the drug can then take place, no quicker than is done with younger adults.

It is important to ensure that the dosing strategy and treatment plan overall are consistent with each patient's clinical context and goals and sometimes priorities of therapy. For medications that are being used for symptomatic relief, upward titration should only be performed to the lowest dose that reasonably controls the patient's symptoms. If at any point during patient follow up, new complaints arise that could be due to an adverse drug effect, the "risk versus benefit" balance may have evolved to favor "risk" and a dose reduction should be attempted. Conversely, it is also undesirable to be too conservative in treating certain conditions. Some diseases require medications to be titrated up to a therapeutic dose, such as HMG-CoA reductase inhibitors in atherosclerotic disease or beta-blockers in heart failure. Being overly conservative in these situations by not attempting upwards titration can leave the patient at doses below those shown to have benefit in clinical trials. Determining the initial dose and titration strategy should keep in perspective the goals of therapy, expected time to benefit, number needed to treat, and number needed to harm in addition to side effect profile, cost, socioeconomic, and logistic factors [4].

Dosing Considerations—Physiologic Changes

As aging occurs, certain pharmacokinetic and pharmacodynamic changes occur that may affect dosing strategies. Changes in organ function, body composition, and receptor sensitivity can cause patients to have exaggerated or blunted responses to medications. Briefly, some of these changes and their implications are as follows [5].

Absorption of most oral medications occurs by passive diffusion in the gastrointestinal tract. A small number of medications do require an acidic environment for oral absorption and their absorption may be decreased in older adults who have a higher pH due to hypochlorhydria. In this context it should also be taken into consideration that many older adults receive proton pump inhibitors (PPI) as a standard prescription increasing the gastric pH with consequences for drug absorption [6]. Examples of medications that require an acidic environment are calcium carbonate and ketoconazole. Absorption through the transdermal route can also be affected. The skin of older adults may have reduced blood flow and atrophy leading to decreased absorption. This can be desirable or undesirable depending if the drug is intended for systemic absorption (e.g., testosterone gel) or for strictly topical purposes (e.g., hydrocortisone cream).

Medication distribution changes with age as body composition and protein concentrations are altered. Older adults tend to have increased fat composition and decreased water constitution compared to younger adults. This means that

medications that distribute to the lipid compartment will have larger volumes of distribution and take longer to eliminate, leading to the possibility of accumulation with repeat dosing. Examples include phenytoin, valproic acid, amiodarone, and diazepam. Serum protein concentrations can be altered as chronic conditions accrue resulting in increased or decreased free fractions of drugs that are usually bound to albumin or alpha-1 acid glycoprotein. This is most observable and actionable for medications that have a narrow therapeutic range and where drug concentrations are monitored. Drugs such as warfarin and phenytoin will have relatively larger free fractions and will need to be dosed more conservatively. When measuring serum concentrations of drugs like phenytoin, it is necessary to consider whether total or free concentrations are being measured and account for altered protein binding.

Drug metabolism varies greatly among younger individuals and can further change as adults age. Many medications pass through phase I and/or phase II metabolism so they can be eliminated from the body through the urinary or biliary systems. Studies of mostly small sample size and varied methodology support that the cytochrome P450 isoenzymes responsible for phase I metabolism can be increased, decreased, or remain the same as patients age. Medications passing through cytochrome P450 1A2 and 2C19 tend to be metabolized more slowly, whereas those that pass through cytochrome P450 3A4 and 2C9 may be metabolized more slowly or remain the same. Cytochrome P450 2D6 function is thought to be relatively unchanged. The phase II processes of glucuronidation, sulfation, and acetylation are unaffected by aging. Medications that pass solely through this mechanism of elimination are likely to behave similarly compared to younger adults.

Drug elimination may also be altered as renal function tends to decrease with age. Medications or active metabolites that are eliminated via the kidney may require dosage reductions. Several equations such as the Cockcroft–Gault or Modification of Diet in Renal Disease equations have been validated to assess kidney function. Dosing for almost all drugs that depend on renal elimination is guided by the estimated creatinine clearance and specific dose recommendations are listed in the package insert. For these medications, reduced doses are necessary or accumulation will occur which can increase the risk of adverse events. Elderly patients should have their creatinine clearance calculated prior to medication initiation and periodically thereafter rather than simply checking to see if the serum creatinine is within normal range.

Changes to pharmacodynamics may necessitate dose adjustments in older adults though less is understood about these effects. Receptor binding, number, and post-receptor alterations can result in enhanced or subdued clinical effects of some medications in older adults. Classic examples of these changes are the exaggerated effects of benzodiazepines, opioids, and anticoagulants where lower starting doses and more gradual titration is necessary. Examples of reduced clinical effects are beta agonists and antagonists, where a suboptimal effect may occur and higher doses will be required.

Many medications will be subject to multiple pharmacokinetic and pharmacodynamics changes. For example, while a beta antagonist may be eliminated more slowly due to a slower first-pass metabolism, its effects are blunted due to

pharmacodynamic changes. Which of the changes associated with aging will predominate is very difficult to predict and we are limited as clinicians to maintain the "start low and go slow and ensure diligent monitoring" mantra.

Dosing Considerations—Functional Changes

Aside from patients' altered physiologic changes that affect medication dosing, there are innumerable functional and social issues related to aging. Though many functional and social issues are not medical in nature, they can lead to confusion and anxiety on behalf of the patient, nonadherence, and inappropriate administration.

These functional deficits are innumerable in nature and number and are difficult to correct. They will often go undetected by a clinician who is not experienced in treating older adults and will be underreported by patients themselves. Once identified, there is often no single strategy that can be applied to correct all of a patient's issues. However, these issues are quite common and predictable and should be considered during the development of a drug product. The ideal care plan may involve a significant investment in time and resources by the patient and their family members and involve physicians in addition to pharmacists and other health professionals.

Management Options

Unintentional or intentional inappropriate medication use occurs for a number of reasons. Complex dosing regimens including multiple doses per day, food restrictions or requirements, medications from multiple providers, medications from both the community and mail order sources, and high pill burden can be daunting for adults of any age. With the common development of cognitive impairment, regimens like this can make adherence near impossible for the patient without the aid of devices, family, or hired personnel. Deficits in manual dexterity and coordination can make it difficult or impossible to split tablets, manipulate some inhalers, and handle small tablets, eye droppers, or ear droppers. Certain inhalers require less manipulation and coordination than others and whole tablet doses should be used if dexterity is an issue. Dosing regimens are often unnecessarily complex, requiring the patient to take a medication several times throughout the day. Meanwhile, in many cases a once daily or extended release version of a medication could easily be substituted.

There are a number of different options to consider when designing or simplifying a medication regimen for an older adult. One of the first considerations is if the patient will be taking the medications on their own or receiving assistance from a caregiver or family member. In either case, minimizing the number of medications and number of doses per day is always a prime objective, as this will hopefully improve adherence and minimize the risk of adverse effects. The use of once-a-day

medications is ideal with a goal of no more than twice a day dosing. If possible, medications that need to be taken with specific instructions, such as "on an empty stomach," should be avoided for ease of administration.

Combination products can be useful to minimize the pill burden for the older patient, though these agents should only be prescribed once the patient is stabilized on doses of the individual components of the product. Sustained-release oral dosage forms are also an option as long as the patient can swallow the product whole. Many sustained-release tablets are somewhat large and older patients with dysphagia may not be able to swallow the intact tablet. If the tablet is scored, it can sometimes be carefully split along the scoring without damaging the sustained-release properties. Some sustained-release capsules can be opened and the contents sprinkled on food such as apple sauce, but it is important to consult the package insert of these medications to insure their stability in food. Orally disintegrating tablets are another useful option in patients who have difficulty with tablets and capsules. Sustained-release products and orally disintegrating dosage forms cannot be used in patients with feeding tubes. Liquid medications can be useful in patients with dysphagia, but care must be taken for proper measurement of the dose.

Non-oral formulations, such as transdermal patches or topical gels can also be useful in patients with swallowing difficulties or adherence issues. Besides the concern about adequate transdermal absorption, a practical concern with transdermal patches is proper placement of the patch and rotation of the administration site (to avoid skin irritation). Older adults with dexterity problems due to arthritis or decreased visual acuity may have a difficult time removing the adhesive backing of the transdermal patch. In addition, older adults with cognitive impairment may forget to remove the old patch.

For older adults with chronic obstructive pulmonary disease or asthma, there are a variety of dosage forms for inhaled medications. The choice between a handheld inhaler versus nebulized solution may depend on the patient's dexterity, cognitive function, and if the patient will be self-administering the medication or receiving assistance. Handheld inhalers are manufactured in a variety of forms (metered-dose inhalers, dry powder formulations, capsules for inhalation) and require specific instruction for appropriate use. An older patient with chronic obstructive pulmonary disease may be on several different inhalers, each with a different mechanism of administration. It is imperative that the patient be observed for proper inhalation technique to insure that the dose is being delivered to the lungs. For patients with difficulty in coordinating their breath and activating the inhaler, nebulized solutions may be preferred. For metered-dose inhalers, spacer devices (e.g. Aerochamber) are available that attach to the inhaler.

For injectable products, most medications that are intended for self-administration (ex. insulin) are now available as "pen" injectors. These products make it easier for patients to give themselves injections, though older adults may still have problems due to dexterity or visual impairment. All older patients should be observed for proper injection technique.

Specifically for older patients with multiple drug products being prescribed, the complexity added by innovative or new drug delivery products, dosage forms, or

administration procedures should not be underestimated by healthcare providers and caregivers. Often such systems require substantial training and retraining of the patients which can be difficult to achieve in routine practice. To ensure ease of use, pharmaceutical products should be tested by elderly patients during the product development phase.

Reminder/Adherence Aids

Adherence aids are available to help patients organize and remember to take their medications. Medication boxes that hold one day's or one week's worth of medication are commercially available in a variety of styles, with some boxes having up to four slots each day of the week to accommodate different dosing times. There are electronic aids that beep or light up when a dose is due, with some devices connected to the phone line to alert a family member or call center if the dose is not taken on time. Additionally, multiple smartphone applications can be downloaded with similar functionality.

There are other products available to assist with the administration of medications. Tablet splitters and crushers can help patients who have difficulty swallowing tablets, though sustained-release products usually cannot be split and should never be crushed. It should be mentioned that swallowing difficulties of solid oral dosage forms by older, multimorbid and frail patients is known to be an issue that can be addressed during the pharmaceutical development by appropriate dosage forms. There are also products to assist with non-oral formulations, such as eye-drop guides. These devices fit onto the bottle of the ophthalmic preparation to help steady the hand and direct the drop into the eye.

Whatever dosing option is tried, it is important to monitor the patient for both effectiveness of the medication and adverse reactions. When necessary, dosage adjustments should be made. Most importantly, patient acceptance of and adherence to the dosage regimen is essential for success. The patient (and family when appropriate) should always be consulted when designing his or her regimen to insure that it is practical and realistic for patient adherence [1].

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Oral Drug Product Use in the Elderly Patient Population

Robert L. Ternik

Abstract This chapter explores in detail the many considerations to be factored into the design of oral drug products for use in the elderly patient. These considerations include characteristics of the dose form and holistic drug product, as well as characteristics of the intended patient population. These characteristics are detailed and discussed. For synthetically manufactured drug substances, oral administration is the most frequent and popular drug administration route used in medical practice today. Subsequently, drug products designed to be administered by the oral route are the most common dosage forms available worldwide. The popularity of the oral route is a result of a number of inherent advantages, and these advantages impact all key stakeholders in the pharmaceutical paradigm, including patients, healthcare providers, manufacturers, and regulators. A few of the advantages of oral drug products over alternative routes of delivery include self-administration, dose accuracy and uniformity, stability, portability, lack of invasiveness, familiarity to patients, and relatively low cost to manufacture. Additionally, to have the best chance at designing an outstanding product, gaining a comprehensive understanding of the target customer behaviors and needs, and incorporating that knowledge into the product design, is a must. The evolution toward drug products that are intentionally designed to meet not only their safety, efficacy and quality requirements, but also provide opportunity for improved outcomes through better patient experience and improved adherence should enhance overall therapeutic outcomes. When designing for an elderly target patient population, the drug product designer and developer should pay particular attention to the specific characteristics of the disease state, target patient population, comorbidities and other emotional, environmental, and sociological factors that have the potential to impact or interfere with the elderly patient's ability to use the product as intended. Failure to take a diligent approach in this regard can result in a greater likelihood of poor adherence and improper usage of the drug product, resulting in lower effectiveness, poor therapeutic outcomes, and potential safety risks.

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S. Stegemann (ed.), *Developing Drug Products in an Aging Society*,
AAPS Advances in the Pharmaceutical Sciences Series 24,
DOI 10.1007/978-3-319-43099-7_15

Keywords Oral dosing · Drug product · Dose form · Elderly patient · Patient centric

Introduction

For synthetically manufactured drug substances, oral administration is the most frequent and popular drug administration route used in medical practice today. Subsequently, drug products designed to be administered by the oral route are the most common dosage forms available worldwide. This has historically been the case, and oral approaches to administering nonbiological drugs will continue to be the most utilized for drug delivery in the foreseeable future. The popularity of the oral route is a result of a number of inherent advantages, and these advantages impact all key stakeholders in the pharmaceutical paradigm, including patients, healthcare providers, manufacturers, and regulators. A few of the advantages of oral drug products over alternative routes of delivery include self-administration, dose accuracy and uniformity, stability, portability, lack of invasiveness, familiarity to patients, and relatively low cost to manufacture [1].

The variety of dose forms available for oral administration is wide and the number of differentiated presentations continues to increase with advances in both materials and manufacturing sciences. Oral dose form presentations encompass solid forms such as tablets, capsules, and multi-particulates and liquid forms such as solutions and suspensions. Within these broader categories of solid and liquids, numerous more subtle but potentially valuable variations exist. Examples of these variations include forms such as orally disintegrating tablets, mini-tablets, and powders for reconstitution. Furthermore, the in vivo performance characteristics of orally administered products can be designed and modified to provide another series of variations that provide value to patients and healthcare providers. Oral dose forms designed for site specific, delayed or sustained release are examples of such in vivo performance modifications and recently technology for producing a sustained release oral liquid has been commercialized.[1] The popularity and advantages of the oral route of administration ensures that innovators will continue to pursue further improvements that leverage these advantages and provide even more effective products.

Before a more detailed discussion can occur, it is beneficial to define a few key terms used throughout this chapter. In this introduction, the terms drug product and dose form occur in various parts of the discussion. In the context of this discussion, the term dose form refers specifically to the physical dose that is ingested by the patient such as the tablet, capsule, or liquid. In contrast, drug product refers to the holistic product presentation as made available to the patient. This includes not only the dose form as defined, but also any primary, secondary or other packaging,

[1]Quillivant XR, Quillavant XR is a Registered Trademark of Pfizer Inc.

devices or dosing aides, labeling and instructions for use and the concept extends to patient support programs as well. When taking a patient centric approach to drug product design and development, and for this discussion an elderly patient centric approach, the inputs for consideration go beyond those related to only the dose form. This approach becomes increasingly vital in special patient populations whose capability may be diminished as a consequence of their disease state or general health condition. The objective of this chapter, however, is not to explore all options and technologies available for manufacture of oral dose forms, but rather to present a more focused perspective on design considerations, advantages and disadvantages for products intended for oral administration in the elderly patient population.

Letting Patient Needs Drive Product Design

To have the best chance at designing an outstanding product, regardless of the industry, gaining a comprehensive understanding of the target customer behaviors and needs, then incorporating that knowledge into the product design, is a must. The primary goal of any customer of a pharmaceutical product is the cure or amelioration of the disease state or symptoms being treated. However, the key to meeting this goal is not solely dependent upon the efficacy of the drug. In fact, an efficacious drug will not deliver the desired effect if the patient cannot or does not use it as intended and prescribed. Recent publications have highlighted and quantified this reality [2, 3]. The human and economic impact of this reality is enormous. Over the last few decades, many approaches or processes for product design have been created and used, and the premise of understanding needs is foundational across methodologies. As a highly regulated and high-risk industry, pharmaceutical companies have been relatively late adopters to the concepts of customer centric design, and in this case patient centric design. However, over the last decade, much more attention is being paid to product criteria that go beyond the safety, efficacy, and quality attributes of a drug product. Criteria related to dose form, such as tablet size and quantity, or administration volume and palatability of a liquid are being given more scrutiny. Other product attributes or elements such as dose aides and devices and adherence aids such a special packaging and labeling, or even connected devices are being seen as ways to improve the overall effectiveness of drug products through their impact on adherence or an overall improvement of patient experience. This evolution toward drug products that are intentionally designed to meet not only their safety, efficacy and quality requirements, but also provide opportunity for improved outcomes through better patient experience and improved adherence should enhance overall therapeutic outcomes.

Given the fact that over 65 % of the drugs prescribed today are used by people over the age of 65 years [4], it seems logical that the majority of drug products would be designed and studied in this patient population. In many instances however, the condition for which a patient is taking a medication may have been diagnosed prior to this age and the use of a drug product is simply a continuation of existing therapy. In these cases, the product design may have been targeted for a user group with characteristics of a younger and oftentimes healthier population, yet as that patient's condition evolves over time, the drug product frequently does not. This can readily create a situation where the product design may have been acceptable for the patient at the time of therapeutic initiation, but the acceptability of that product reduces as a function of time [5]. The development and commercialization of line extensions or alternative dose forms of a given drug product may occur for some products, but this practice tends to be the exception rather than the rule in the pharmaceutical industry today.

The discussion above in many ways simplifies the complexities inherent in designing and developing drug products for use in the elderly population. Many factors affect a person's overall health condition. Genetics, environment, lifestyle, injury, or prior disease history are just a few factors that impact a patient's condition in addition to common age-related declines in physical, biological, and cognitive function. Further complicating matters is the reality that these factors impact individuals at different points of life and to varying degrees of severity. This variability results in an increased heterogeneity in the overall health condition of individuals as they age [6]. While it is impossible at this time to customize all elements of pharmaceutical product design to a specific patient's situation, there are a number of common and predictable elements to aging and disease trajectories that can be considered when designing and developing oral dose forms for elderly patients. While many of the other chapters in this text are directed to a more specific discussion of these patient centric factors and variables, it is worth summarizing a few of these key characteristics that may impact the design of oral dose forms and products.

Characteristics of the Elderly Patient

Every patient is an individual and as such will have a unique set of capabilities, needs, and desires in regard to treatment of their condition. This is true irrespective of the chronological age of the person. It is very unlikely that the design of a pharmaceutical product can meet all of an individual patient's needs, but active consideration and prioritization of these needs will help in optimizing the patient experience and delivering the intended therapeutic outcome. When designing an oral dose form for the elderly patient, the following are some important considerations that should be incorporated into the product design discussion. Table 1 summarizes some of these key patient considerations.

Table 1 Important characteristics of the elderly patient and design considerations for oral drug products

Patient characteristic	Product design consideration
• Overall health condition – Specific disease states – Independence	• How will the product be used • What are the patient's overall capabilities • Are there specific patient limitations that are associated with the specific disease state the product is intended to treat • Will the product be self-administered or dosed by a caregiver
• Co- and multi-morbidity – Polypharmacy – Dosing regimens – Dosing restrictions – Dosing flexibility Renal or hepatic insufficiency Narrow therapeutic index	• What common comorbidities accompany the disease state to be treated in this target patient population • What are the standard of care treatments for those comorbidities – Do they incorporate other oral medications • What is the typical pill burden for this patient population • What is the dosing regimen for the new product and how does it integrate with the patients existing regimen • What are the dosing regimens for commonly coadministered oral medications • How will the product be dosed with respect to food intake • What level of dose flexibility is required for the product
• Physical Limitations – Strength and dexterity Neuropathy Pain – Swallowing difficulties – Visual acuity	• How should the product be packaged to ensure safe and reliable access to the dose – Blister packaging design – Child resistance requirements – Bottle and closure design • What is the patient's ability to feel and manipulate the dose form for oral dosing • What is the incidence and prevalence of swallowing difficulties in the target population – General – Disease state specific (e.g. PSP, AD)[a] • What is the incidence and prevalence of visual limitations in the patient population – Ability to see dose form or use dose aide or device to measure dose accurately – Ability to identify between products (polypharmacy)
• Cognitive limitations – Memory – Understanding Disease state Product use Dose regimen	• How well can/does the patient understand their health condition and specific disease states • Does the patient (or caregiver) have the ability to understand, recall and execute the proper use of the product • Can the patient understand the proper dose regimen and any accompanying restrictions on use
• Emotional state – Depression – Denial – Indifference	• Does the patient accept their therapy • Do medications remind them of their illness and affect attitudes toward compliance • Does the disease state or comorbidity interfere with the patients desire or ability to treat their disease • Therapy impact on social life and stigmatization

[a]Progressive Supranuclear Palsy (PSP) and Alzheimer's Dementia (AD)
Other patient population specific characteristics should also be identified and considered

Overall Health Condition

The overall health condition of the target patient population should be understood and evaluated for impact on the design of the dose form and drug product. This includes any underlying general considerations, but more specifically the impact of the disease state being treated. Common disease states in the elderly include the majority of chronic conditions most prevalent in society today such as diabetes, heart disease, cancer, depression, and in the elderly population neurological diseases such as dementia. Those disease states that are symptomatic will likely have the biggest impact on product design, as they typically manifest in some decrease in either physical or cognitive capability, or both. For example in the Alzheimer's Dementia patient, multiple physical and cognitive capabilities can be affected as the disease progresses that could limit the utility of an oral dose form altogether at the advanced stages of the disease. Swallowing difficulties are common in this patient group as a result of reductions in both physical capability and emotional/cognitive willingness to ingest an oral dose form [7]. Another important consideration in oral drug product design for the elderly patient is the patient's level of independence in managing their dosing. If the product is being designed for use in a patient population that is, or will become, dependent upon other caregivers for the management of their medications, consideration should be given to that caregiver population as well.

Co- and Multi-morbidity

The prevalence of patients with co- and multi-morbidities is the consequence of overall improved health and greater longevity. Designing products for patients with a high likelihood of multi-morbidity increases the challenge greatly, both from an understanding perspective and a product design perspective. In some instances where the rate of a specific comorbidity is known to be high, a product may need to be designed to address a need not directly related to specific disease state that product is intended to treat. Polypharmacy, defined as an individual patient taking five or more medications to address their health condition, is a frequent consequence of multi-morbidity [8]. The occurrence of polypharmacy in elderly patients results in an increase in pill burden. This pill burden can create difficulties for patients in being able to ingest their medications as prescribed. It is not uncommon that patients may begin to select which medications they can or will take on a given day or dosing period, because they cannot manage to ingest all the medications they are prescribed. Many times this is related to the amount of water or liquid that patient needs to ingest in order to swallow the dose form. Anecdotal evidence suggests that strategies such as starting with the smallest pill and working up in size until that patient can no longer ingest their remaining medications are common. This practice would suggest that the elderly patient may prefer a smaller, easier to

ingest dose form. Rotating or alternating dosing regimens is also a practice to manage a large pill burden.

Dosing regimen is another key consideration in the multi-morbid patient population. Designing oral products that require once daily administration are considered optimal, as once daily is the most common oral dosing regimen and most preferred by patients. Once daily administration facilitates compliance and reduces medication management issues. Twice daily dosing regimens are also well accepted by most patients. Oral dosing regimens that require more than twice daily administration are associated with poorer adherence. In addition to dose frequency and number of dosing moments as a key criterion in dosing regimens, dosing restrictions also play an important role. In particular, the need for coadministration with food or administration requiring the avoidance of food for a particular period of time greatly increases the complexity of managing polypharmacy and non-adherence. Finally, the potential for interactions between medications in a polypharmacy routine is a factor to be considered.

Dosing flexibility needs also play an important role in the design of an oral drug product. Both patient and drug specific variables play a role in determining the need for dosing flexibility. For single unit solid oral dose forms like tablets and capsules, dose flexibility is limited to the use of multiple units, which can exacerbate the issue of pill burden. Tablets have the potential to be scored to facilitate breaking, but this strategy comes with risks related to dose uniformity and dose accuracy if tablet breaking is not carried out properly. Liquid dose forms provide the opportunity for more flexible dosing, provided that the product is designed as such and comes with a robust device or dose aide to simplify accurate dose measurement and delivery. However, in any instance of dose measurement or modification, the visual and dexterity capabilities required to perform those tasks have a high prevalence to decline with age and multi-morbidity. The specific advantages and disadvantages to the more common oral dose forms are discussed in more detail later in this chapter.

Physical Limitations

Many elderly patients experience physical limitations that develop as a result of both the natural aging process and as a consequence of specific disease states. Common physical limitations that impact the overall ability to use oral drug products include, but are not limited to, hand strength and dexterity, swallowing difficulties and visual impairment.[2] Hand strength and dexterity can significantly reduce and elderly patient's ability to access the dose form in the product package. This is particularly true in regions that require products be packaged in child resistant packaging. Both bottle and blister packaging can present difficulties. For

[2]Prevalence of Age-Related Macular Degeneration in the United States, The Eye Diseases Prevalence Research Group, Arch Ophtalmol. 2004;122:564–572.

tablets and capsules, a common work around for patients is to remove all of the doses for a period of time, for example one week or one month, and place them into an alternative package. Frequently this is a pill minder or similar personal packaging tool. Many patients find that the pill minder can also help with compliance, assuming it is filled properly. The down side of pill minders is that products are comingled, less protected from ambient conditions and the dose form is separated from the original package and its labeling. For certain tablets, like oral disintegrating tablets, exposure to ambient conditions can negatively affect the physical performance of the dose form through the absorption of moisture. Moisture sorption can result in tablet swelling and physical failure of the dose form in the pill minder or a slowing of disintegration in the mouth creating a negative patient experience. Separating the dose form from its labeling can increase the likelihood of dosing errors, particularly related to medication mix-ups and confusion on dosing restrictions such as dosing with food. Recently, more attention is being paid to the packaging aspect of product design and improved packaging configurations are being introduced into the pharmaceutical product space. However, the examples above illustrate how a patient's physical limitation can translate into a dosing error or unintended misuse of a product as a result of the work-around strategies they may employ. Understanding real-world use scenarios related to the use of the product can help identify opportunity to design out potential product failure modes.

Difficulty in swallowing dose forms is not uncommon in the elderly patient population [9]. Difficulty in swallowing, or dysphagia, can be a result of the normal aging process for some individuals, and is also a symptom of some disease states that disproportionately affect the elderly. Progressive supranuclear palsy is a neurodegenerative disease that frequently results in a significant loss in the swallowing function. Design of an oral dose form for this indication would require particular attention to this physical limitation. Alzheimer's Dementia is an example of a disease state that comes with an increased incidence of swallowing difficulties, typically attributable to both physical and cognitive decline in the patient. For single unit solid oral dose forms, the size, shape, and texture of the dose forms are variables that appear to affect swallowability [10]. For oral liquids, the taste, volume and texture of the solution or suspension can affect the overall palatability of the dose form. Depending upon the dose form chosen for development, these specific attributes should be evaluated in the overall design of the drug product.

Another common physical limitation affecting the elderly patient population is the loss of visual acuity. Glaucoma, cataracts, macular degeneration, and other retinopathies related to natural aging process or disease states have the ability to interfere with the proper use of oral dose forms. The ability to see, handle and identify dose forms and ability to read labels and instructions is a basic capability required to ensure the proper use of oral dose forms. This is particularly true when the patient is required to perform dose measurement activities, such as measuring an oral liquid for dose administration. Designing products to eliminate or simplify handling and increase readability of instructions can help mitigate the risks for patients who have diminished vision.

Cognitive Limitations

Mild cognitive impairments, like physical limitations, can impact the proper use of oral dose forms. Poor memory resulting in forgetfulness is a common cause of product misuse and poor adherence in the elderly patient. The patient's ability to understand and remember the proper way to use the product is critical in ensuring the desired outcome is achieved. If the product has restrictions associated with its dosing regimen, such as coadministration with food, it is even more likely that elderly patients with mild cognitive limitations will misuse the product. In any case, consideration of how the dose is to be administered should be discussed during the design of the clinical program, to ensure that the food effect on the product is well understood and steps can be taken to try to reduce or eliminate any food effect. Similarly, simplifying the dosing regimen to a once, or at most, twice a day frequency is a strategy that should be considered for elderly patients. Depending upon the pharmacokinetic attributes of the drug, this may entail developing a controlled release dose form and this approach needs to be highly integrated with the clinical strategy.

For oral products that require some level of dose preparation, the ability to understand and accurately perform those preparation steps can be a source of frustration, error, and avoidance. For example, using an oral dosing cup or syringe to measure a dose of liquid medication can be confusing and lead to medication errors. Simplifying the dose preparation and measurement process is something that should always be considered in the product design. Consideration should be given to using unit dose packaging strategies to simplify and eliminate use errors in patient populations that have a higher than normal incidence of mild cognitive limitations.

Emotional Status

The emotional state of the elderly patient is another factor that can impact the use of oral medications and should be considered in the design of the product. In many cases, depression is present in elderly patients. Dealing with chronic or terminal illness and the disability or limitations that come with these disease states leaves this patient population particularly susceptible to emotional fluctuations. Ideally, patients do not want to be reminded of their health condition. The drug product and dose form should be designed to fit into normal routines and be as discreet as possible. Designing a drug product with the holistic patient experience in mind can provide an overall positive experience and avoid introducing emotional stress on the patient.

Similarity to Pediatrics

In many ways, the challenges of designing and developing oral products for use in elderly patient are similar to those encountered when designing products for use in children. A recent article by Liu et al. [11] provides a perspective on both similarities and differences between pediatric and elderly patients and the design of pharmaceutical products. This article identifies swallowability as a key attribute in oral dose form design for elderly patients. As such, the approaches to dose form design taken to improve the overall swallowability for pediatric patients might provide some options to also be employed for the elderly patient.

The above discussion on characteristics of the elderly patient in relation to their ability to use oral drug products is intended to illustrate some of the more common and important factors to consider when designing and developing a product. This discussion does not and cannot investigate all the special situations and circumstances that the product development scientist may encounter. This fact is why it is critically important to take a disciplined and holistic approach to each product design challenge in order to identify the optimum product characteristics and make the appropriate tradeoff decisions when conflicts between design elements arise. Developing a thorough understanding of the patient and their characteristics, as well as the specific disease state to be treated, is foundational to designing and developing an appropriate drug product and dose form for the elderly patient.

Oral Drug Product Use in the Elderly Patient

Orally administered dose forms are and will continue to be a standard of practice in medication administration across patient groups, including the elderly patient populations. The advantages of this route of administration have been outlined previously in this chapter. In the following sections, some specifics of oral dose forms will be described and discussed in the context of use for the elderly patient and some of their common characteristics. Unfortunately, given the heterogeneity of this patient population, there is no single dose form or product design that will meet every patient's complete set of needs. Therefore, a thoughtful approach that considers the individual advantages and limitations of specific dose form and product characteristics is recommended. Some of the most common dose forms, their characteristics, and considerations relative to the elderly patient are presented in Table 2. This tabulation is not comprehensive. Specialty and niche oral products such as buccal and sublingual product are not specifically discussed. However, for certain drug substances and use scenarios, these types of dose forms can be advantageous and should be considered. For example, advantages such as speed of onset, local effect and bypassing first pass metabolism are all potential advantages of the buccal or sublingual route of delivery. A more detailed discussion on the

Table 2 Common oral dose forms and product design considerations

Oral dose form characteristics	Product design considerations
• Tablets – IR – MR – Oral disintegrating – Chewable – Dispersible	• Tablet size, shape, color and identifying markings • Dosing frequency • Number of dose units required per dose • Need for targeted release – For efficacy – For tolerability • What is the patient's ability to swallow and or chew • For ODT applications, is xerostomia (dry mouth) a symptom or comorbidity • What are the implications of tablet splitting or crushing • Should the tablet be scored to facilitate dose splitting and flexibility • Will the product be stable in personal repackaging situations • What, if any, food effect may be present • Liquids to use for dispersible tablets – In-use stability, compatibility
• Capsules – IR – MR – Sprinkle	• See above for tablet • Is opening the capsule to ease administration a desired feature
• Liquids – Solutions – Suspensions – Powder for reconstitution	• Taste and overall palatability • Volume to administer • Product concentration and dosing flexibility • Ability to easily resuspend • Storage requirements • Dosing device design – Handling and use – Dose accuracy – Cleaning and storage – Portability
• Other – Gels or jellies – Films – Minitablet – Multi-particulate	• See considerations above • Do the specific advantages of the alternative dose form address specific patient needs without elevating other risks – Risk/benefit analysis

advantages and limitations of multi-particulate oral drug products is presented in a separate chapter of this book and will not be specifically discussed in this chapter.

Oral Tablets

Oral tablets are the most common and diverse set of oral dose forms. Tableted dose forms have the advantages of unit dose accuracy, portability, convenience, stability, and familiarity to patients. They are also cost effective to manufacture and

distribute. If designed appropriately, in many cases tablets can be safely repackaged by the patient into pill minders to facilitate compliance and portability. For many elderly patients, depending upon their health condition and specific therapeutic needs, an oral tablet may be the best dose form to provide.

The most common oral tablet is the immediate release or IR tablet. It is designed to provide for rapid dissolution and absorption of the drug substance in the gastrointestinal tract to provide systemic exposure of the medication. The ability to provide accurate dosing over the course of therapy is a key advantage to this dose form. Important physical characteristics of the IR tablet include the dose form size, shape, and coating. The overall size of the tablet dose form is typically dictated by the dose of the drug substance to be administered, as well as its physical and chemical properties. For low dose drugs, excipients are used to increase the size of the dose form in order to facilitate manufacture and handling of the tablets. Generally speaking, the optimum tablet size ranges between 100 and 400 mg total tablet weight, or about 6–10 mm in diameter for a round tablet. This size range seems to be the best compromise between the dose form being large enough to handle and small enough to easily swallow. For the elderly population, the ability to see and handle tablets confidently tends to raise the lower end of the tablet size range up to 200 mg as more preferred. Tablets over 600 mg in total tablet weight, irrespective of shape tend to be viewed less favorably due to concerns over swallowability in the general population. For the elderly patient population, it is likely the preferred tablet size remains below about 500 mg in total tablet weight. Balancing the patients' needs with regard to handling and swallowing a tablet is a key consideration, but the overall flexibility in the tablet manufacturing platform provides a good level of flexibility in this regard.

One strategy to minimize the negative effects of a larger tablet size is through shape modification. An inherent advantage to tablets is the flexibility to vary the shape of the tablet in three dimensions. Manufacturing tablets in a capsule, oval, elliptical, or oblong shape can improve the overall appearance of the tablet and improve the perception of the ability to swallow the dose form [12]. Another potential advantage to modifying the shape of a tablet dose form is improved product identity. In general, patients have a desire to be able to identify their dose forms and associate them with the specific condition the product in intended to treat. Being able to differentiate between the products used to treat their diabetes and those used to treat hypertension is important for the patient and their caregivers. In addition to shape, the color of a tablet dose form can play a similar role in product differentiation. Color selection can also have an impact on the overall aesthetics of the dose form. Generally, lighter colors are preferred over darker colors in the general population and this is likely to be true in the elderly population as well.

Modified release (MR) tablets differ from immediate release tablets in that they are designed to release the drug substance in some other way besides immediately upon ingestion. Enteric coated tablets, sustained release tablets, and variations such as timed, targeted, or pulsatile release fall into this category. The use of modified release technology can significantly improve both the therapeutic effectiveness of a

drug and the patient experience with the drug product. Enteric coating is frequently used to minimize potential GI irritation that is commonly cited as a concern in elderly patients. Employing a sustained release technology can serve to simplify the dosing schedule by reducing the frequency the drug product needs to be administered. Tablet dose forms are particularly amenable to these types of modifications through the rational use of specialty excipients and coatings.

More specialized tablets, such as orally disintegrating tablets (ODT), chewable tablets, and dispersible tablets fall into the overall solid oral dose form category. These more specialized tablets may provide substantial benefit for certain patient populations and disease states, including the elderly patient. Oral disintegrating tablets are designed to reduce or eliminate the need to swallow the intact dose form and can be beneficial to the patient with dysphagia. The downside of these dose forms are typically the lower physical robustness and the inherent taste attribute that comes with a product that disintegrates or dissolves in the mouth. The ODT platform typically places some additional limitations on the overall dose that can be delivered. Nevertheless, this dose form has some specific advantages and can be considered appropriate for the elderly patient population when taken with sufficient liquid. Chewable tablets, as their name suggests, are to be chewed prior to swallowing. Many times this dose form is applied when the dose to be administered is large and difficult to incorporate into a single easily swallowed dose form. One potential downside to this dose form in the elderly population is the requirement to chew the dose form. Poor dental health and loss of dentition can make the chewable tablet difficult or impossible to use for many elderly patients. Careful consideration should be given to the overall health condition of the target elderly population in evaluating the usefulness of chewable tablets. Dispersible tablets are tableted dose forms, but their intended presentation to the patient is as a liquid solution or suspension. The advantages of a tablet for reconstitution relate again to unit dose accuracy, physical and chemical stability and improved convenience of dose preparation relative to other liquid dose form presentations. As with all liquids, taste considerations are critical, but the possibility of the patient using the liquid of their choice for reconstitution is a potential advantage over a ready to use solution or suspension. More specifics on the advantages and disadvantages to oral liquids are discussed below.

Oral Capsules

Capsules for oral administration have a number of the same characteristics and accompanying advantages and disadvantages as tablets. However, capsules do have some differences and these will be discussed in the context of the capsule dose form for use in elderly patients. The most common capsule used in the pharmaceutical industry today is the two piece hard capsule. Capsules can provide an advantage to tablets when the physical or chemical properties of the drug substance are not amenable to the manufacturing operations of tableting. Capsules are also a very

popular dose form with patients, and some evidence suggests that capsules are perceived to be easier to swallow when compared to tablets, based upon the shape, appearance, and surface texture. One minor limitation to hard capsules is that they come in fixed sizes and their shape is fixed as a necessity for efficient, high-throughput dose form manufacture. However, a variety of capsule sizes exist to meet most needs and hard capsules from size 4 to size 1 are generally in the range of acceptability for most elderly patients. Like tablets, capsules can accommodate both immediate release and modified release products, although the technology required to produce modified release capsules is often different. Hard capsules also offer the opportunity to be designed to be either swallowed or opened and the contents sprinkled out and onto a food or liquid. This flexibility can be valuable to patients that have swallowing difficulty. Hard capsules can incorporate a wide variety of colorants and opacifying agents to provide a broad palate of color choices and combinations to aid in the visual identification of products. They can also be printed to aid in differentiation. Over the past decade, alternatives to gelatin as the capsule material have been developed, and are being increasingly considered in product development.

An alternative to hard capsules are soft capsules. These capsules expand that ability to formulate a drug into a solid oral dose form that might otherwise not be possible through allowing a solution or suspension of drug to be encapsulated. In relation to the elderly patient, care should be taken to consider the overall size of the dose form to ensure adequate swallowability.

Oral Liquids

Oral liquids, while less common and generally less preferred when compared to solid oral dose forms, are a useful product presentation to the elderly patient in certain circumstances. Oral liquids have the advantage of greater dose flexibility when compared to tablets and capsules. With liquids, the dose can be adjusted by varying the volume of liquid administered. Ideally, the volume to be administered should be minimized, while still being sufficient to be readily measured by the patient or caregiver. For elderly patients a target volume of 5–10 mL is generally acceptable. This flexibility can be of significant therapeutic advantage in treating elderly patients as the frequency of renal or hepatic deficiencies or comorbidities is higher. Physicians may value this flexibility as way to manage risks related to tolerability or safety and the use of a well-designed oral liquid may reduce risk of dosing errors that accompany the modification of dose when using a tablet or capsule. Some disadvantages to oral liquids include palatability issues, dose measurement concerns, storage constraints, microbiological contamination risks, and portability limitations. Many of these risks and concerns can be minimized or even eliminated through proper dose form and product design, but these risks need to be identified and worked through early in the development process. Taste is frequently cited as a major disadvantage to oral liquid products. The use of sweeteners, flavors,

and taste masking agents can improve the overall taste of a product, but individual and regional preferences make finding a universally acceptable formulation difficult. For elderly patients that are being treated with multiple medications, it is unlikely that each of their medications will be available as oral liquids, and this fact could interfere with established routines. In the instance that a patient population is identified in which multiple oral liquid medications are being administered, total volume of product to be ingested as well as conflicting taste profiles can pose barriers to the use of this dose form. Once again, the heterogeneity of the population makes identifying a product design that fits all patients difficult, but these factors need to be considered.

The development of a high-quality dosing device or dosing aide is essential when considering an oral liquid dose form. Poor device design has frequently been reported as a cause of inaccurate dosing when using oral liquid products.[3] Focusing on ease of handling, minimizing dose prep and measurement steps and providing legible dosing gradations and labeling are product characteristics that need to be optimized. For multiuse oral liquids the incorporation of preservatives is frequently required to prevent microbial contamination and the ability to effectively clean the dosing aide or device over the course of therapy without compromising its functionality also needs to be considered. Chemical stability is also a greater concern for many products in a liquid form. One mitigation strategy can be to use refrigeration to slow degradation, but this puts an additional burden on the patient in managing their medication routine. Finally, oral liquid products tend to be less portable as compared to tablet or capsule dose forms and this can create issues if the target population still maintains an active lifestyle and travels.

Oral liquids can be further categorized into solutions and suspensions. Solutions have the inherent advantage of being homogeneous with respect to drug content and distribution. In those instances where the solubility or other attributes of the liquid prevent the use of a solution, a suspension is acceptable. Suspensions need to be optimized to provide for good physical stability to ensure ease of homogeneous suspension at the time of dose measurement. The use of unit dose packaging for oral solutions and suspensions in a potential mitigation strategy that can be employed for products intended for self-administration in the elderly patient population. As illustrated by this discussion, the holistic design of oral liquid products needs to be considered when this dose form is evaluated for development. In many ways, the packaging and device design for oral liquids is as much a determinant of overall therapeutic effectiveness as the dose form itself.

[3]Guidance for Industry: Dosage Delivery Devices for Orally Ingested OTC Liquid Drug Products; U.S. Dept. of Health and Human Services, Food and Drug Administration (CDER); May 2011.

Multi-particulate Dose Forms

Multi-particulate dose forms are a well-established approach to creating oral dose forms. They have the ability to incorporate some of the specific advantages of tablets and capsules, combined with a level of improved dosing flexibility as seen with oral liquids. However, like all of the dose form options discussed in this chapter, multi-particulate dose forms also have their limitations and disadvantages. The reader is referred to the chapter in this text specifically discussing the use of multi-particulate products.

Other Oral Product Alternatives

While the variety of tablets, capsules, and oral liquids discussed above comprise the majority of oral dose forms commercially available today, a number of variations intended to provide specific advantages to the patient have been developed and are worth considering for use in the elderly patient population. In Japan, oral jelly presentations have found their way into the marketplace.[4] The primary advantage to this dose form is improved swallowability, and some evidence suggests that this dose form may also help in improving the palatability of the dose form. Oral disintegrating films are another emerging dose form for specific patient populations and could potentially have use in the elderly patient population. Once again, the primary advantage of these dose forms relates to improved ingestion due to a reduced need to swallow and intact dose form. Dose flexibility is achieved through simply varying the size of the film strip administered. However, limitations on the overall drug load constrain the use of the oral film dose form to low dose drugs [13]. Taste, handling and inability to personally repackage are likely disadvantages to the elderly population, and in the event the patient cannot self-administer their medication, the film dose form may be difficult for a caregiver to administer. While these examples provide a high level perspective on a few more recent dose form innovations that may be applicable to the elderly patient population, it is incumbent upon the product designer and developer to consider all the specific advantages and liabilities of their intended product in light of their target patient population to ensure the best presentation is selected.

[4]Aricept® Oral Jelly is a registered trademark of Eisai Co. Ltd.

Additional Considerations in Oral Product Design for Elderly Patients

The preceding section of this chapter focused on some common oral dose forms, their potential advantages and disadvantages and some key product design considerations. As indicated previously however, the dose form is just one element of the holistic drug product that can affect the overall patient experience and the resulting therapeutic effectiveness. This section will provide more insight into some other key features of oral products in relation to their use in the elderly patient population. While it is impractical to list out all the potential product design scenarios, Table 3 summarizes some of these additional oral product characteristics and associated product design considerations.

Dose flexibility requirements can be an important consideration in the elderly patient population. The effects of aging, disease, and concomitant drug use are likely to impact drug metabolism and elimination in elderly patients increasing the need for more flexibility in dosing medications. As the development of oral oncology treatments increases, a dose titration approach is becoming more common for addressing tolerability and safety risks. Frail patients may be at greater risk for adverse events. It is not uncommon for physicians to advise elderly patients to take a half tablet or use alternate day dosing to manage these risks. The abundance of commercially available pill splitters and crushers is evidence of this practice. The discussion on dose forms above discusses the relative advantages of various oral dose forms to facilitate dosing flexibility. The pharmaceutical product designer must work very closely with the clinical research physicians to understand not only the clinical trial design and dosing strategy but also understand what the likely commercial use of the product will entail. This collaboration will help ensure the best drug product is developed.

Similarly, consideration should be given to using the release profile of the dose form to address potential risks in the elderly patient population. Modifying the release profile to reduce dosing frequency is one common approach to help aid ease of safe use and effectiveness. For drugs whose tolerability may be limited by the peak plasma concentration of the drug or its metabolites, slowing the release profile can mitigate these effects. One potential risk to modified release products designed for these purposes is dose dumping, the unintentional release of the entire drug payload at one time. A risk assessment with the specific patient population under consideration must be performed to ensure that a serious adverse event would not occur in the dose form failed to perform as intended. Given the common practice of dose splitting in elderly patients, modified release dose forms using technology requiring the dose form stay intact may be a significant risk, and steps should be taken to eliminate or minimize this risk.

The use of fixed dose combinations (FDC's) is a strategy that could provide benefit to the elderly population. Various dose forms have the ability to incorporate more than one active drug substance, and the choice of the appropriate technology needs to be considered on a case by case basis. Any attempts at developing a fixed

Table 3 Additional characteristics of oral drug products and design considerations

Additional oral product characteristics	Product design considerations
• Dose flexibility – Efficacy – Safety/tolerability – Titration	• What level of dose flexibility will be required to tailor treatment • Can the tolerability of the treatment be improved through dose adjustment • Will the treatment require titration (raising or lowering the dose) to achieve optimal effectiveness
• Release profile – Dosing frequency – Tolerability	• Can the dosing frequency be reduced through changing the dose form release profile • Can the tolerability of the drug be improved by reducing C_{max}
• Fixed dose combinations (FDC's) – Reduce pill burden – Improve compliance – Reduce cost	• Can therapies be combined to reduce pill burden • Can outcomes be improved by ensuring coadministration through FDC's
• Packaging – Primary – Secondary	• Has the packaging been designed to minimize difficulty in opening primary packaging (yet provide safety/security) • Can primary and/or secondary packaging be designed to improve adherence • Can secondary packaging provide a durable storage system for oral liquids and devices
• Devices and dose aides – Design – Human factors	• Has the design of the dosing device been optimized for the target population • Does the device work equally well for self-administration and administration by a caregiver • Are human factors tests required for product optimization and/or registration
• Instructions for use (IFU) and labeling – Intuitiveness – Health literacy	• Is the product information and patient instruction for use intuitive and simple • Has the wording been evaluated for health literacy concerns
• Use environment factors	• Where will the product be used (e.g. home, travel, institution) • Are any additional resources required to dose as intended (e.g. food, water, dose prep or measurement, cleaning capability) • Are there disposal or environmental waste concerns
• Patient support programs – Mechanism to deliver	• Have patient support programs been design to fit the target patient population and the way they prefer to get information • Do multiple mechanisms exist to accommodate for learning preferences or capability

combination product need to be based on a legitimate medical benefit and the regulatory requirements and pathways for developing fixed dose combinations must be understood and incorporated into both the clinical and product development strategies. From a patient perspective, the potential to minimize pill burden can be an advantage and may improve compliance and therapeutic effectiveness as a result. Depending upon the drugs incorporated into the FDC, the potential for reduced cost of therapy exists. One potential drawback of FDC's relates to dosing flexibility.

Fixing the levels of two or more drugs in a single product may not be desirable in instances where careful titration of individual therapies in indicated, and elderly patients are more likely to have the need for individual customization of doses. Given the complexities involved with FDC development and the characteristics of the elderly patient, the product development scientist is advised to thoroughly investigate all potential advantages and disadvantages before initiating FDC development.

The design of the packaging for oral pharmaceutical products can greatly impact the patient's experience with the product. This is true for all dose forms, but the impact can be intensified when more complex or protective packaging needs to be used to support an alternative or less common dose form. Across pharmaceutical products, complaints related to packaging are one of the more common classes of complaints. This stands to reason, as the package is the first experience that a patient has with the product, and sets the tone for the overall product experience. Packaging that makes the dose form difficult to access, requires the use of scissors or other tools to open, or demands that the patient rely on another person to open their medication is common and can present real barriers to product use. However, regulatory requirements in various regions of the globe require child resistant packaging which often incorporates technology that makes packages very difficult for elderly patients with reduced strength, dexterity, or vision to open. Rational package design can minimize these barriers. On the other hand, a well-designed package has the potential to improve the overall patient experience and enable compliance and the desired therapeutic outcome. Incorporating compliance enabling features on the printed package material, such as color coding or symbols can increase the intuitiveness of product use. Portability of the product should also be considered, especially for products like oral liquids that have dosing devices associated with them. Travel kits are commonly available for injectable therapies, like insulins, and may be appropriate for certain oral products as well. Printing on packaging should be legible and use language that is targeted to the level of health literacy for the patient population.

Like packaging, the design of devices for dose measurement and administration can impact the appropriate use of oral drug products. Considerations on how the device will be used should be evaluated and ideally tested through the use of formative and summative human factors studies in the target patient population to ensure that common use errors are designed out of the product.[5] Formative studies can also be used to collect design insight from the intended patient group and incorporated into the product design for further evaluation in the clinical program for the drug.

[5]Draft Guidance for Industry and Food and Drug Administration Staff: Applying Human factors and Usability Engineering to Medical Devices; U.S. Dept. of Health and Human Services, Food and Drug Administration (CDRH); February 3, 2016.

The printed package material and any accompanying information intended for the patient or caregiver as the primary audience should be carefully considered when written. While regulatory requirements on the information provided exist, product developers should consider the layout and use of graphics and text to maximize the ability for the patient to understand this information and use the product appropriately. Health literacy of the patient population needs to be considered and written instructions should be reviewed with these patients in mind.[6]

The environment and use scenarios in which the product will be commonly used should be considered, particularly for those products and dose forms that require access to additional materials or resources to properly use the product. For products intended to be mixed in food or beverage to aid administration, specific instructions for appropriate use should be provided. For example, the types or amounts of foods and liquid that are known to be effective and safe to use should be listed. More importantly, any specific restrictions or contraindicated materials should be highlighted for the patient. The in-use stability and any limitations to such should be discussed and presented to ensure the safe use of the product. For products that require the use of a device for dose measurement and administration, consideration should be given to the associated cleaning and disposal requirements. In those instances when special or difficult to access resources are required, these resources should be incorporated into the product itself, or measures take to ensure the patient, physician, or caregivers are aware of these required resources and have access to them.

One mechanism to provide such information and resources may be through the use of patient support programs. These programs are typically available for expensive or specialty products, but could be considered for any product. For the elderly patient population, it is important to understand the preferred mechanisms for this type of information. For example, the use of Internet-based or connected solutions may not be as valuable to an elderly patient population as a more traditional approach to patient support through their healthcare provider.

Adherence

Throughout this chapter the theme of adherence in the elderly patient population has been discussed in the context of the patient, the dose form and the overall drug product. It is evident from these discussions and in independently published research that adherence is both a major concern and opportunity for the pharmaceutical industry. Many of the specific drivers of poor adherence and the risks associated with poor adherence are exemplified and exacerbated in the elderly

[6]Guidance for Industry (Draft): Safety Considerations for Product Design to Minimize Medication Errors; U.S. Dept. of Health and Human Services, Food and Drug Administration (CDER); December 2012.

Table 4 Adherence factors and oral drug product design

• Polypharmacy – Pill burden
• Swallowability – Size of dose form – Number of units per dose – Dose volume for liquids
• Dose regimen – Frequency of administration – Fit into routine
• Product handling and dose preparation – Dose measurement and accuracy – Tablet splitting/scoring – Packaging attributes – Device design – Cleaning and storage
• Label restrictions – Food effect requirements – Coadministration restrictions with other medications

patient population. It is also evident that there is no single solution to this problem. Adherence barriers such as cost, access, and perceived lack of efficacy are not able to be readily addressed through a specific product design, but other drivers discussed throughout this chapter can be influenced. Table 4 lists a number of adherence facing factors that might be influenced through the design of oral dose forms. Simplifying regimens, eliminating restrictions, and allowing the patient to develop and maintain a medication administration routine are all approaches that can improve adherence in the elderly patient population and improve the overall effectiveness of drug therapy.

Conclusion

The benefits of using the oral route of administration for nonbiological drugs are many, as discussed throughout this chapter. These benefits hold true for the general population from adolescence through seniority. However, when looking specifically at an elderly target patient population, the drug product designer and developer should pay particular attention to the specific characteristics of the disease state, target patient population, comorbidities and other emotional, environmental and sociological factors that have the potential to impact or interfere with the elderly patient's ability to use the product as intended. Failure to take a diligent approach in this regard can result in a greater likelihood of poor adherence and improper usage of the drug product, resulting in lower effectiveness, poor therapeutic outcomes, and potential safety risks. The consequence of these undesired results directly affects those at greatest risk, the patients themselves, and also affects other key stakeholders involved including families and caregivers, healthcare providers, payers,

regulators, and society as a whole. Increased patient involvement along with innovation in health system payer approaches will likely enhance the value of pharmaceutical products to all stakeholders. A thoughtful consistent approach to design and development of drug products can reduce the risk associated with improper use of medicines and enhance the outcomes that medical innovation through pharmaceuticals promises.

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Drug Product Development for Older Adults—Multiparticulate Formulations

Norbert Pöllinger

Abstract The multiparticulate drug product concept covering micropellets, pellets, and mini-tablets is presented as a highly feasible approach to present convenient and patient friendly medication for the geriatric population. Improved swallowability and optimized administration regimen going along with defined drug dosage are achievable. Extemporaneous preparation of medicines from standard medication can be avoided going along with improved patient safety. With one multiparticulate pellet, micropellet, or mini-tablet bulk formulation a broad range of final drug products is presentable applying well-established manufacturing technologies at viable cost.

Keywords Multiparticulates · Micropellets · Taste masking · Fluid bed technologies · Mini-tablets

Introduction

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. More significant will be the shift of composition of the elderly population over the next four decades toward more people above 80 years of age, because of increasing life expectancy and the generation of baby boomers passing the age of 65 years. 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 [1].

With our increasing medical knowledge and the heterogeneity of patients, the therapeutic approaches will 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

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S. Stegemann (ed.), *Developing Drug Products in an Aging Society*,
AAPS Advances in the Pharmaceutical Sciences Series 24,
DOI 10.1007/978-3-319-43099-7_16

development will have to change its paradigm by including the geriatric patients and heading toward an approach of integrating new medicinal products into a disease management concept [1].

ICH Guideline "Pharmaceutical Development Q8 (R2) (2009)" requires under "approaches to Pharmaceutical Development": "In all cases, the product should be designed to meet patients' needs and the intended product performance" [2].

The multiparticulate formulation approach is meant to positively support the aspects of patient safety, usability, and compliance by offering drug products considering the overall health status of geriatric patients.

The Elderly Patient

Aging is a gradual change of various physiological, biological, physical, and social functions of the human being. Along with age-related gradual changes, the incidence for chronic diseases and comorbidity, chronic drug therapy becomes very challenging and complex with the increasing number of drugs for the treatment [1].

The major age-related changes and differences compared to a young adult concern the physiological functions, the cognitive, visual, motoric, and swallowing capabilities. Geriatric patients often require different doses that are often not available and dosage form splitting by the patient or the caregivers is required [1]. Geriatric patients, due to their limited and varying motoric capabilities might have considerable problems for accurate splitting of tablets (Figs. 1 and 2).

Elderly people often experience problems with swallowing of solid oral dosage forms due to dysphagia, disease conditions or due to polypharmacy, and the number

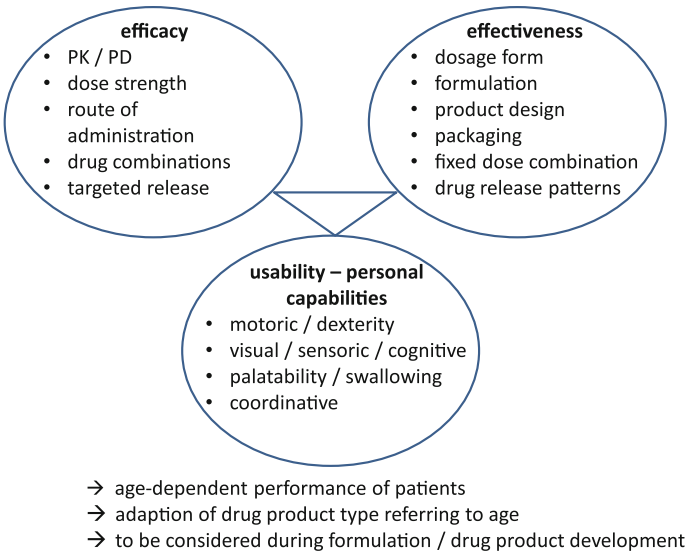


Fig. 1 Considerations for geriatric drug products [48]

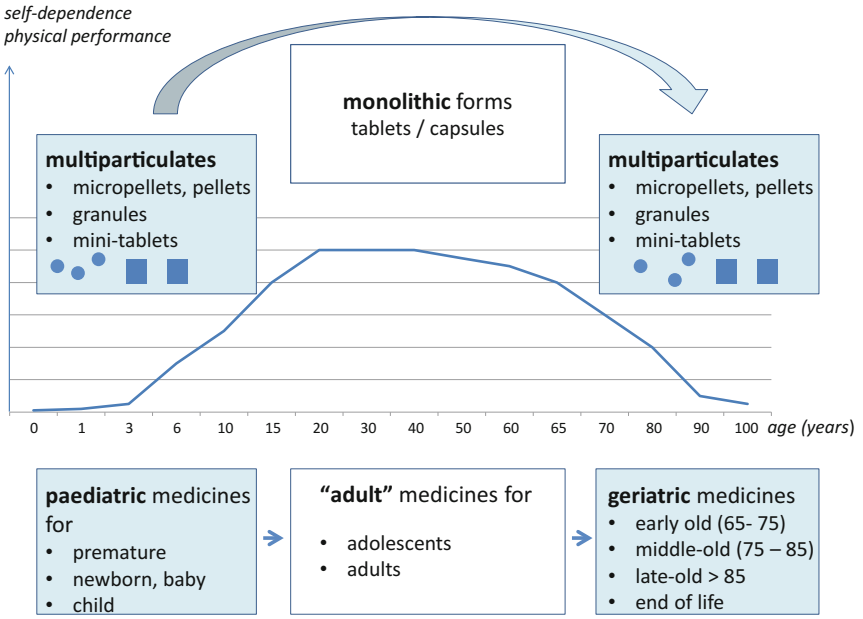


Fig. 2 Age-dependent capabilities of patients and feasible drug product concepts

of medications that need to be swallowed every day. Swallowing difficulties have been described as a major health care problem in older adults that advances with increasing age, affecting about one third of patients in nursing homes [3]. Swallowing dysfunction and dysphagia is an unrecognized challenge for oral drug therapy. While smaller sizes are generally easier to swallow this is not considered during prescription and mainly noticed by professional nursing staff [4].

Once the appropriate medications have been prescribed, compliance and adherence to the prescription remains the most critical aspect in reaching the expected therapeutic outcomes [1].

In an ideal world, doses of medicines would be tailored for the specific patient with the specific condition. If combinations are indicated, preferably, all drugs would be administered in one oral dosage form once or twice daily and the taste of the drugs would be concealed [5].

Drug Products for Children and Elderly—Communalities and Synergies

In 2007, EMEA required that for each new drug substance pediatric formulations have to be developed. The guideline deals in detail with pediatric formulation development [6]. Aspects such as age-appropriate form, size, strength, and

precision of dose delivery as well as taste and palatability are covered. Administration of the medication with specific administration devices or the ability to mix with food should be possible [7].

The new EU legislation for the development of new pediatric drugs may also stimulate the research into drug delivery for the elderly [8].

The unpleasant taste of drug substances is a very important challenge for pediatric as well as geriatric drug product formulation. This especially applies to multiparticulates used as sprinkle formulation to be mixed with soft food or in beverages, which have shown to be a suitable option for pediatrics [9].

Even though there is a difference between geriatrics and pediatrics, product development can benefit from experiences in pediatric drug development by applying principally similar strategies in terms of systematic evaluation of acceptance criteria [9].

Extemporaneously compounded products used for pediatric and geriatric patients may not be able to maintain a good quality due to modification of the dosage form potentially outside the label claims, which might affect treatment efficacy [10].

Sprinkles and multiparticulates like mini-tablets or micropellets could be a good option for both ages. In any case, some learnings from pediatric development may be directly transferable, e.g., taste masking, multiparticulate platform technologies [11].

Multiparticulate Formulations Rationale and Advantages for the Elderly

Very young children and geriatric patients are often unable to swallow monolithic oral solid dosage forms intact. It is well acknowledged that patients, caregivers, and indeed healthcare professionals often need to physically alter currently available dosage forms, for ease of administration, to obtain the appropriate pediatric or geriatric dose, or both. The risk of physical modification of dosage forms, from both a safety and efficacy perspective, are well recognized and as such, this practice should be surpassed by the development and authorization of rationally designed pediatric and geriatric formulations [12].

Multiparticulate systems such as micropellets are versatile platform technologies with considerable promise in pediatric and geriatric pharmaceutical development [12]. These forms consist of multiple small discrete units, which are further processed to produce other solid formulations including MUPS tablets, capsules, dispersible and orodispersible tablets etc.

Multiparticulate systems—in contrast to classical single-unit dosage forms like tablets—contain a plurality of subunits, typically consisting of thousands of spherical pellet particles with a diameter of typically 0.1–2 mm or on mini-tablets having a diameter of 1.5–4 mm. Micropellets offer an ideal size range for a broad variety of administrations (Fig. 3).

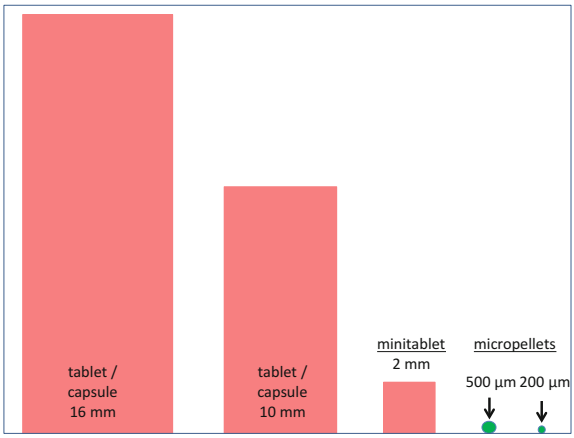


Fig. 3 Comparison of monolithic and multiparticulates size

Another key advantage for multiparticulate solid dosage forms is the opportunity for the development of formulations such as modified, prolonged, delayed release systems etc. in addition to taste masking. Targeted drug delivery and optimized pharmacokinetic profiles can be a benefit for patients by reducing dose frequency and minimizing burden of lifestyle [12]. In contrast to single-unit forms multiparticular offers several advantages:

- reduced variability of the gastric emptying and dependency on the nutrition state
- minimized risk of high local drug concentrations within the gastrointestinal tract
- reduced risk of sudden dose dumping
- lower intra- and inter-individual variability
- controlled onset time of drug release
- delivery of the active ingredient to distal sites within the GI tract

Multiparticulates offer complete and accurate dose delivery in uniform dose units or packages like sachet, stick packs, or capsules, which are easy to administer. From a manufacturing standpoint, multiparticulates can be manufactured in a variety of dosage strengths from one single basic micropellets, pellets, or mini-tablets formulation.

Development of appropriate formulations is a global health challenge that also applies to emerging markets. The World Health Organisation (WHO) has recommended prioritizing the development of formulations which would also be suitable for use in developing countries at appropriate cost. Solid formulations have the added advantage of superior stability and low bulk and weight, thus being easy to transport and store [12] (Fig. 4).

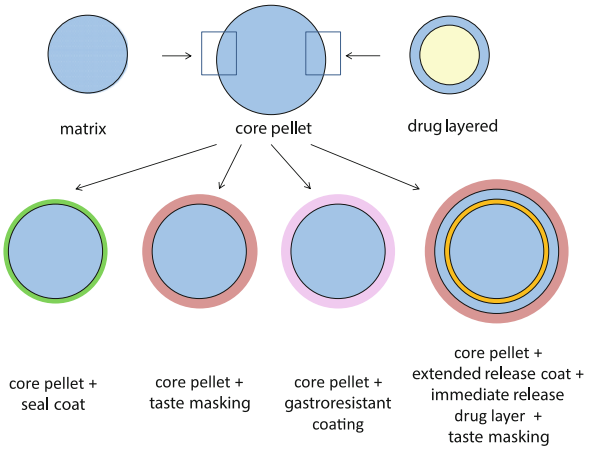


Fig. 4 Pellet and micropellet formulation options applying different functional coatings

Formulation Approaches and Manufacturing Technologies for Multiparticulates (Pellets, Micropellets, Mini-Tablets)

Formulation Approaches for Multiparticulates

Core Pellets/Micropellets

The pellets and micropellets concept allows a multitude of formulation approaches, which are based on one single basic core pellet or micropellet containing the active principle. Core pellets containing the Active Pharmaceutical Ingredient (API) can be drug layered type or matrix type pellets. The drug core pellets can provide an immediate drug release as well as a sustained or controlled drug release characteristic for drugs with short half-life or gastric instability.

Drug Layered Core Pellets/Micropellets

The active drug substance is layered on top of starter pellets. Depending on the final drug product, the size of the starter pellets, and the resulting drug core pellets is of high importance.

Starter pellets (sugar pellets, cellulose pellets, etc.) from 100 to 1500 µm in diameter can be used. In particular for high-dosed APIs the starter pellets should be as small as possible when finally micropellets <500 µm must be achieved.

In order to provide a stable and robust drug layer, usually a binder substance, e.g., Hydroxypropylmethylcellulose (HPMC), Hydroxypropylcellulose (HPC), or Polyvinylpyrrolidone (PVP) is part of the drug layer. Viscosity grade as well as the concentration of the binder with respect to the API plays an important role for the physical stability of a drug layer.

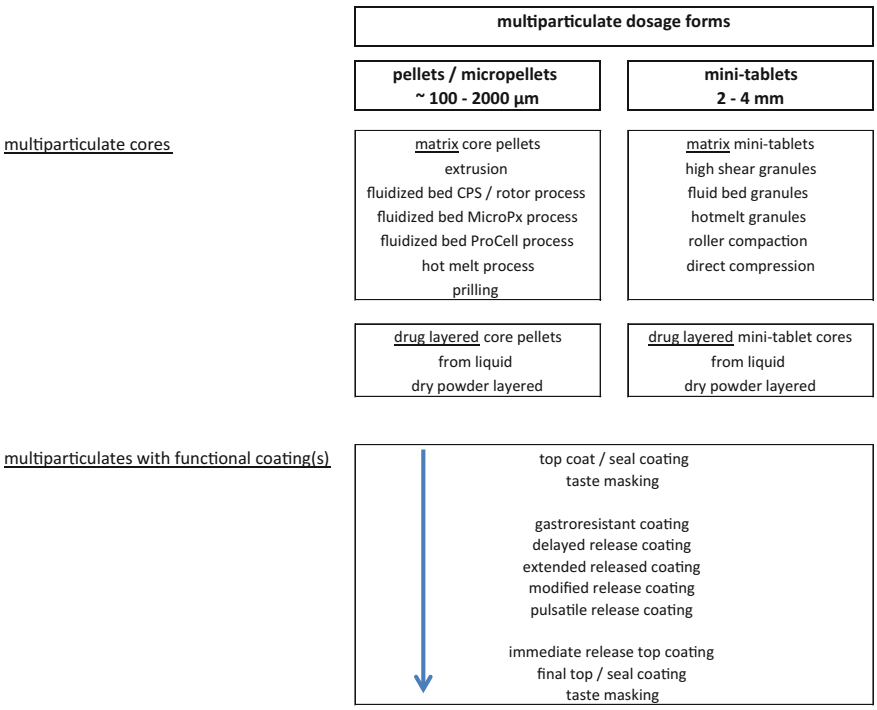


Fig. 5 Formulation concepts for multiparticulate dosage forms

Drug layering formulation and process can also provide improvement of the water solubility and thereby of the bioavailability of a sparingly soluble API. A crystalline, water-insoluble drug can be transferred into an amorphous form applying the co-precipitate technology for the API drug layering step: the water-insoluble API and a feasible polymer are dissolved in organic solvent(s). The organic solvent-based API/polymer solution is processed using an appropriate fluidized bed configuration in order to provide a co-precipitate layer on starter beads in one single processing step. Solubilizers can be integrated into the drug layer in order to optimize solubility (Fig. 5).

Matrix Type Core Pellets/Micropellets

Matrix type (micro)pellets are prepared without a starter core. Besides the API, the pellet matrix may contain a smaller or larger quantity of inactive excipients in order to build up a physically stable pellet matrix. Depending on the process technology, a lower or higher API content is possible. With extrusion/spheronization a drug load of up to ~60 % is achieved. Applying a continuous spray granulation/pelletization fluidized bed technology allows for API content of regularly 90–95 %.

Mini-Tablet Cores

Mini-tablets are a unique dosage form, which afford the advantages of multiparticulates with regard to ease of administration and dose flexibility, coupled with the established, and efficient manufacturing techniques of tableting. The size ranges is usually 2–4 mm in diameter [12, 13] but not more than 4 mm according to the WHO mini-tablets definition [14].

In addition to the API(s), mini-tablet cores can include excipients such as dry binders (e.g., microcrystalline cellulose), diluents (e.g., lactose, mannitol, sorbitol, sucrose), pharmaceutical binder for granulation (e.g., HPMC, HPC, PVP), lubricant (e.g., magnesium stearate, stearic acid, talc) and glidant (e.g., amorphous silicon dioxide). In principle, mini-tablets can provide the same variety of release characteristics as pellets and micropellets as well as be coated with an appropriate fluidized bed process as mentioned in Section "Drug Layered Core Pellets/ Micropellets."

Functional Coating for Multiparticulates

Depending on the composition of pellet, micropellet and mini-tablet cores, a particular drug release profile is achieved. In many cases, pellet and micropellet cores are immediate release intermediates. A specific drug release profile can be achieved with specific coatings. Mini-tablets being larger sized multiparticulates can also apply controlled release technologies as for tablets (e.g., matrix tablets).

In case the multiparticulates are used as sprinkle or dispersible forms, a taste masking will most likely be required in order to cover the bad taste of an API and provide palatability.

In order to achieve an optimal product in terms of pharmacokinetics, tolerability, taste masking, etc., one or more functional coating can be applied to the core pellets, micropellets, and mini-tablets (Figs. 6 and 7).

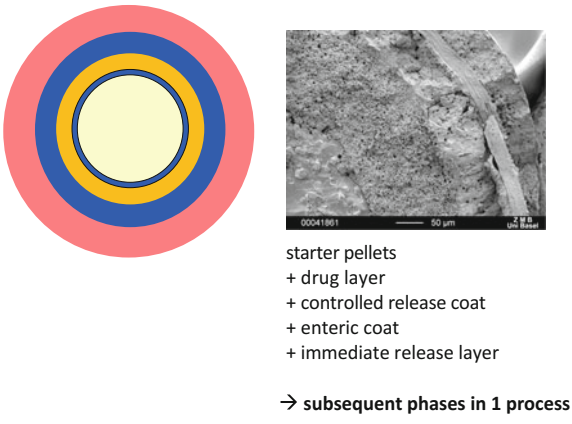


Fig. 6 Complex multiparticulate formulation (example)

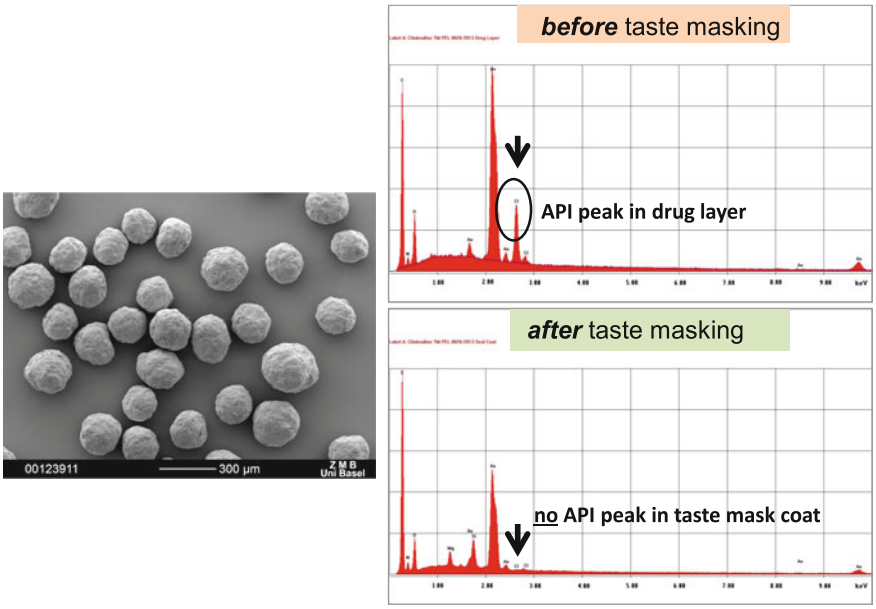


Fig. 7 Evaluation of API migration in taste masked micropellets with EDS (energy dispersive X-ray technology) (Reproduced with permission from Glatt GmbH, 79589 Binzen/Germany, 2014)

Top/Seal Coating

A top coating is applied to seal and to physically stabilize a drug layer or a matrix core pellet/micropellet. Top coatings on top of potentially sticky controlled release films facilitate handling, help to avoid unwanted sticking, and agglomeration phenomena.

Seal coatings are applied to separate a drug layer from a functional film coat with the aim to exclude any potential interaction of the API with functional film coat. Acid sensitive proton pump inhibitors (PPI) are classical candidates for seal coat applications. In order to avoid chemical interaction between the acid sensitive PPI and a gastroresistant coating dispersion (e.g., aqueous dispersion of a poly-methacrylic acid derivative), a seal coating is applied on top of the API core pellets before the gastroresistant coating is processed. By this means, a mechanical and chemical barrier is introduced in between the API and the functional coating assuring the chemical stability of the API.

In case of taste masking approach, a seal coat placed on top of an API core pellet, micropellet or mini-tablet helps to prevent API migration into the functional film. Migration of API into controlled release films potentially modifies the drug release profile and breaks the taste masking properties.

Usually, water-soluble polymers, such as HPMC, HPC, or PVP are used for top and seal coating applications. Depending on the solubility of the API concerned,

processing from aqueous or organic solvent-based liquid must be considered. In order to end up with an optimal result, the application of a seal coat on a highly water-soluble API would be processed from an organic solvent(s) system in which the API is less soluble than in water. Anti-tacking agents such a silicon dioxide or talc facilitate the coating process. Plastisizers such as polyethylenglycol (PEG) could be integrated to increase the flexibility of films.

Taste Masking Coating

Strategies to minimize exposure of orally delivered solid drug substances to the sensory system responsible for taste perception are summarized as taste masking strategy. Taste masking is mainly achieved by a taste concealing approach, which aims to minimized direct exposure of the drug to taste sensors during the time of mouth exposure. Just adding a flavor element to reduce a bad taste is not adequate (Fig. 8) [15].

Taste masking/concealing must remain effective for up to several minutes as drug particles can remain trapped for a certain time between the teeth or in other places of the oral cavity. The integrity of the taste masking must be secured during the manufacturing of the finished dosage form as any fracture of taste masked particles, e.g., during tableting may compromise the taste [15].

Mouthfeel of the medication mainly in terms of the multiparticulates size has to be considered [15, 16]. Too large particle fracture easily, contribute to a gritty mouth feel or initiate a biting reflex, which would destroy them. Too small particles are more easily trapped longer than larger particles. In general, feasible taste masked particles are in the range of 50–500 µm (Fig. 9).

	neutral tasting API	inconvenient tasting API	very bad tasting API
taste masking required ?	-	+	+++
Oral solid dosage forms			
granules	√	√	-
powders	√	√	-
minitablets	√	√	√
micropellets			√
Taste masking options			
flavors, sweeteners	-	√	-
complexation	-	√	-
salt formation	-	√	-
cyclodextrins	-	√	-
coating	-	coating of API	coating of API micropellets
Oral liquid dosage forms			
solutions	√	√	-
suspensions	√	√	suspension with micropellets

Fig. 8 Taste masking concepts

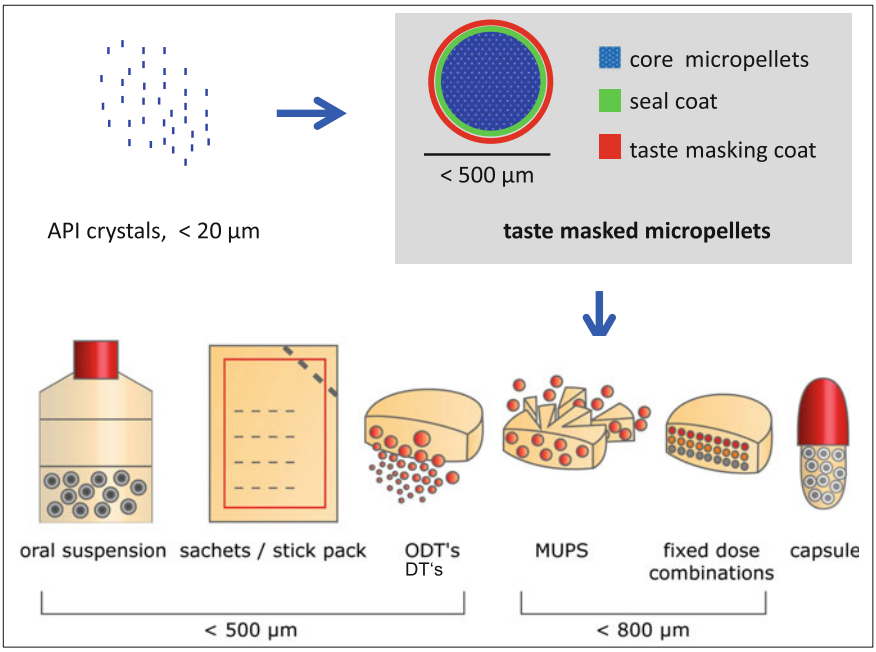


Fig. 9 Taste masked micropellets and resulting drug products

The quality of a taste masking approach can be tested in vitro (electronic tongue, drug release studies, cell-based models) or with in vivo methods (rat taste panels with BATA model, human taste panel) [17]. The ability of an electronic tongue to help rationalize the development of oral taste masked formulations was evaluated with diclofenac acid, sodium, and potassium salt. The study was performed with an TS-5000Z electronic tongue (Insent Inc., Japan) equipped with seven lipid membrane sensors representing bitterness, sourness, saltiness, umami and astringency with corresponding aftertastes. The underlying measurement principle is potentiometric. Multivariate analysis, i.e., principal component analysis (PCA), was used to reduce the multidimensional space (seven independent sensors) without losing information. Using PCA, the most abundant information contained in original data could be transformed into the first principal component PC-1 (x-axis), and the second most abundant information into the second component (PC-2, y-axis). Clusters could be obtained in a PCA map by plotting PC-1 against PC-2. The taste sensing system was capable of differentiating diclofenac acid from its salts. Based on the screening, the diclofenac acid form was selected to formulate taste masked preparations [18]. Evaluation of different taste masked Ibuprofen granulates showed that Ibuprofen test granulate GRA 3 being close to pure Ibuprofen drug substance (IBU) results provided insufficient taste masking while Ibuprofen test granulate GRA 4 and 5 are located towards placebo PL-GRA 3, 4, 5 results showing a sufficient taste masking effect (Fig. 10) [19]. The electronic tongue proved to be a valuable tool for assessing and predicting the taste of APIs in the early development stage.

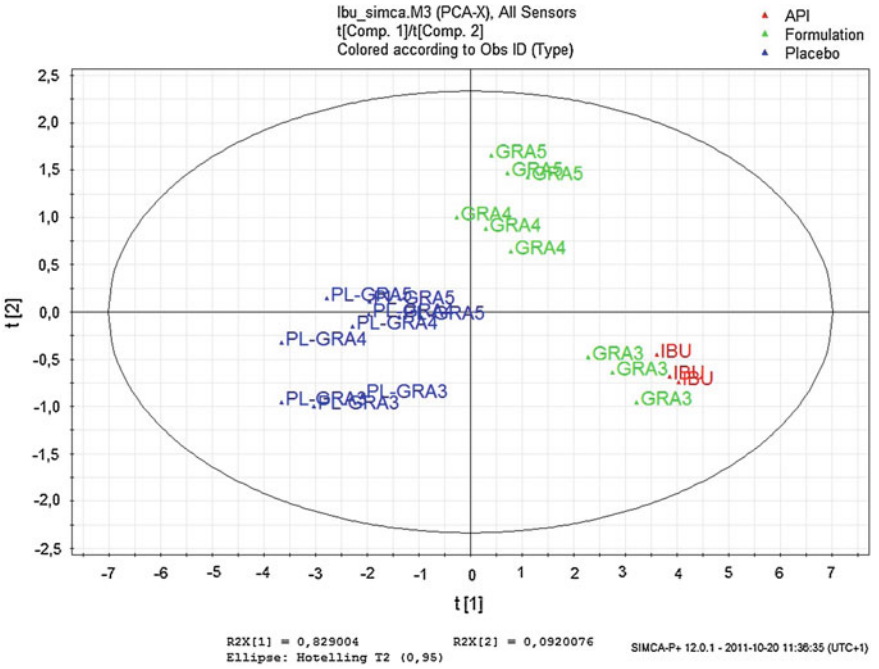


Fig. 10 E-tongue results incl multivariate analysis in development of tasted masked Ibuprofen [19]

Taste masking is mostly achieved with film coating on API crystals, pellets, micropellets, or mini-tablets. Polymers applied for taste masking can be e.g. polymethacrylates with dimethyl aminoethyl groups (Eudragit® E), water-soluble polymers, such as HPMC, PVP, ethylene oxide vinyl acetate copolymers (Kollicoat® IR), and others. A good balance between taste masking and drug release must be achieved: masking a bad taste perfectly and achieving an immediate release profile is not a trivial task and a challenge for development. Figure 11 shows the

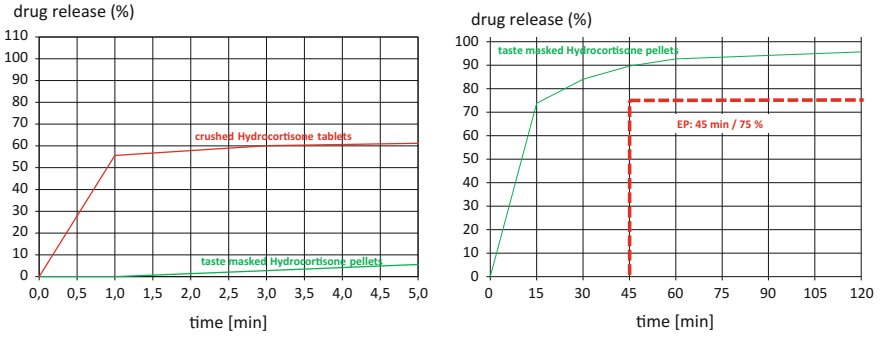


Fig. 11 Taste masked Hydrocortisone pellets: taste masking efficiency at pH 7 and in vitro dissolution at pH 1.2 (Glatt/Diurnal 2014)

taste masking efficiency in phosphate buffer pH 7 and the in vitro dissolution profile in simulated gastric fluid pH 1.2 (USP paddle 75 rpm) of taste masked Hydrocortisone pellets. A good balance between appropriate taste masking and immediate drug release is achieved when a coating level of only 1 % was applied.

Different taste masking polymers to be applied on top of core micropellets, pellets or mini-tablets are available: pH dependent soluble polymers (insoluble at physiological pH 7 in the mouth, soluble in the stomach at pH 1) or pH independent soluble polymers or combination of polymers, e.g., ethylcellulose (EC) and hydroxypropylmethylcellulose (HPMC) can be used. A point to consider is the thickness of the taste masking film having a pronounced impact on taste masking and drug release performance.

Gastroresistant (Enteric) Coating

Gastroresistant (enteric) coatings are recommended when an API is irritating or damaging to the stomach mucosa, is instable in gastric juice or requires a release in the intestine. A typical class of drugs requiring gastroresistant coating are PPI.

Polymers frequently used for gastroresistent coating are methacrylic acid copolymers (Eudragit® L, S), methacrylic acid ethyl acetate copolymers (Kollicoat® MAE), hydroxypropylphathalate, celluloseacetatephathalate, shellack, etc. The polymers may be combined with plastisizers (e.g., triethylcitrate) and antitacking agents (e.g., talc, magnesiums stearate, silicon dioxide, etc.). Enteric coatings can be processed from aqueous dispersions or organic solvent-based solutions.

Delayed/Extended/Modified/Pulsatile Release Coating

Modified release dosage forms are used in order to reduce the dosing frequency, to achieve a delivery in a targeted area of the GI tract as well as to optimize the pharmacokinetic profiles (e.g., reduce side effects due to high plasma peaks, colonic targeting).

A big variety of options is available to convert an immediate release pellet, micropellet, or mini-tablet into a product with different and complex drug release characteristics (Fig. 12). Different drug release kinetics can be achieved by using specific formulation approaches: from immediate release to the delayed, modified or pulsatile release, from the gastro resistant to the taste masked form (Fig. 5) [20].

A variety of polymers is available: e.g., insoluble and swellable polymers such as derivatives of polymethacrylic acid (Eudragit® RL, RS: ionic with quaternary ammonium groups and chloride counter ions; Eudragit® NE: neutral with ester groups), polyvinylacetate (Kollidon® SR), ethylacetate methyl methacrylate copolymers (Kollidon® EMM) or ethylcellulose and combinations with water-soluble compounds. Processing from aqueous dispersion as well as organic solvent solution is possible. The coating quality and thickness is of high importance for the

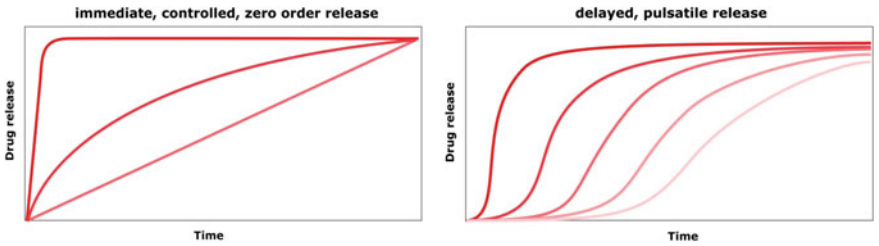


Fig. 12 Different in vitro dissolution profiles of drug products

drug release profile. Release kinetics such as 0. and 1. order can be achieved. A pulsatile release including a lag time of, 2–10 h provides even higher convenience for the patient when the medication can be taken in the evening—waking up during nighttime for medication intake is no longer required.

Manufacturing Technologies for Multiparticulates (Fig. 13)

Manufacturing Technologies for Mini-Tablets Cores

One way to manufacture mini-tablets is the direct compression approach. The narrow diameter of the die used in mini-tableting requires excellent flow properties of the formulation blend to obtain mini-tablets with a narrow weight range.

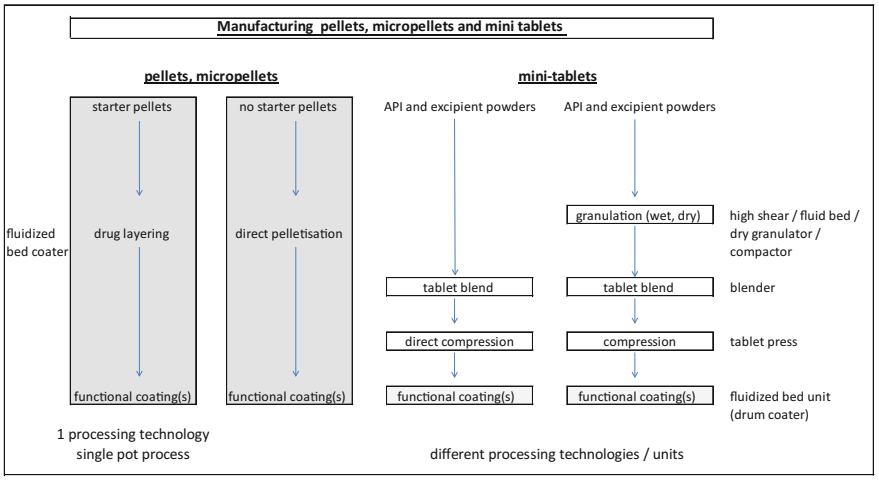


Fig. 13 Manufacturing technologies for (micro)pellets and mini-tablets

Therefore, granulation of the powder will be required to achieve the powder flow and sufficient compressibility. For mini-tablets a smaller particle size and a narrower particle size distribution is required. In order not to damage the small sized mini-punches, compression force is limited to ~2 kN [12].

Matrix type and coated extended release mini-tablets with Carbamazepine prepared with direct compression were investigated. In vitro dissolution profiles of mini-tablets depend on the size of the cores and are different for mini-tablets and larger tablets. It was easier to develop matrix type mini-tablets than coated mini-tablets in order to achieve a defined Carbamazepine release profile for 12–24 h [21].

Manufacturing Technologies for Matrix Pellets/Micropellets

For the processing of matrix type pellets and micropellets different technologies are available.

Matrix type pellets with or without functional polymers in the matrix can be made with either batch-wise or continuous-wise working fluidized bed processes or via extrusion/spheronization (Figs. 14 and 15).

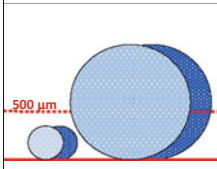
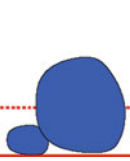
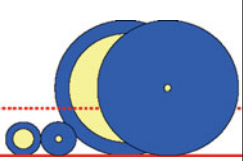
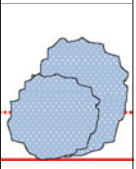
fluidized bed **rotor / CPS™** process	fluidized bed **MicroPx™** process	fluidized bed **ProCell™** process	fluidized bed **Wurster (bottomspray)** process	extrusion + spheronisation process
matrix pellets	matrix pellets	matrix pellets	drug layered pellets	matrix pellets
batch process	continuous process	continuous process	batch process	continuous process
				
micropellets possible	micropellets possible	micropellets possible	micropellets possible	—
drug load ~ 0,01 – 90 %	drug load ~ 90 – 100 %	drug load ~ 90 – 100 %	drug load ~ 0,01 – 80 %	drug load ~ 0,01 – 60 %

Fig. 14 Different types of core pellets and core pellet manufacturing technologies

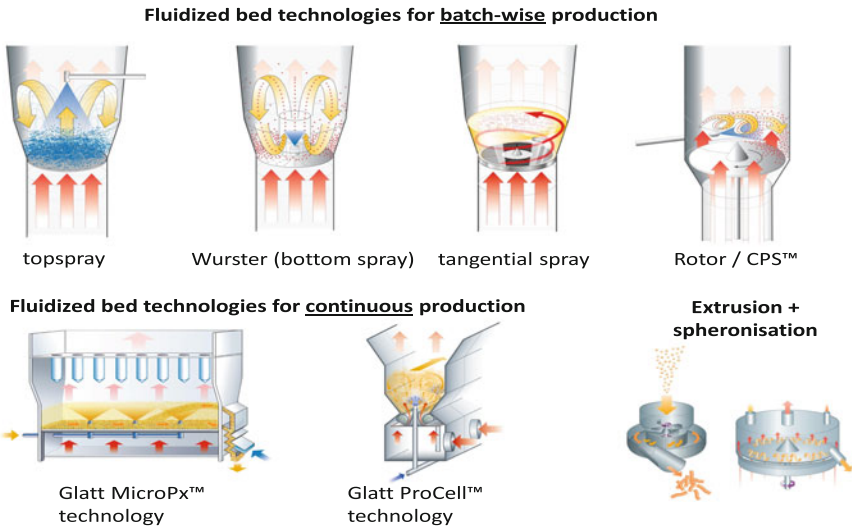


Fig. 15 Manufacturing technologies for pellets and micropellets (Reproduced with permission from Glatt GmbH, 79589 Binzen/Germany, 2015)

Fluidized Bed Rotor and CPS™ Technology

The fluidized bed rotor technology has been known for a long time as a process technology to directly transfer powders into pellets (direct pelletisation). The CPS™ technology is an advanced fluid bed rotor technology allowing the preparation of matrix pellets with particular properties in a batch process. Extremely low-dosed drugs can be formulated to matrix pellets as well as high-dosed APIs (drug concentration from <1 % up to 90 %). Compared to the fluidized bed rotor system the CPS™ Technology works with a conically shaped rotating disk and additional devices ensuring a directed particle movement and optimized process. In the first direct pelletization process phase, the powders are wetted in order to form a granulate. In the second process phase, spheronization of the previously irregular shaped aggregates into spherical (micro)pellets takes place. For the direct pelletization CPS™ Technology starter beads are not required. Typically, microcrystalline cellulose powder is used as a basic excipient; moreover, other functional compounds like polymers, disintegrants, solubilizers, and others can be part of the pellets formulations in combination with the API to achieve the desired performance.

Fluidized Bed MicroPx™ and ProCell™ Technology

The MicroPx™ Technology is a continuous fluid bed agglomeration process for high dose (90–95 % API), providing matrix type pellets in the size range of 100–

500 µm. Functional pharmaceutical excipients, e.g., for bioavailability enhancement or controlled drug release can be integrated into the micropellet matrix.

For the continuous MicroPx™ Technology starter beads are not required. Typically, all components like the API, pharmaceutical binder(s) and other functional ingredients are contained in a liquid, which is fed into the MicroPx™ process via spray guns; the spraying liquid can be a solution, suspension or emulsion. The direct pelletization process starts with spraying the API containing liquid into the empty MicroPx™ fluid bed unit to generate distinct initial particles, which are continuously layered with API containing droplets from the bottom-spray nozzles. An online acting zig zag air sifter provides a narrow particle size distribution without an additional sieving step.

With highly water-soluble Metoprolol succinate, micropellets with a drug load of 80–96.4 % were produced. Narrow particle size fractions of 250–355 and 400–630 µm were achieved [22]. MicroPx Ciprofloxacin [23] and Clarithromycine [24] micropellets have been shown to provide an ideal substrate for taste masking application in Wurster fluid bed. In order to optimize the drug release and bioavailability of Clarithromycine from the taste masked micropellets, a solubilizer is integrated into the core micropellets transferring the crystalline API into a solid dispersion.

The ProCell™ Technology is a spouted-bed type direct granulation and pelletising process for the preparation of very high concentrated multiparticulates for which inert starter beads are not required. Either, solutions, suspensions, emulsions, or melts containing the API, can be processed. Ibuprofen micropellets <400 µm consisting of Ibuprofen (75 % w/w) and Carnauba Wax (25 % w/w) were manufactured with the continuous ProCell™ process. Bitter tasting Ibuprofen having a melting point of ~77 °C was molten with Carnauba wax. A taste masking effect going along with immediate drug release resulted without further taste masking coating [19]. The formation of Ibuprofen/carnauba wax pellets out of the melt takes place by means of spray solidification and agglomeration. By this means, high-throughputs and cost effective processes are achieved.

Extrusion and Spheronization Technology

Extrusion of pre-wetted masses or melts followed by spheronization is a well established technology to manufacture matrix pellets. The lower limit in particle size is ~700 µm. Micropellets in a size range of 100–500 µm cannot be produced via extrusion/spheronization due to technical limitation of the extrusion tools. Compared to drug pellets manufactured with fluid bed technologies, extruded pellets provide a less spherical and less smooth surface (Fig. 16).

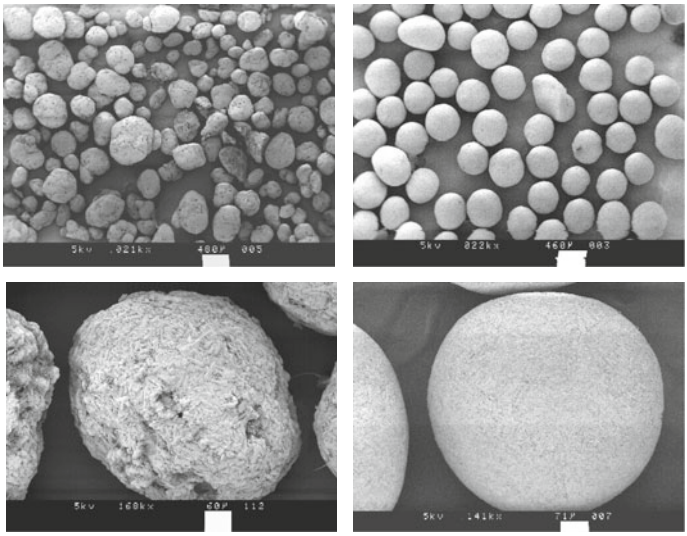


Fig. 16 API pellets manufactured with extrusion/spheronization and fluidized bed CPS™ process

Manufacturing Technologies for Drug Layering and Functional Coating Applications

Fluidized Bed Wurster (Bottom-spray) Technology

The Wurster (bottom-spray) fluidized bed technology is most frequently applied for all layering and coating applications on multiparticulates (Fig. 15) [25]. The parameters to be selected for a particular process depend on the coating liquid properties being mainly determined by the properties of the coating polymer(s). Minimum film forming temperature MFT is of highest importance for the formation of a uniform and dense film from an aqueous dispersion. As stability issues with respect to the in vitro dissolution profile were frequently experienced when polymers were processed from aqueous dispersions, a revival of organic solvent-based coating liquids took place in the past years.

In particular for the layering and coating of multiparticulates, such as micropellets, pellets, and mini-tablets, the Wurster (bottom-spray) technology is highly recommended.

The Wurster partition divides the fluid bed into zones of differing airflow: the so-called "up-bed" and the "down-bed" zone. This particular configuration generates a defined and controlled circulation of all particles to be processed. The rising stream of particles is sprayed concurrently with drug layering or coating liquid. The resulting fluidization pattern causes the particles to be individualized and highly scattered when they pass the nozzles spray zone layering them with drug or coating

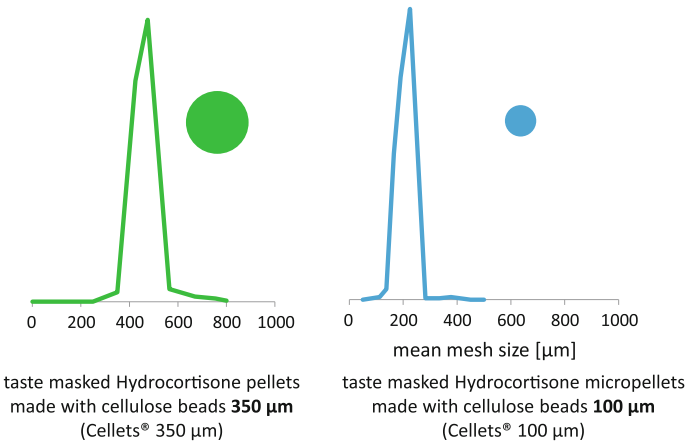


Fig. 17 Particle size distribution of taste masked Hydrocortisone multiparticulates manufactured with fluidized bed Wurster (bottom-spray) technology depending on the particle size of the starter beads

liquid. The risk of unwanted particle agglomeration can be mostly ruled out as long as suitable process parameters are chosen.

With feasible equipment, configuration, and processing knowhow very small starter pellets, e.g., 100 µm in size can be optimally layered with drug and finally coated with functional films (Fig. 17).

With one drug layering step, a drug load of up to 60 % is achievable. For higher drug load of up to 80 %, a batch split must be applied. Very low drug loads are safely achievable with the Wurster (bottom-spray) fluid bed technology resulting in excellent content uniformity of the drug loaded pellets. Scale up of the process from lab scale to pilot and commercial scale has been a worldwide well-proven exercise over decades [26]. The process provides even complex multilayer multiparticulates at viable production cost in particular when the different layers and coatings are applied sequentially without interrupting the overall process (Fig. 18).

Fluidized Bed Tangential Spray Technology

In contrast to the Wurster (bottom-spray) processing mode the tangential spray technology administers atomized layering or coating liquids through under-bed spraying. The control of the process and process parameters is very comparable with Wurster (bottom-spray) technology (Fig. 15). The risk of particle agglomeration is naturally higher as the spray liquids are sprayed directly into the product bed in an under-bed manner.

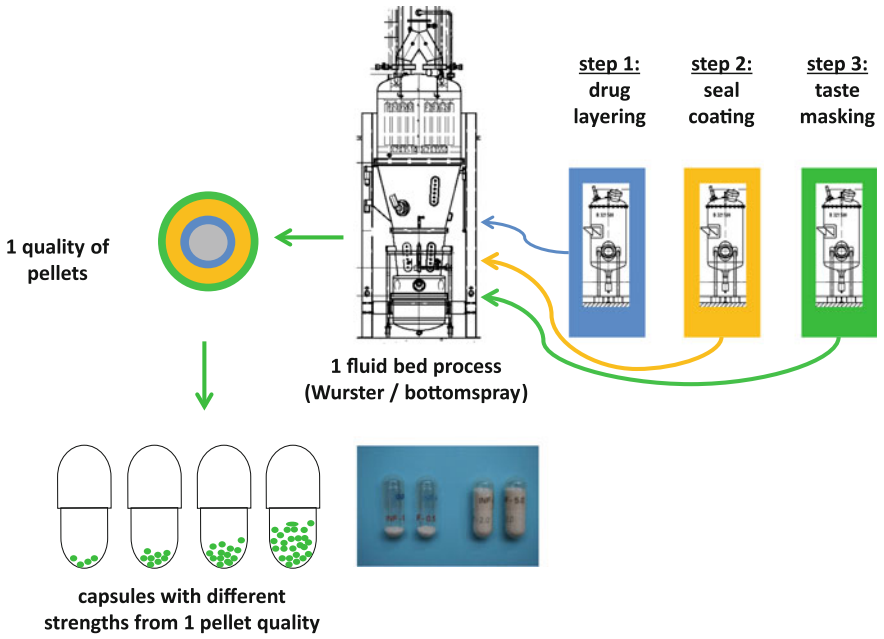


Fig. 18 Processing of drug layered/seal coated/taste masked Hydrocortisone pellets with fluidized bed Wurster (bottom-spray) process: a single pot process

Fluidized Bed Top-Spray Technology

Fluidized top-spray technology is an excellent technology for particle agglomeration, which is sometimes used also for drug layering and coating (Fig. 15). For these applications, it is less effective than the Wurster (bottom-spray) and tangential spray technologies.

Fluidized Bed Dry Powder Layering Technology

The fluidized bed dry powder layering technology is mainly applied when a high-dosed and moisture sensitive API must be layered on starter beads (Figs. 19 and 20). After application of the powder fraction incl, e.g., API, binder and glidant a gain in weight of 300 % meaning 4× the initial weight was be achieved within ~50 min (results of a process development and scale up study to commercial batch size performed by Glatt Pharmaceutical Services, 2014).

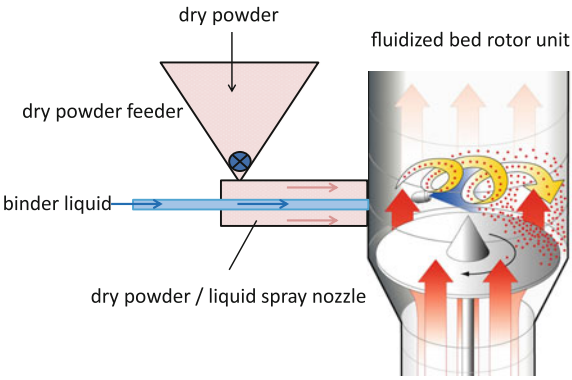


Fig. 19 Fluidized bed rotor dry powder layering technology

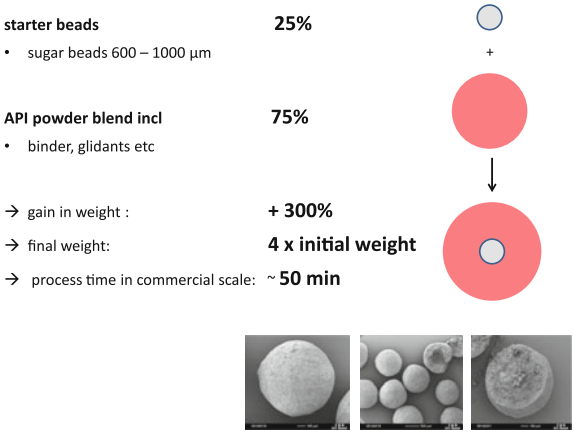


Fig. 20 Dry powder layering of a water-sensitive API using fluidized bed rotor powder layering technology (Reproduced with permission from Glatt GmbH, 79589 Binzen/Germany, 2015)

Drum Coating Technology

Mini-tablets can be coated using a perforated drum coater as it is used for standard tablets sizes. The risk of agglomeration is considered to be higher as with Wurster (bottom-spray) fluidized bed process, where all particles are individualized by means of the particular equipment configuration and fluidization pattern. Particular mesh insert must be used in order to avoid that mini-tablets are falling through the drum perforations.

Drug Products Based on Multiparticulates

Mono-products and Combination Products

Fixed dose combination products (FDC) are considered for the older and multi-morbid patient population as they help to reduce the pill-burden and can improve

pharmacokinetic performance of drugs, and thus, the efficacy and quality of patients' lives [9, 27].

Dose titration may become simpler with a multiparticulate-based combination product [11]. Multiparticulate platform technologies have the potential to produce fixed dose combinations, which combine multiple drugs, release profiles, and dose strengths into a single dosage form for convenient and reliable administration [12].

By using multiparticulates such as pellets, minipellets, and mini-tablets, the necessary dose combination can be achieved through co-packaging of different multiparticulates into a capsule, sachet, or stick pack and may avoid the need to perform PK studies to bridge between clinical and commercial products. This approach to develop combination products can potentially accelerate the availability of products to the market and the patients [13].

A classical combination product example is Levodopa/Carbidopa for Parkinson's disease treatment [9]. The multiparticulate formulation concept does not allow only to combine different actives in one product but allows also individual drug release profiles for each of the multiparticulate compounds [28] (Fig. 21).

Direct Oral Application or Sprinkling of Multiparticulates with Capsules, Sachets, Stick Packs

Multiparticulates, such as pellets, micropellets, or mini-tablets can easily be filled into capsules or sprinkle capsules, sachets, or stick packs (Fig. 9). Different multiparticulate products can be filled in one packaging unit like different APIs and drug release profiles.

The content of a single-unit package can be directly administered to the mouth. Alternatively, multiparticulates are sprinkled on a small portion of soft food or small volume of beverage. For this application, the compatibility and stability of the sprinkled products with the soft food or beverage must be proven.

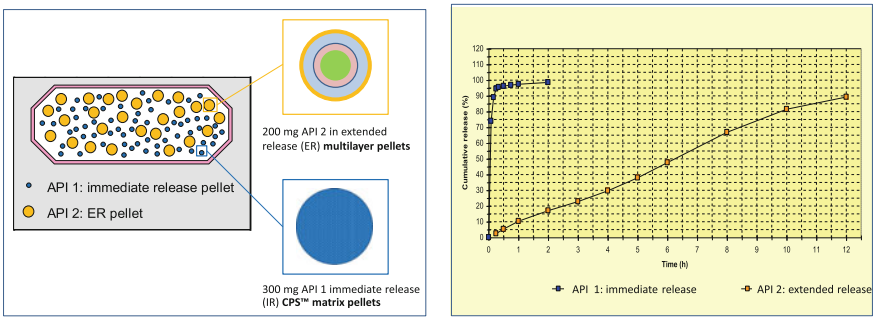


Fig. 21 In vitro dissolution from MUPS combination tablets made with IR pellets and ER pellets (Glatt)

Filling multiparticulates into capsules is a standard "packaging" technology. Very large capsule sizes can be used as the capsules are acting as primary packaging material only and must not be swallowed. Hydrocortisone taste masked pellets were filled into capsules size 00 elongated (Fig. 18). Excellent content uniformity of capsules with different dosage strengths was achieved, when one single pellet population had been encapsulated [29, 30].

Sprinkle capsules are a new generation of capsule shells having an innovative closure that needs less force to open. Opening of capsules is made easier and safer for elderly patients and caregivers [31].

Sachet or stick pack filling is more challenging than capsule filling from a technical point of view. Laminated aluminum foils, which can even include desiccants, are processed.

Device for Repeated Dosing of Multiparticulates

Current multiparticulate delivery methods including tablets, capsules, sachets, stick packs, and dose sipping technology allow flexible dosing but only dispense a single dose. A medical device is presented facilitating the dosing of free-flowing multiparticulates and allowing repeated dosing with a hopper-based device. As part of early-stage designs for a multiparticulate dispenser, methods for achieving precise, accurate, timely, reproducible, and robust weight-based dosing have been investigated [32].

Tablets with Multiparticulates—MUPS Principles

Compaction of multiparticulates to MUPS (multiple-unit pellet system) tablets is one of the more recent and challenging technologies [33].

Controlled release, enteric release, or colon targeting could be achieved applying a feasible coating on multiparticulate cores. The compression of multiparticulates to a MUPS tablet goes along with considerable challenges referring to tablet weight variation and segregation phenomena. De-mixing is usually due to differences in size, shape, surface, and density differences between pellets and extragranular tableting excipients. If pellets with a narrow size distribution are compressed together with additives of similar size and shape, adequate uniformity of mass, and content can be achieved [33]. A threshold of at least 50 % w/w pellet content should be attained in any tableting blend to avoid segregation [33].

The biggest challenge in compaction of pellets into MUPS tablets is damage to the coating with a subsequent loss of the controlled release, gastroresistance or taste-masking properties. Damaging to the pellet coating membrane during compaction of MUPS can be avoided when feasible fillers or cushioning agents as well as pellet core and coating qualities are used [33] (Figs. 22 and 23).

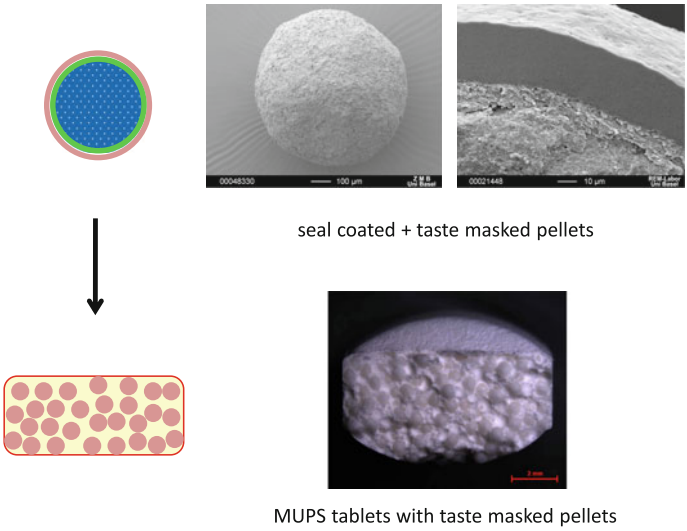


Fig. 22 MUPS tablets with taste masked pellets (Glatt)

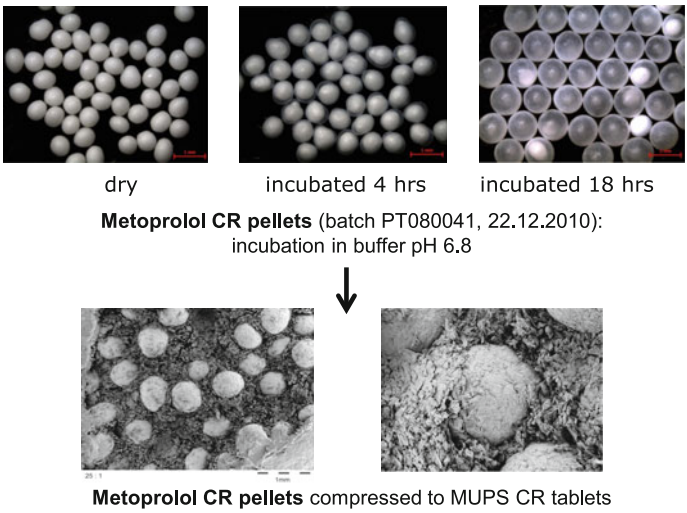


Fig. 23 Metoprolol CR pellets and MUPS tablets (Glatt)

Dispersible Tablets (DT)

Dispersible tablets including multiparticulates negate the need to swallow large units intact and can potentially provide a flexible and individualized approach to drug delivery [12].

Dispersible tablets are tablets to be dispersed in a liquid, which is then be drunken by the patient. The tablet size can be selected freely as the tablet must not be swallowed. Taste masked API crystals or micropellets can be compressed to dispersible tablets. The excipients selected for the dispersible tablet composition should easily disperse or dissolve in water at ambient temperature. Ideally, in order to prevent sedimentation of the multiparticulates at least for a short period of time, viscosity-increasing polymers could be integrated. Dispersible MUPS tablets should disintegrate within 3 min in a small amount of water, to yield a homogenous dispersion [12].

Orodispersible/Orally Disintegrating Tablets

Orodispersible or orally disintegrating tablets (ODT) with multiparticulates are disintegrating in the oral cavity within a few seconds. A high porosity of the tablets is supporting the disintegration.

A more expansive alternative to tablets is to freeze-dry a liquid including multiparticulates ending up with a very porous and fast "melting" and disintegrating structure [34]. The matrix forming excipients added to the multiparticulates should be highly water-soluble (e.g., mannitol). The taste masking and controlled-release properties of the multiparticulates must not be impaired by the solution preparation process prior to the lyophilization step nor by the lyophilization process itself. The liquid including multiparticulates can be filled into blisters and lyophilized.

Manufacturing methods for dextromethorphan hydrobromide ODTs and the effect of formulation variables on disintegration time and t50 were investigated. The concentrations of both diluent and disintegrant had a significant impact on ODT properties [35]. A basic study with orodispersible mini-tablets (ODMT) including 20–50 % w/w multiparticulates was reported for 8 mm ODTs and 2 mm ODMTs [36].

Chewable Tablets

Chewable tablets are intended to be chewed before being swallowed. For taste masked multiparticulates such as micropellets the risk of being damaged by the chewing activities must be considered to be rather high. In addition, the consequences of swallowing chewable tablets intact should be investigated [12]. For said reasons, chewable tablets are considered not as first choice for geriatric application.

Oral Liquids with Multiparticulates

Liquid formulations are a suitable oral dosage form for the pediatric and geriatric age group. They require a stable, dissolved, or suspended form of the drug that

meets release, bioavailability, and taste requirements [37]. Today, liquid formulations are well accepted by children. [38].

Especially to elderly people and patients who have difficulty in swallowing, high-dosed drugs in form of large-size tablets presents considerable challenge. Well-designed oral liquids including multiparticulates, such as taste masked micropellets , are suitable drug products for the elderly.

Multiple-Dose Oral Liquids (Ready-to-Use Suspensions, Dry Suspensions)

Small multiparticulates such as micropellets can be used to prepare an oral suspension-type liquid. The dose of the active substance is contained in a small volume of liquid which is applied to the patient, e.g., with a medicine spoon.

Multiparticulates <500 μm can be suspended in an appropriate dispersion medium. Sedimented particles must be easily redispersible and must not form a solid cake. The multiparticulate and dispersion medium composition must ensure that the functionality and quality of the drug product is not negatively impacted during storage until use. Taste masking and drug release must comply with the specification over the whole in use time of the product.

In order to avoid any instability issues of a ready-to-use suspension containing functionally coated multiparticulates the dry suspension concept is often preferred to the ready-to-use suspension concept. The composition of a dry suspension is almost identical with the one of a ready-to-use suspension. The main difference is that the physical and chemical stability of a suspension prepared from a dry suspension prior to first us usually must cover a 2–4 weeks time period only which is much easier to fulfill than a 3–5 years expiry date.

A liquid formulation of the chinolone antibiotic Ciprofloxacin was presented in order to facilitate the administration of the high-dosed API (250/500/750 mg per dose) to elderly. Taste masked Ciprofloxacin micropellets are combined with an oily dispersion medium based on middle chain triglycerides. The dispersion medium moreover contains lecithine as a wetting agent and to increase the water tolerance of the oily liquid. Density-increasing and thus suspension-stabilizing additives such as sucrose or other sugars and sugar substitutes are included. As oily suspensions are almost water-free, preservatives are usually not required. Prior to first use, the taste masked Ciprofloxacin micropellets are transferred into the oily carrier liquid in order to provide the ready-to-use suspension [23].

Extremely bitter tasting Clarithromycine micronized drug substance is processed into core micropellets applying the MicroPx™ pelletization technology (Figs. 9 and 24). As Clarithromycine is sparingly soluble in water, it is transferred into a solid dispersion by coprocessing with a potent w/o surfactant of the polyoxyethylene-polyoxypropylene type. In a second step, the Clarithromycine core micropellets are coated with a seal coat followed by a taste masking film. For a medication period of 14 days efficient taste masking and immediate drug release is achieved [24].

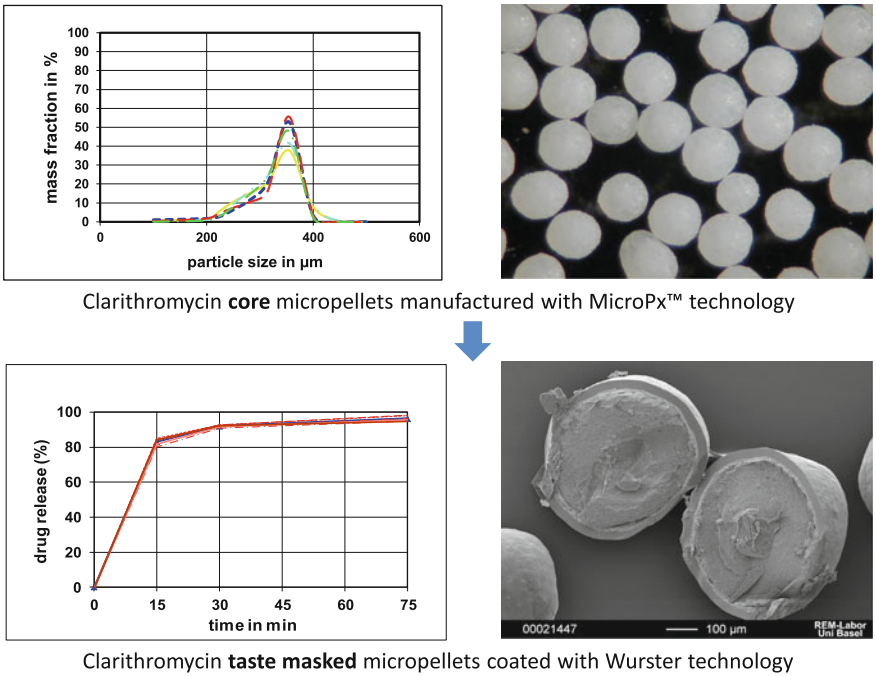


Fig. 24 Clarithromycine core micropellets made with MicroPx™ technology/particle size distribution of Clarithromycine core micropellets/in vitro dissolution of taste masked Clarithromycine micropellets at pH 6.8/SEM picture of taste masked Clarithromycine micropellets (Reproduced with permission from Ref. [49])

Single-Dose Oral Liquids

Sachet, Stick Pack

Sachets and stick packs are monodose pack solutions for multiparticulates which can be filled with or without additives.

Ciprofloxacin taste masked micropellets as used for the preparation of a dry suspension can also be presented as a dry blend filled into powder bags (sachets, stick packs) together with suitable excipients. The total weight of one sachet is normally 1–5 g.

Since the taste masked Ciprofloxacin micropellets must suspended in liquid (e.g. water), a physical stabilization of the resulting suspension should be provided. For this reason, density-increasing substances such as sucrose and immediately swelling viscosity-increasing excipients such as acacia gum or other water-soluble polymers are included. Flavors and colorants may be added in order to optimize the taste and appearance of the suspension. Antimicrobial compounds are not required as the liquid prepared from the sachet or stick pack should be administered immediately after preparation [23].

Dose Sipping Straw (Drinking Straw)

A defined dose of multiparticulates can also be filled into drinking straws. One or more APIs in a taste masked multiparticulate form can be filled. The geriatric can enjoy their favorite drinks with the straw while taking the exact amount of medicine prescribed and not experiencing an unpleasant taste or issues with large dosage form swallowing. Especially, drugs which are dosed individually can be produced without difficulty by filling different amounts of bulk multiparticulates in different doses [39, 40]. While the patient is drinking, a control filter element moves upwards driven by the sipping activity, which ensures that the complete amount of active multiparticulates is administered [9]. The application method guarantees a complete and comfortable administration [40]. Excipients in addition to the multiparticules are most likely not required as the movement of the filter element provided by the patients' sipping effect ensures that they are transported towards the patient's mouth. The dose sipping technology is suitable for FDC and doses of up to 1 g. which is beneficial for the use for geriatric patients. Clarithromycine and Ciprofloxacin taste masked micropellets as actually presented in a dry suspension could easily be administered with a drinking straw.

Interestingly, the dose sipping technology has been found to be self-explanatory thus making it suitable for a variety of applications—patients intuitively handle the drinking straw correctly. Caregivers can easily control whether the whole dose was sipped off by the patient (Fig. 25).

Oral Syringe

Household teaspoons with a capacity of ∼1.5–9 ml are commonly used to administer small volumes of liquid medications to patients with a potential for dosing errors. With an oral syringe (Fig. 25) accurate dosing, e.g., 5 ml ± 0.5 ml is guaranteed [9]. Adjustable dosing syringes especially designed for the application of oral liquids including microsized multiparticulates for pediatric and geriatric

Fig. 25 Drinking straw (Fa. DS Technology GmbH); Dosing syringe for oral liquid (Fa. Raumedic AG)

patients are available [41]. Using the adjustable dosing syringe for oral liquids, convenient, flexible, and precise drug delivery is ensured. When the oral syringe is being emptied at the inside of the cheek a pharyngeal reflex (gag reflex) or tussive irritation followed by immediate spitting of the dose can be avoided [42].

Medical Spoon

A single dose of drug product, e.g., multiparticulates such as taste masked or/and functional micropellets or granules, could be fixed on a medical spoon by means of a microperforated membrane. After having kept the medical spoon in a liquid such as water the drug product is wetted and starts swelling forming an easily swallowable pulp. After removal of the membrane, the patient can take the medication [4].

Nasogastric/Gastric Tubes/Gastrostomy Tubes

Elderly not being able to swallow or refusing food have to be fed via nasogastric or gastric tubes, which can be used for liquid medication as well [43]. Application of medication via tubes is a particular challenge. Many oral products, such as enteric coated tablets or controlled release tablets should not be crushed as their functionality could be impaired [44]. Overdosing phenomena are reported when caregivers crashed controlled release morphine granules and Nitroglycerine tablets with a mortar in order to make them applicable via tubes. The API quantity contained in controlled release granules and tablets which should act over a 24 h period of time was immediately released as such and thereby harming the patient [45].

The diameter of a nasogastric tubes usually used for feeding and medication have a diameter of 5–16 Charriere = ∼1.7–5 mm. Multiparticulates such as micropellets having a diameter in the range of 0.1–0.5 mm can be administered easily as a liquid with a syringe [46] (Fig. 26).

Personalized Geriatric Medicine

Increased knowledge into personalized medicine has demonstrated the need for individual combinations and dosing. Orally applicable multiparticulate systems, such as pellets, micropellets, or mini-tablets could be individually combined and dosed filling them into capsules, sachets, stick packs, or drinking straws [6].

Novel approaches such as various dispensers for multiparticulate drug formulations are proposed enabling a flexible and appropriate therapy. Most of the proposals made for personalized medicines still have to prove their applicability in practice [47].

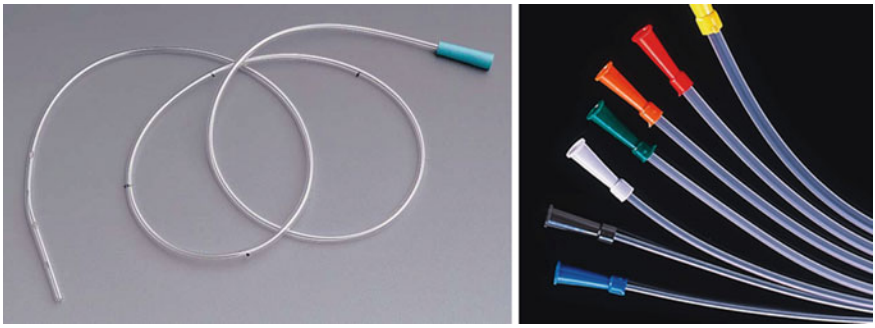


Fig. 26 Single lumen small bore Levin catheter for administration of medication or nutrition

Conclusions

Multiparticulate technology platforms, such as micropellets, pellets, and minitablets are to provide a broad palette of drug products for the geriatric population. Disadvantages, risks, and drawbacks of nonspecific drug products applied to elderly patients in the form of extemporaneous preparations with standard products or crushing of tablets can be avoided. In particular, micropellets having a particle size of ~50–500 μm provide high potential to formulate age-appropriate oral solid dosages forms as well as liquids with one single bulk formulation. Oral application and administration via gastric or enteral tubes is possible. Almost every drug release profile going along with taste masking is realizable with multiparticulates. Drug products for pediatrics and geriatrics can be developed in parallel providing considerable synergies. Established and innovative processing technologies are in place to set up commercially viable processes and products in any production scale.

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Considerations for Topical and Transdermal Drug Delivery in Older Adults

Sven Stegemann

Abstract The transdermal delivery of drugs to the systemic circulation is an established route of drug administration for a variety of small molecules. Transdermal drug delivery is characterized by constant plasma profiles through zero-order drug release for up to several days, the circumvention of the first-pass metabolism as well as its noninvasive alternative to oral dosing. Several drugs have been developed for chronic or acute conditions affecting older adults like for example pain, M. Alzheimer and M. Parkinson. Transdermal drug delivery offers some key advantages for the treatment of older adults, but also requires special attention when prescribed to older patients taking into account the individual risk–benefit profile. This chapter is intended to provide a short overview on transdermal drug delivery with the focus on older patients and reviews the major transdermal drug delivery products.

Keywords Transdermal systems · Older adults · Topical administration

Introduction

The topical administration of therapeutic entities already dates back to the ancient Egyptians and Sumerians using salves and ointments of plant, animal, and mineral extracts [29]. However, rationally developed transdermal drug delivery systems in form of therapeutic patches for systemic delivery of drugs just started in the mid 1970s after establishing a better mechanistic understanding of the skin and the pharmacokinetic behavior of drug transport through the skin [33]. This was enabled by biophysical techniques and in vitro methods for percutaneous drug permeation

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S. Stegemann (ed.), *Developing Drug Products in an Aging Society*,
AAPS Advances in the Pharmaceutical Sciences Series 24,
DOI 10.1007/978-3-319-43099-7_17

in the mid 1970s. The research was further stimulated by early successes in transdermal delivery like the scopolamine patch for travel sickness [15].

The skin is an organ with a surface area of 1.5–2.0 m^2 in an adult person that fulfills a variety of vital functions like protection from loss of organ fluids, body temperature control, protection from light, excretion of body waste products, immunological protection, and barrier functions as well as sensory functions. The skin is further characterized by a body area-dependent skin thickness, cell type composition (e.g., sebaceous cells, hair follicles, etc.), skin hydration, and skin temperature. As any other organ, the skin is affected by aging due to intrinsic and extrinsic factors. There is a general decrease in skin proliferation, loss in subcutaneous fat, bone, and cartilage as well as water content that can contribute to skin irritations and malignancy. It is estimated that the general decrease in the epidermal thickness is about 6.4 % every 10 years of life; however, the integrity and barrier function of the skin remains unchanged [7].

The transport of drugs through the skin is mainly dependent on the epidermis with the keratinized cells in the lipid bilayer structure acting as a major barrier for drug absorption through the intact skin. The transport of the drugs occurs either through the transcellular or the intercellular route, which are characterized by a lipophilic environment. The absorption through the intact skin is dependent on the skin thickness, the skin surface properties due to excretion of sebaceous gland and epidermal cell lipid, the skin hydration, and the skin temperature. The major drug characteristics determining a suitable drug candidate is the solubility and diffusivity of the drug in the stratum corneum, which also depends on the drug melting point, the drug–stratum corneum interaction as well as the molecular weight and molar volume. It is well established today that suitable drug candidates are characterized by a molecular weight of <500 Da, a log P between 1 and 5 and a melting point below 250 °C. Moreover, due to the drug transport rates, which are normally in the area of $\mu g/cm^2$, suitable drug candidates for transdermal drug delivery are generally high potent drugs that provide their therapeutic effects at very low dose or plasma level concentrations. The transport through the skin expressed as the steady-state flux through the skin can be estimated using the first Fick's law of diffusion:

$$J_{\max} = (D/h) \times K_{SC/\upsilon} \times C_{\upsilon,\mathrm{sat}} = k_{p,\upsilon} \times C_{\upsilon,\mathrm{sat}}$$

whereby D is the diffusion coefficient of the compound through the stratum corneum, h is the diffusion path length, $K_{SC/\upsilon}$ is the partition coefficient of the drug, and $D_{\upsilon,\mathrm{sat}}$ is the saturation solubility of the drug in the vehicle [45].

As the skin physiology depends on the site of the body, the bioavailability of the drug can dependent on the body area of administration. For example, drug absorption of estradiol from a patch applied to the buttock had a significantly higher plasma level than applied to the abdomen [40], while other studies done with a norelgestromin/ethinyl estradiol patch did not show a patch application-dependent drug absorption profile. However, there is evidence that application of the patches on areas of the trunk (e.g., chest) and the upper arm lead to similar drug absorption profiles over the time of administration [29]. Despite age-related changes in the skin

physiology [18], there is no evidence that in general drug absorption through the skin in older people differs from younger people even though conflicting data exist [19].

To increase the drug transport through the skin, different drug delivery technologies have been developed to overcome the barrier function of the skin through various mechanisms. The noninvasive approaches include the increase of moisture through skinocclusive systems, the use of absorption enhancers, and the application of iontophoresis to charged molecules. Minimal invasive delivery technologies include the local mechanical or physical destruction of the epidermis to create pathways for the molecules into the hypodermis. Such minimal invasive technologies use microneedles, electroporation, laserporation, or sonophoresis in conjunction with the transdermal patch [12].

Transdermal drug delivery represents an annual market of more than 1 billion USD derived from more than 50 launched transdermal patch products representing 17 different drugs and fixed dose combination products as listed in Table 1. However, except for rotigotine, all transdermal products have been developed as a line extension of their oral or injectable form [45].

Transdermal drug delivery provides several advantages that can be used to improve the therapeutic outcomes in older patients. Transdermal drug delivery can provide constant therapeutic plasma levels for up to several days avoiding high plasma peaks or plasma level fluctuations, which might trigger adverse drug reactions or suboptimal plasma profiles. The zero-order kinetics and constant drug input rates from transdermal drug delivery systems over the period of several days reduce the dosing frequency and increase the adherence, especially in cognitively impaired older patients. Transdermal drug administration can circumvent drug

Table 1 Drugs and fixed dose combinations launched in transdermal patch systems [45]

Scopolamine
Glycerol trinitrate
Clonidine
Estradiol
Fentanyl
Nicotine
Testosterone
Estradiol and Norethisterone acetate
Norelgestromin and ethinyl estradiol
Estradiol and levonorgestrel
Oxybutynin
Selegiline
Methylphenidate
Rotigotine
Rivastigmine
Granisetron
Buprenorphine

exposure to gastro-intestinal environment and absorption directly into the portal vein avoiding pre-systemic and first-pass metabolism. Transdermal drug delivery provides a noninvasive administration route for older patients with swallowing impairment like patients with dementia, stroke, or Parkinson.

The major limitations in the delivery of drugs through the transdermal route are the limitations in the deliverable dose to the systemic circulation, as well as the potential drug or excipient-induced skin irritation either as irritant or allergic contact dermatitis [29]. It should be considered that the independent administration of patches by older patients might be challenging due to potentially impaired mobility and dexterity as well visual limitations to administer or remove the patches. In order to avoid medication errors, the patch should contain a defined single drug dose and the dosing is not matter of calculation of the patch size by the patient [23, 25, 42]. Moreover, illicit or accidental swallowing of patches has been reported by the FDA with lethal and life threatening health outcomes. Especially when designing a transdermal delivery system for older adults, the packaging as well as the back foil should be clearly marked to support easy opening. Transparent patches should be avoided in order to remain visible and identifiable after application for the patient and care giver to simplify removal and renewal and prevent medication errors due to a remaining patch at the next dosing time.

Transdermal Drug Delivery Systems

The first transdermal drug delivery systems were derived from the drug being solubilized or suspended in a liquid or semi-solid vehicle and delivered through a rate-controlling membrane. These “reservoir”-type patches had a relative large size and beard the risk of uncontrolled drug release upon leakage of the patch. This issue could be overcome by the development of solid matrix patches, in which the drug release is controlled by drug diffusion through the matrix. The “matrix” patches were smaller and more flexible than the reservoir-type patches but still required an inert adhesive layer to be fixed on the skin. Later on, the drug was directly incorporated into the adhesive material which than provided both properties, sufficient matrix for zero-order release as well as adhesive properties to be positioned on the skin. These patches were even smaller, more flexible and achieved a high level of patient comfortability [29]. To increase the drug transport through the skin, the addition of absorption enhancers like ethanol, oleic acid, glyceryl monooleate and laury lactate, 2-nonyl-1,3-dioxolane, and others has been used in the formulation of transdermal delivery. The main mechanisms for the enhanced drug transport are increased drug diffusivity, increased drug solubility in the skin, or higher drug saturation in the formulation [27]. Another formulation approach to enhance the drug transport through the skin is the use of microemulsion systems, whereby the microemulsion components act as penetration enhancers. For example, phospholipids penetrate into the stratum corneum altering partition, diffusion, and solubility of the drug in the skin [21].

To overcome the limitations in broader applications of transdermal drug delivery to more hydrophilic and larger molecules, several other delivery technologies including device based systems have been suggested during the past decades. Iontophoresis, electroporation, laserporation, sonophoresis, microneedles, and jet injection have been explored as ways to disrupt the stratum corneum by skin poration by minimal invasive technology. Despite the great hopes in iontophoresis generated already more than 20 years ago as well as the other technologies, technical, commercial, and consumer issues have prevented successful marketing of such transdermal delivery technologies until today [44].

Advances in micro-manufacturing technologies enabling the manufacturing of patches consisting of microneedles that penetrates the epidermis to deliver the drug directly into the dermis have driven the most recent transdermal drug delivery technology. Recent clinical studies have shown the successful delivery of measles vaccine and activated swine-origin influenza A/H1N1 virus vaccine by microneedle transdermal drug delivery technology [5, 37]. While there is good hope that vaccination through microneedles can deliver on its promise, further studies will have to be performed to prove its efficacy and safety in the targeted patient populations.

The Aging Skin

With 1–2 m^2, the skin represents a large organ of the human body that is easily accessible as an area for drug delivery. The skin is composed of three major layers, the epidermis, the dermis, and the hypodermis with the subcutaneous tissue. The epidermis is divided into the stratum corneum, stratum lucidum, stratum granulosum, stratum spinosum, and stratum basale with a total thickness of 60–120 μm. The dermis is composed of a papillary and a reticular layer containing the sebaceous glands, the small vascular, and neuronal system of the skin. The hypodermis is the subcutaneous tissue containing the larger vascular system, the sweat glands, hair follicle, and the adipose tissue. The skin acts as the main barrier of harmful microorganisms and chemicals, prevents loss of essential body fluids, protects from injury and sun light/irradiation, regulates body temperature, excretes waste products, as well as is an important sensory organ.

The physiological aging of the skin is triggered by intrinsic and extrinsic factors causing a number of morphological and functional changes [20]. The epidermal and dermal thicknesses start to decline due to a loss in keratinocytes, in metabolic function, and the occurrence of cell biological senescence [26, 28]. The changes in the melanocytes and dendritic cells affect the immunological response of the skin [26]. A loss in the matrix structure, the fibroblasts, the dermal vascularization, as well as the neuronal receptors occurs in the aging skin leading to impaired mechano-elastic properties [6, 13, 32]. The reduced blood flow in the skin is accompanied by a reduced activity of the sebaceous and sweat glands. Moreover, the changing water/fat ratio observed with age also affects the skin with a reduced subcutaneous fat content in the face, hand, and foot regions and an increased fat

tissue in the leg and hip regions [10, 17]. This also leads to a reduced content of physiological moisturizing agents in the skin and hence the moisture content of the skin as well as the transport of moisture from the body to the outside [14]. While many older people are suffering from a low-grade inflammation [24, 35], the aging skin is getting more susceptible to the entry of irritants and allergens leading to increased skin reactions. Such skin reactions might be triggered by general age-related health conditions like multimorbidity, polypharmacy, kidney diseases hyperthyroidism, diabetes mellitus, or peripheral neuropathy [8].

It should be noticed that these age-related changes of the skin physiology might have an impact on transdermal drug delivery and should be considered during the development phase [19]. While an aging skin in general does not have an altered transdermal drug transport, nevertheless it is recommended to avoid the use of transdermal drug delivery systems with potentially irritating compounds (e.g., dithranol, salicylic acid) or long-term occlusive transdermal drug delivery systems. Moreover, special attention should be given to patients suffering from dermatosis as the pharmacokinetics of the transdermal transport can be substantially altered [47].

Transdermal Drug Delivery Systems for Older Adults

Hormone Patches (Estradiol)

There are multiple hormonal compounds for which transdermal delivery has been applied successfully. These hormones are used for different indications. For young woman, estradiol is used in contraception patches, while for older woman it is being used in hormone replacement therapy (also referred to as "heat patches"). Estradiol was among the first candidates of transdermal delivery due to the low required therapeutic dose and physicochemical properties providing sufficient flux through the intact skin. The first formulation (Estraderm®) contained ethanol as a permeation enhancer without having evidence that ethanol was really required to achieve the therapeutic plasma levels. The observation that the blood levels decreased on the second and third day after application of this patch led the conclusion that from the second day onward changes in the formulation composition and thermodynamics became more important for the transdermal penetration. It became finally evident that Estraderm® was indeed difficult to copy even by modern matrix formulations. The major reason for the decreasing plasma level was the crystallization into the much less-soluble estradiol hemihydrate. In order to prevent the transformation estradiol transdermal formulation had to be replaced by formulation that do not contain an ethanolic, water fluid phases, and that are kept dry during storage.

It is thus no surprise that bioequivalence is the biggest issue of generic formulation of estradiol. Rohr et al. [34] compared the performance of three already marketed matrix patches that were considered interchangeable. Except for the T_{max},

the results showed significant differences in the performance with regard to AUC, C_{max} as well as fluctuations. The authors concluded that despite the fact that the products claimed to have the same rate and extend of absorption, the in vivo performance of the different patches in postmenopausal woman did not provide evidence for bioequivalence.

Pain Patches

Transdermal drug delivery has successfully being used to deliver constant plasma levels for the treatment of chronic pain, which is a major symptom affecting older people. The two main compounds used in transdermal delivery are buprenorphine and fentanyl. Fentanyl is a potent lipophilic μ-opioid receptor agonist with a molecular size of 336 g/mol. In contrast to this, buprenorphine is a semi-synthetic, lipophilic compound with agonistic and antagonistic effects at different opioid receptors with a molecular weight of 467 g/mol. Due to the agonistic and antagonistic pharmacology, buprenorphine shows a ceiling dose to its analgesic effect.

Fentanyl Patch

Fentanyl patches are available to release between 12 and 100 μg/h over a period of 3 days. The 100 μg/h patch provides a constant 1.5–2.0 μg/ml steady-state serum concentration of fentanyl. After removal of the patch the serum concentration declines slowly due to the remaining fentanyl concentration in the skin and reaches about 50 % of the original plasma concentration 17 h after removal. The main side effects observed are drug-related hyperventilation and respiratory depression. Therefore, transdermal delivery of fentanyl is only indicated in patients with a previous use history of fentanyl [4].

When designing fentanyl patches for the use by older adults special attention should be given to the clear identification and user instructions for the patients in order to prevent medication errors. For example, a 58-year-old man from Essen (Germany) used a fentanyl patch from his aunt who passed away as he believed it was an over-the-counter heat patch to treat pain. He developed a serious opioid poisoning syndrome with no palpable pulse before he was taken into the hospital by his wife [43].

Another potential issue with fentanyl transdermal delivery is the development of dependency. In a case report, a 54-year-old male person used the fentanyl patches prescribed to his wife suffering from painful lung cancer. He started to wear patches but later started to chew those in order to receive the desired opioid effects. The patient was hospitalized and received appropriate treatment for the withdrawal symptoms and underlying depressive disorder [9]. Additional studies confirmed the high incidence of fentanyl transdermal product misuse or abuse, which should have to be taken in consideration during the development [22, 41, 48].

Buprenorphine

Buprenorphine transdermal systems for once a week administration have been brought to the market for the management of moderate to severe chronic pain in patients requiring a continuous, around-the-clock opioid analgesic for an extended period. The patch is available in 5, 10, and 20 μg/h strengths.

A bioequivalence study comparing a population of 50–60 years old with 75 years and older patients provided evidence that the AUC of buprenorphine and norbuprenorphine was slightly affected by age. The ratio of the geometric mean levels at steady state between the older and the younger population was 81 % and the 90 % confidence interval for the ratio was 64.7–102.9. The results also demonstrated that a higher interpatient variability was observed in the older patients, which contributed to the failure to establish bioequivalence between the groups [1].

In contrast to fentanyl, buprenorphine has much less misuse potential. The major side effect of buprenorphine is the skin reaction profile which is more pronounced compared to fentanyl. In one case study, a 70-year-old patient who developed skin reaction after buprenorphine patch administration used corticosteroids to treat the skin reaction at the site of application [3]. Compared to the oral forms of buprenorphine, the typical systemic adverse drug reactions (nausea, dizziness, sleeping, and vomiting) are milder for the transdermal patch; however, local adverse drug reactions in the form of erythema and pruritus occur in one-third of the patients [30]. Schmid-Grendelmeier et al. compared buprenorphine and fentanyl transdermal patches in 46 healthy volunteers with respect to the potential to cause skin reactions. In this study only one case of skin reactions was reported for fentanyl and six cases in the buprenorphine group, confirming a higher potential for skin reaction for buprenorphine [38].

Nicotine Patches as Smoking Cessation Aid

Nicotine patches are OTC products to support smokers to quit. They are offered with 16–24 h release of nicotine and were brought to the market between 1991 and 1992 [31]. The major adverse reactions are itching and local erythema affecting about half of the patients. Nicotine patches are rarely misused but have a risk for dose escalation. This is happening due to the recreational purpose of nicotine at an extremely high tolerance level. However, the misuse potential is higher with nicotine chewing gum formulation. This might be due to the higher nicotine blood plasma variability in the gum formulation compared to the relatively stable blood concentration of the transdermal delivery of nicotine. Replacement studies have shown the dependency of the pharmacokinetics of delivery in a large-scale trial with 1518 smokers. The range of final misusers rank from 13 % in the case of the fast bioavailable nasal spray compared to less than 2 % of users in the case of the slow absorbed patch formulations [16, 36].

Nitroglycerin Patches

Nitroglycerin is a fast acting vasodilator used in the acute and preventive treatment of angina pectoris. The transdermal patches are solely used to prevent episodes of angina in patients with coronary artery disease, a common disease in older people. The tolerability of modern patches has been investigated in a recent study. The study included three different doses and different user groups for the treatment of chronic stable angina. The 954 patients enrolled in the study were follow-up for a period of 12 weeks. Patients were distributed as follows: 132 to the 5 mg/24 h patch, 727 to the 10 mg/24 h patch, and 95 to the 15 mg/24 h patch. Furthermore, the efficiency of therapy was evaluated by means of the variations observed in the severity of angina crises. Within the study result, ninety-four patients (9.8 %) showed signs of cutaneous irritation. Thirty-two patients (3.3 %) showed erythema, and one patient (0.1 %) showed erythema and induration. Thirty-nine patients (4.1 %) had skin reactions not attributable to erythema or induration. The number of patients with angina crises and the number of weekly angina crises decreased significantly [2].

Rivastigmine (Exelon^{TM})

Rivastigmine is a cholinesterase inhibitor used for the treatment of Alzheimer's disease. Maintaining high plasma levels is an important criterion for drug efficacy. A transdermal patch was developed that released 9.5 mg/24 h providing similar plasma levels than the highest dose of the oral form. A clinical study provided evidence that the efficacy was comparable to the highest oral dose but had three times fewer adverse drug reactions like nausea and vomiting and a good skin tolerability profile [46].

For older patients suffering from Alzheimer's disease, transdermal drug delivery might be of special value due to the expression of this disease making it sometime impossible to administer oral drugs of such patients.

Rotigotine

Rotigotine is a non-ergot dopamine agonist that is used for the treatment of Parkinson's disease. Rotigotine was the only drug that has been developed first line as a transdermal formulation. In 561 early Parkinson's disease patients, efficacy of rotigotine was evaluated as a transdermal delivery of 8–12 mg/day. Rotigotine was titrated over a period of up to 13 weeks followed by a maintenance therapy of 33 weeks. The responder rate of rotigotine was significantly higher compared to placebo (52 vs. 30 %). Tolerability of the rotigotine transdermal patch was

acceptable with adverse drug reactions being mild or moderate skin reactions at the administration site, nausea, and somnolence [11]. For advanced Parkinson's disease, the combination with levodopa reduced the critical 'off' time in the patients and significantly improved the motor functions and ADL compared to levodopa alone [39].

Conclusion

Transdermal drug delivery has several advantages over other drug delivery forms, especially to achieve constant and long-lasting plasma profiles. For older patients, this can result in reduced complexity of the therapy, for example, for chronic pain treatment as well as in more appropriate treatment options for dementia patients. Local skin reactions, limited deliverable doses, as well as restrictions in terms of the physicochemical properties of suitable drugs remain the major limitations for transdermal delivery. For older patients a special emphasize has to be put on the usability of the transdermal patches in order to prevent medication errors.

Acknowledgments I would like to thank Michael Horstmann, Transdermalpharma UG, Neuwied (Germany) for his contributions and support to this chapter.

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Parenteral Drug Delivery for Older Patients

Sagarika Bose

Abstract Parenteral drug delivery is widely used for older adults to achieve and maintain therapeutic concentration of drugs that have a narrow therapeutic index or have poor oral bioavailability. Parenteral products are usually available in solution, suspension or emulsion form; liposome, microsphere and implants are available as well. Intravenous, subcutaneous, intramuscular, intradermal, and epidural deliveries are mostly used for parenteral administration of drugs to older patients. Other routes of parenteral drug delivery include: intraarterial, intraventricular, intrathecal, intracisternal, intraarticular, intraocular, intracardiac, and intraperitoneal. Continuous intravenous infusion is administered to maintain a constant and sustained drug level within a therapeutic concentration range for effective treatment in aging adults, especially for drugs with very short biologic half-lives. The intramuscular route is beneficial for larger injection volumes and also for oil-based formulations, where the subcutaneous route is used for chronic diseases and vaccines, among many others. The intradermal route is useful for allergy testing, antigens and vaccines. Epidural administration of analgesics are very beneficial for older adults during surgeries. The progress in targeted or controlled release drug delivery—such as, the application of microspheres, liposomes, gels, suspensions, in situ forming implants, lipophilic solutions, solid lipid nanoparticles (SLN), and drug eluting stents—have reduced the dosing frequency in seniors, which may provide improved patient compliance. Parenteral delivery is also beneficial for delivering total parenteral nutrition to older adults.

Keywords Parenteral · Route of administration · Self-administration · Infusion · Nutrition · Vaccines

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S. Stegemann (ed.), *Developing Drug Products in an Aging Society*,
AAPS Advances in the Pharmaceutical Sciences Series 24,
DOI 10.1007/978-3-319-43099-7_18

Introduction

The world is moving towards a population with a growing percentage of people above 65 years of age [1]. Many developed and developing countries are facing an ever-growing need to supply constant care and support for their older populations. The term "geriatric" is used for people over 65 years of age or older. They are also referred as older or aging adults or seniors. In developed countries, the total population of seniors is estimated to grow from 14.9 % in 2010 to 21.1 % in 2030 and 24.5 % in 2050 [1]. In developing countries, the population of seniors is projected to grow from 5.8 % in 2010 to 9.7 % in 2030 and 14.4 % in 2050 [1]. Over the past 30 years, the number of Europeans over 60 years of age has risen by about 50 %, and now represents more than 25 % of the population. Within the next 20 years, experts estimate that this percentage will rise to one-third of the European population, or more than 200 million people. Between 2000 and 2020, the populations at age 65 and older and age 80 and older in Japan are projected to increase 54 % (17.1–26.2 %) and 107 % (3.7–7.5 %), respectively [2]. Many people over 65 years of age require multiple medications and people over 85 years often require continuous monitoring and daily care. The change in demographic composition is predicted to increase the cost of long-term services in the United States from $195 billion in 2010 to $540 billion in 2040 [3].

Pharmaceutical dosage forms are evaluated for efficacy to treat a disease as well as their use in improvement of quality of life, cost, safety, ease of use, and patient compliance. It is important for the health care system to increase patient compliance through drug delivery systems that reduce the pill burden and complexity of therapeutic intervention. Parenteral drug administration is a useful route of administration when oral administration is contraindicated. Parenteral pharmaceutical products are defined as those preparations intended for injection through the skin or other external boundary tissue, rather than through the gastrointestinal tract, so that the drug formulations are administered directly into a blood vessel, organ, tissue, or lesion.

Parenteral drug delivery with intravenous, subcutaneous or intramuscular injection can gain easy access to the systemic circulation. Intravenous injections provide rapid drug availability, where intramuscular and subcutaneous injections provide slower delivery of drugs to the systemic circulations compared to intravenous. The parenteral administration route is often used for the delivery of drugs with low or highly variable oral bioavailability and narrow therapeutic index. With the development of new biotechnology-derived products as well as new and enhanced infusion-related technologies, parenteral products have become an essential part of the care of older patients in hospitals and home health care settings.

Physiological Changes in Seniors

Older adults may encounter challenges with medications as the aging process introduces some major physiologic changes in their bodies, including homeostatic, immune system, cardiovascular, skin, and connective tissue changes. Several

common physiologic changes affecting aging adults are listed in Table 1. Older patients commonly show changes in their gait that result in imbalance, muscular weakness, and falls. In 10–15 % of older adult patients, balance and gait disorders are very common and treatment and care costs for fall-related fractures reach nearly $10 billion each year [4]. Normal hand function may be impaired due to arthritis, neurological problems, vascular disease, or trauma. The ability to grasp and pinch, which is needed for dressing, grooming, toileting and feeding, may be diminished. Hearing loss limits patients from understanding conversations, and occasionally leads to social isolation. Another major change is the change in vision, which reduces quality of life, life satisfaction and involvement in home and community activities. Dementia is the most common cause of mental decline among older adults. Dementia is defined as a significant decline in two or more areas of cognitive functioning. It is cited that 13.9 % of people age 71 and older in the United States have Alzheimer's disease or other types of dementia [5]. In this situation, it is

Table 1 Physiological changes in older adults

Physiologic changes	Effects
Total body water	Seniors have reduced total body water; reduced volume of distribution of water soluble drugs and increased volume of distribution of lipid soluble of drugs; require reduction in dose and/or dose interval
Cardiovascular and respiratory changes	These two changes combined, contribute to a slower response to blood loss, fluid depletion, shock, and acid-base imbalances
GI changes	This change results in altered digestion and absorption due to decreased GI tract motility, esophageal sphincter tone and abdominal muscle strength
Renal changes	Older adults have decreased glomerular filtration rate, which may result in kidney damage or kidney failure
Memory	Seniors have difficulty remembering their medication schedules which may result in missing doses and in lower therapeutic concentration of required medications in blood
Skin	Older people have decreased skin elasticity due to gradual loss of subcutaneous fat and elastin thus, resulting in reduced thickness and amount of connective tissue in dermal layer
Eyes and vision	Older people may have difficulty reading labels on prescription and over-the-counter products
Ears and hearing	Older adults may have difficulty hearing instructions from health care professionals, which may result in not understanding the information
Dexterity	Seniors with arthritis and certain types of disabilities may have difficulty: opening bottles, breaking tablets, handling medications such as eye drops, inhalers for asthma and other lung disease, and insulin injections.
Ability to Swallow	Dysphagic older patients may have difficulty swallowing tablets or capsules. Many prescription and over-the-counter products are available in a variety of dosage forms such as a liquid, skin patch, or suppository, greatly reducing the difficulties associated with swallowing. These alternative dosage forms are preferred

Table 2 Medication factors for older adults

Other issues	Effects
Scheduling numerous medications	A significant challenge for older persons and caregivers is incorporating medication schedules into daily routines; often, multiple daily medications make medication scheduling particularly difficult
Compliance/adherence	Rate of compliance/adherence is estimated to be about 50 % in older adults and often depends on the number of drugs, frequency of dosing, and complexity of the treatment
Multimorbidity and Polypharmacy	85 % of older adults have one or more chronic diseases; 30 % of them may have three or more chronic diseases. So, use of multiple medications at the same time (also referred to as "polypharmacy") is very common. Many chronic conditions or diseases, like diabetes, heart disease, Parkinson's disease, arthritis, incontinence, high blood pressure, pulmonary disease, osteoporosis, Alzheimer's disease often require the use of multiple medications. The appropriateness, effectiveness, and safety of all prescription and over-the-counter medications are required

difficult for older patients to administer multiple medications by themselves. Table 2 describes medication factors that may affect the daily lives of older adults. All of these factors should be considered when designing a dosage form for geriatric use.

Advantages and Disadvantages of Parenteral Drug Delivery for Older Patients

Parenteral therapy provides a continuous systemic concentration of the drug to older patients. Novel drug delivery technologies such as biodegradable implants, or novel drug carriers such as liposomes, nanoparticles, or controlled release intramuscular depot injections, play a major role in drug delivery for older adults. Novel preparations provide sustained, targeted and controlled drug delivery to older patients with less dosing frequency which helps to reduce the pill burden when seniors are taking multiple medications. This route of administration has many advantages for patients who cannot take drug products by other routes and/or drugs that require rapid onset of action, e.g., such as unconscious patients [6]. Parenteral therapy provides the means of correcting serious disturbances of fluid and electronic balances. Hospitalized and bedridden patients may require parenteral nutrition like fluids, electrolytes, or nutrients through a parenteral route [7]. It is also beneficial for healthcare providers as they can more readily monitor patients, especially in situations with a high risk of non-adherence, such as schizophrenia or depression. Also, parenteral administration can be designed to achieve local effects, for example, in dentistry and anesthesiology.

Despite the many benefits, parenteral formulations are typically more expensive than conventional formulations. Parenteral formulations require specialized equipment, devices and techniques to prepare and administer parenteral formulations [8].

Table 3 Advantages and Disadvantages of Parenteral Administration

Advantages	Useful for older patients who cannot take drugs orally due to dysphagia or who may not remember to take drugs on time due to dementia
	Useful for emergency situations where rapid onset of action can be achieved, if necessary, which can be a prime consideration in clinical situations, such as cardiac arrest, asthma, and shock
	Required for drugs that are not effective orally or that are destroyed by digestive secretions (e.g., insulin, other hormones, and antibiotics) or susceptible to first-pass metabolism by the liver (targeted drug delivery)
	Important for uncooperative, nauseous, or unconscious patients where parenteral delivery can help achieve accurate drug delivery
	Useful for patients who have problems with dexterity or difficulty opening child-resistant caps
	Can be used for self-delivery of drugs (e.g., subcutaneous insulin) as well as in hospitals, ambulatory infusion centers, and in home health care
	Sustained release implants and intramuscular depot formulations help reduce the frequency of drug administration as well as doctor's office/hospital visits
	Useful for correcting serious disturbances of fluid and electronic balances and delivering fluids, electrolytes, or nutrients (i.e., total parenteral nutrition)
Disadvantages	More expensive and costly to produce
	Potential for infection at site of injection, sepsis, thrombophlebitis, fluid overload, air embolism, extravasation if not done correctly
	Psychological distress in the patient
	Usually requires healthcare providers to administer the injection (except self-administration)
	Requires sterility as well as specialized equipment, devices, and techniques during preparation and administration
	Potential for pain upon injection
	Potential for tissue damage upon injection
	Risk of needle-stick injuries and exposure to blood-borne pathogens from health care worker

The injectable formulations often must be administered by trained personnel and require more time than those administered by other routes. Also, pain on injection is a common fear among patients. If the pH, osmotic pressure or solubility of the medication is not compatible with the body tissues, tissue damage may occur. Despite these problems, parenteral formulations hold a top place for the treatment of hospitalized patients. Some of the major advantages and disadvantages of parenteral delivery are listed in Table 3.

Type of Parenteral Products for Geriatric Uses

Conventional parenteral formulations for older patients mainly include solutions, suspensions and emulsions [9].

Solutions

Solutions are the simplest and most convenient form of injectable products. Generally, solutions are aqueous and isotonic which have a pH close to that of blood and body tissues (pH 7.4). The parenteral solution products can be divided into 2 groups depending on the volume of the product.

(1) Small Volume Injection (SVI)

A small volume injection (SVI) is an injection that is packaged in containers labeled as containing 100 mL or less [10]. Therefore, all injectable products packaged in vials, ampules, prefilled syringes, cartridges, bottles, or any other container that is 100 mL or less, fall under the classification of SVI [10].

SVI's may be injected by intravenous, subcutaneous, intramuscular or intradermal routes or by various other routes such as intraabdominal, intraarterial, intraarticular, intracardiac, intracisternal, intraocular, intrathecal, and intraventricular injections. SVI formulations are relatively simple, which are composed of the active ingredient, a solvent system (preferably aqueous), a minimal number of excipients, and the appropriate container and closure packaging system. If the active ingredient is unstable in solution or suspension, the product can be a dry powder for reconstitution, processed either by lyophilization or by sterile crystallization.

(2) Large-Volume Injection (LVI)

Many IV parenteral products are often administered to older patients via large-volume injection (LVI) solutions. In such cases, the solubilized portion of the product can be withdrawn directly from the ready-to use solution or from the dry product, and then directly added to the diluent bag or through the Y-site of the IV administration set. LVI are aqueous solutions, usually supplied in volumes of at least 100 mL, with sizes of 250, 500, 1000, 3000, and 5000 mL, being the most common. LVIs usually involve intravenous infusion, dialysis, or irrigation fluids containing electrolytes, sugar, amino acids, blood, blood products, and fatty lipid emulsions. They are usually terminally sterilized, whereas SVIs can either be terminally sterilized or by aseptic filtration.

Suspensions

Parenteral suspensions are useful dosage forms for administering insoluble or poorly soluble drugs to patients. Parenteral suspensions provide more prolonged release as compared to administering solutions from the injection site. Suspensions

are delivered using the subcutaneous and intramuscular routes. In order to disperse the drug uniformly, the suspensions need to be shaken well before use. The amount of solids in the suspension as well as the nature of the vehicle determines the viscosity of the product which is very important for syringeability [11].

Emulsions

An emulsion is a two-phase system prepared by combining two immiscible liquids, one of which is dispersed uniformly throughout the other and consists of globules that have diameters equal to or greater than those of large colloidal particles [12]. Parenteral emulsions are administered through the intravenous, subcutaneous and intramuscular routes. Emulsions are generally used in administration of total parenteral nutrition (TPN) for older adults who are unable to get their nutrition by eating, (e.g., coma, surgical recoveries, etc.). Commercially available intravenous fat emulsions include Liposyn®, Liposyn® II and Liposyn® III, Lipofundin® MCT/LCT 10 and 20 % (medium and a long chain triglyceride emulsion), Intralipid® 10 and 20 %. A further discussion of TPN is discussed later in this chapter.

Needle Sizes and Their Application to Older Patients

Hypodermic products are used to introduce medications or fluids into or under the skin. Hypodermic needles are available in stainless steel with a wide variety of outer diameters described by gauge numbers. Gauge numbers are inversely proportional to the outer diameter of the needle (i.e., the smaller the gauge number, the larger the outer diameter). The inner diameter of the needle depends on both gauge and wall thickness, and may be described as regular wall, thin wall, or ultra-thin wall. Thin-wall needles have identical outer diameters as regular wall needles, but larger inner diameters for a given gauge, and thus provide a higher flow rate. Hubs (where the needles are attached to the syringe) as well as labels are color coded by ISO standards for gauge identification [13]. There are several factors which need to be considered in choosing the size of a needle to use for an injection. The larger diameter needles are used for viscous medications or to mix IV medication. The clinicians determine which needle can be used for a particular patient depending on the type and viscosity of the medication, the age of the patient, the mobility status of the patient and the desired absorption rate for the medication (for example, subcutaneous vs. intramuscular). Table 4 describes the gauge sizes, outer diameters, colors of the hub as well as some typical uses of the gauge size. Figure 1 shows the colors and gauges for standard needles.

Very small diameter needles with gauge 31 and higher, which do not yet have an ISO standard, are used for diabetes care (subcutaneous route). For example,

Table 4 Colors, gauges and typical uses of needles

Outer diameter (mm)	Gauge size	Color [12]	Typical uses
0.3	30	Yellow	SC, ID
0.33	29	Red	SC, ID
0.36	28	Blue-green	SC, ID
0.4	27	Medium grey	SC, ID, IM
0.45	26	Brown	IV, SC, ID, IM, IV infusions
0.5	25	Orange	IV, SC, IM, IV infusions
0.55	24	Medium purple	IV, SC, IV infusions
0.6	23	Deep blue	IV, IA, IM
0.7	22	Black	Blood collection, IM, IV, IA, IV infusions
0.8	21	Deep green	Blood collection, IM, IV
0.9	20	Yellow	Blood collection, IM, IV, IV infusions, blood and blood components, and other viscous infusions
1.1	19	Cream	Blood collection
1.2	18	Pink	Blood collection, administration of blood and blood components and other viscous infusions
1.4	17	Red-violet	Rapid fluid infusion in large amounts
1.6	16	White	Trauma, rapid fluid infusion in large amounts

IV intravenous, *SC* subcutaneous, *ID* intradermal, *IM* intramuscular, *IA* intra-arterial

Fig. 1 Colors and gauges for standard needles (K-pack II needles, ©Terumo®)

Terumo®'s tapered pen needle, the Nanopass, is a 34 G (Terumo®) pen needle (not available in the United States and Canada) and used for insulin delivery. These thinner needles (30–34 G) are also used for intradermal applications.

Maintenance of Sterility During Administration

Parenteral products are introduced directly into the blood and are required to be properly sterilized and pyrogen free. Thus, a strict aseptic technique is practiced during the administration procedure. The skin over the site of administration should be disinfected (usually with 70 % isopropyl alcohol) prior to injection to maintain a healthy hygiene in all parenteral administration. In older adults, the skin may have wrinkles or cracks, thus more precautions should be used as microorganisms from the skin flora may access the blood by the needle at the time of injection, resulting in complications.

Major Routes of Parenteral Administration

The major routes of parenteral administration are intravenous (IV), subcutaneous (SC), and intramuscular (IM). These three routes are mostly used for administering drugs through parenteral routes in seniors, (1) for therapy (definitive or palliative), (2) for diagnosis, (3) for prevention, and (4) for temporarily altering tissue function (s) to facilitate other forms of therapy. They have good absorption characteristics and provide good bioavailability of drugs. Other routes of parenteral administration include intradermal, intraarterial, intrathecal, intraocular, intracardiac, intraperitoneal, and epidural. The angle of administration and depth of the injection for intra-dermal (ID), subcutaneous (SC), and intra-muscular (IM) administration are shown in Fig. 2.

A brief description of the most commonly used routes of parenteral administration is discussed in the following sections.

Intravenous Route

Intravenous (IV) injections or infusions involve administration of a drug directly into a vein. Generally, an 18–26 G needle is used for IV administration. The length of the needle depends on the application. It is one of the most common parenteral routes employed in hospitals for seniors. IV administration provides immediate pharmacological effect, especially in emergencies (e.g., treatment of arrhythmias or seizures), to treat serious, life-threatening infections or conditions, or to restore electrolyte and fluid balance, as well as to deliver continuous nutrition. Some drugs

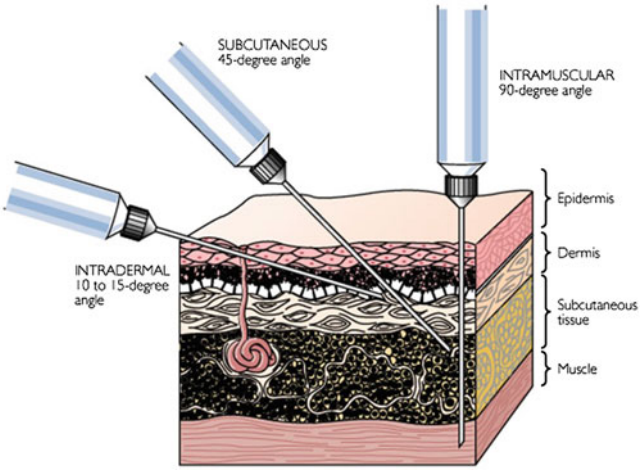

Fig. 2 Intra-Dermal (ID), Subcutaneous (SC), and Intra-Muscular (IM) administration (courtesy of Terumo Medical Corporation)

like analgesics, general anesthetics, antivirals, antibiotics, immunosuppressives, antifungals, antibacterials, antihypertensives, vasodilators, antiarrhythmics, and chemotherapeutic agents are commonly administered by the IV route for all adults. Moreover, the IV route may be useful for a variety of other purposes for older adults, such as blood transfusion, plasmapheresis, and hemodynamic monitoring. Moreover, whole blood or specific blood components may be administered into the circulatory system of older adults using the intravenous route. Commonly infused blood components are packed red blood cells (RBCs; for anemia), white blood cells (WBCs; to prevent infection), platelets (to help clotting), plasma, albumin (as a volume expander), and cryoprecipitate (a clotting factor) [14]. Medications can be given to older adults by IV push (bolus), intermittent infusion (IV drip), or continuous infusion. IV injections are administered directly into the venous circulation, and hence highly vascular and perfused organs, such as the heart, lungs, liver, and kidney, rapidly acquire the drug. Older adults risk toxic and adverse effects on vital organs if there is a sudden increase in serum drug concentration. This can be prevented by giving a slow IV bolus injection or controlling an IV drip. Proper selection of the diluent and slow IV administration can facilitate adequate mixing of poorly water soluble drugs into the circulation reducing the chance of precipitation from solution and possible embolism (e.g., phenytoin IV injection).

IV push medications can be given into a continuously infusing IV set or into a capped IV port. Large volumes of bolus dose can be rapidly infused by intravenous route from an infusion bag (IV drip or infusion). Figure 3 shows the picture of a standard IV winged infusion set with sharps injury protection which can be used for IV infusion. A continuous IV infusion may be used for strong analgesics because it produces less fluctuation in serum concentrations of the drug compared to intermittent IM injections. Patient-controlled analgesia (PCA) is another application of

Fig. 3 Standard IV winged infusion set with sharps injury protection (Winged Infusion Sets with needle protection (Surshield™), ©Terumo®)

IV route where IV bolus doses are delivered in addition to a slow, continuous IV for narcotic analgesics such as fentanyl, methadone, and morphine. PCA usually has programmable infusion pumps with limited patient controls where the patient is allowed to receive an additional dose within limited time periods. The IV route is often useful for delivering lipid-soluble drugs that often need to be administered by specialized routes of delivery that bypass the blood brain barrier (BBB) (especially central nervous system drugs (e.g., sedatives, depressants).

Complications that may occur from using the IV route include (1) thrombosis with or without complicating infection at the site of injection or infusion; (2) injection of microorganisms, toxins, particulate matter, or air; (3) the occurrence of physical or chemical incompatibilities between agents prior to or at the time of injection; (4) uncontrolled or excessive administration of drugs or fluids; and (5) extravasation of injections or infusions at the site of administration.

Intramuscular Route

An intramuscular (IM) injection is administered directly into the relaxed muscle. Intramuscular tissue is richly supplied with blood vessels. Thus, absorption of medications administered via the IM route is slower than IV administration, but faster than the SC route [14]. In certain life-threatening conditions, the IM route is

preferred over the subcutaneous (SC) route for rapid rate of absorption. For example, it is reported that the administration of epinephrine via the IM route causes a higher peak plasma concentration in comparison with the SC route [15]. There are few pain receptors in muscular tissue, thus viscous and irritating drugs can be injected with less discomfort and possible tissue damage. Various muscle sites including the gluteal, deltoid, triceps, pectoral, and vastus lateralis muscles are used for IM administration. In seniors as well as younger adults, the site of choice often is the gluteal muscle, because large volumes of drug may be injected and tolerated. The vastus lateralis of the thigh may also be used for large volumes of medication because it is located away from major blood vessels and nerves. For rapid absorption and small volumes (<2 mL), the deltoid muscle is preferred [9].

The IM route can be used for prolonged release of drugs formulated as aqueous or oily solutions or suspensions. Drugs commonly injected by IM administration include lidocaine, cephalosporins, amino glycosides, diazepam, phenytoin, insoluble salts of penicillin G (procaine penicillin G), corticosteroids, narcotics, narcotic antagonists, and contraceptive steroids. The IM route is not used in people with significant heart failure or shock, where uptake into the vascular compartment may be expectantly poor; or if immediately high serum or plasma concentrations of the drug are desired; or if rapid distribution to a distal organ is mandatory.

IM injections go into the muscle below the subcutaneous layer, so the needle must be longer to ensure that the medicine is injected into the proper tissue. A larger volume of medication per injection as well as a wider variety of medications can be administered into IM sites than SC sites [14]. In general, 19- to 25-gauge, 5/8–1½ inches long, stainless steel needles are used for IM injections [14]. For a thin person with very little fatty tissue, 25–27 gauge needle with 1 inch length can be used. In obese patients, 1.5–2 inches (sometimes 3 inches) needles may be necessary due to a thicker fat layer.

The main precaution with IM injections is to avoid entering a blood vessel (especially an artery), which might lead to infusion of the entire dose directly to an organ or tissue. Also, accidentally striking or injecting into a peripheral nerve may result in a case of peripheral nerve palsy for seniors with or without sensory damage. Occasionally, during a large bolus of drug injection into the muscle, local damage or muscle infarction may result, leading to a sterile abscess or elevation of serum levels of muscle enzymes. Sometimes, the Z-track technique is useful for some injections like the iron dextran injection (stain upper tissues), diazepam injection (irritate tissues) or hydroxyine injection (irritate SC tissues). In this process, first the skin is displaced laterally before the injection, then the needle is inserted and the injection is administered slowly and smoothly. Then the skin is released, which seals the medication at the site and blocks migration of medication to SC tissues.

Subcutaneous Route

A subcutaneous injection (abbreviated as SC, SQ, or sub-Q) is administered into the subcutis layer (below the dermis and epidermis) of skin [9]. Usually, the volume of injection is between 0.5–1 mL (sometimes 1.5 mL). This route of administration is very effective in administering vaccines to older individuals as well as medications like insulin, heparin, low molecular weight heparin, narcotics (e.g., morphine, diacetylmorphine), epinephrine, and vitamin B12. This route is also useful for drugs that cannot be administered orally to seniors due to lack of absorption or inactivation by the contents of the gastrointestinal tract, or if the patient is unable to swallow medications by mouth (e.g., unconscious patients) or if self-administration of parenterals (e.g., insulin) is desired. Although usually fluid medications are injected, occasionally solid materials such as steroid hormones may be injected in small, slowly absorbable pellets to prolong their effect (Vantas® implants).

Injection sites include the abdomen at the level of the umbilicus, upper back, upper arms, upper buttocks, or thigh. There are many pain receptors in these tissues so only non-irritating, water-soluble medications in small doses should be given by the SC route. When a medication is injected via the SC route, absorption is usually slow, sustained, and complete. Absorption varies with the site of injection. If medications are injected in the abdomen, they are absorbed more rapidly, injections into arms are absorbed intermediately, and injections into the thigh and upper buttocks are absorbed slowly [14]. Medications may be absorbed faster when administered to a malnourished senior with little subcutaneous tissue. Absorption of drugs via the SC route is less predictable compared to the IM route due to less vascularity. The SC route cannot be utilized for delivering medication to seniors where heart failure, shock, or vascular collapse exists. Also, highly acidic, alkaline, and irritating medications, which may cause inflammation, necrosis of tissues, or pain, are not administered by this route.

Generally, a beveled, 26–34-gauge, 3/8–5/8 inch long, stainless steel needle is utilized for SC delivery. As mentioned before, recent advancement in needle technology has provided a 34 G, 0.157 inch tapered pen needle (e.g., Nanopass, Terumo®, not available in USA or Canada) for insulin delivery (Fig. 4). Prior to injection, aspiration should be attempted to be certain that the needle has not inadvertently entered a blood vessel. For long-term therapies (e.g., insulin or human growth hormone), injection sites are changed/rotated to avoid potential tissue damage or dents (lipodystrophies).

Intradermal Route

Intradermal injection (ID) is administered into the dermis, which is located just beneath and adjacent to the epidermis. This route is useful for delivering a number of diagnostic agents, allergy testing, antigens (e.g., tuberculin skin testing) and

Fig. 4 Nanopass, Terumo®'s tapered 34G pen needle (not available in the United States and Canada, ©Terumo®)

vaccines (e.g., smallpox) to older patients. It consists of injecting small amounts (typically ≤ 0.1 mL) of material into the dermis. Absorption by the intradermal route is faster than the SC or IM route. These injections are given in an area where the skin and hair are sparse, usually on the inner part of the forearm. Generally a beveled, 26- to 33-gauge, as low as 0.5–1.5 mm in length, stainless steel needle is commonly used for ID injections. The needle is inserted at a 10°–15° angle. Sometimes, ID injections produce localized swelling of the skin, giving the appearance of an orange peel. Precautions should be taken when administering ID injections as drug formulations may leak out of the needle tip due to the act of injecting the drug right beneath the skin rather than inserting completely into the skin.

Intra-arterial Route

The intra-arterial route has little use for treating older patients. It is generally limited to organ-specific chemotherapy, such as treating certain localized cancers (e.g., malignant melanomas of the lower extremities), where regional perfusion with high concentrations of toxic drugs (IV route may be associated with serious systemic

reactions) can be achieved. The intra-arterial route is also used for diagnostic purposes, such as injecting radiopaque substances for roentgenographic studies of various organs or tissues (e.g., arteriograms for coronary, cerebral, pulmonary, renal, enteric, or peripheral arteries). This route of administration should be used with caution because products administered intra-arterially are not diluted or filtered by the lungs, liver, or kidneys before contact with peripheral tissues or vital organs nourished by the artery. Serious complications or reactions, such as infection (either intra-arterial or extra-arterial) or arterial thromboembolism or vasospasm may occur if products are contaminated with microorganisms, endotoxin, and/or particulate matter. This may lead to serious complications like ischemia, infarction, or gangrene of the tissues or organs supplied. A suitably sized, smooth-bore, stainless steel needle or a short, flexible, plastic catheter is used which is surgically inserted into the desired artery. Occasionally, a lengthy catheter is guided over a stylet or needle through a percutaneous entry site (sometimes under fluoroscopy) until the desired artery, organ, or tissue is reached. Sometimes, the skin over the artery may be punctured directly, and the needle is inserted into the artery.

Intraventricular Route

In intraventricular administration, the drug product is injected or infused directly into the lateral ventricles of the brain. This route is used mostly in the treatment of infections (such as bacterial or fungal meningitis and/or ventriculitis) or of malignancies (such as leukemic infiltrates of the meninges or carcinomatoses) involving the membranes and cerebrospinal fluid surrounding the central nervous system. This route of administration is used in conditions where the drugs are known to diffuse or pass poorly from the vascular compartment into the ventricles and subarachnoid space and/or where reduction of systemic side effects from a particular agent are desired. Sometimes, IV administration of the same drug is needed as a complete therapy along with intra-ventricular therapy.

The intraventricular route can be beneficial when intracranial pressures are high. Also, radiopaque tracers or radiolabeled dyes may be injected into the intraventricular space for anatomical studies of the system or for studies of the flow of cerebrospinal fluid. Cerebrospinal fluid comes in contact with critical organs such as the brain and spinal cord and works as a protective or cushioning fluid for these organs; thus, any disturbances of this fluid or of the membranes containing it may be unsafe and possibly fatal. Strict aseptic techniques should be followed as any chemical or biological extraneous material may initiate inflammatory response if it enters the system. Generally, a 3.5 inches long, smooth-bore, 18-gauge, stainless steel, blunt-ended ventricular needle is used to deliver drugs via this route.

Intrathecal Route

An intrathecal injection is administered into the spinal canal (intrathecal space surrounding the spinal cord), which may be used for spinal anesthesia, chemotherapy, or pain management. This route is also used for delivering drugs for post neurosurgical infections. Drugs given via the intrathecal route has to be preservative-free, often compounded by the pharmacist prior to administration. This route is commonly used for a single 24-h dose of analgesia (opioid with local anesthetic). Extreme control has to be taken during dosing, because, most narcotic pain medications can cause a late onset respiratory depression in older patients and others when administered via this route. Isotonicity is very important for formulations delivered through intrathecal route, as disturbances in osmotic pressure can cause headache and vomiting. Sometimes, intrathecal administration can be performed through an intrathecal pump, implanted just below the skin of the stomach with a tube connected directly to the base of the spine, where it bathes the appropriate nerves using low doses of drugs (e.g., baclofen) [16]. It is the preferred route for long-term management of spasticity in seniors with cerebral palsy for whom other procedures, such as rhizotomy or orthopedic surgery, are not suitable.

Generally, a 3.5 inches long, smooth-bore, beveled, 20- to 22-gauge stainless steel spinal needle is used for intrathecal administration. The needle is inserted posteriorly at the midline into any space below the third lumbar spinal process. This route is not used if intracranial masses are suspected. In addition, a real threat of tonsillar or brain stem herniation (and possibly death) exists if this procedure is performed while intracranial pressure is elevated. Great care must be exercised to avoid this complication, which usually occurs one to two hours or sooner after removal of fluid.

Intracisternal Route

Intracisternal injections involve the administration of drug products directly into the cisternal space surrounding the base of the brain. This route is mostly used for diagnostic purposes. Sometimes, this route is used to decrease elevated intracranial pressures and reduce the risk of herniation of the brain. The intracisternal route can also be used to treat diseases involving the cisterns or nearby contiguous structures. Intrathecal or intracisternal injections cannot be used for disease within the ventricles. Some of the concerns involving this route include the threat of physicochemical irritation of the substances injected as well as the danger of producing permanent, serious, neurological injury or death due to possible damage to the midbrain. The space entered is relatively small, and the insertion of a needle into the site should be attempted only when other routes are contraindicated.

Epidural Route

The epidural injection is administered by placing a catheter into the epidural space (or extradural space or peridural space) in the human spine. Epidural injections are useful for loss of sensation and analgesia by blocking the transmission of signals through nerves in or near the spinal cord and involve injection of drugs through a catheter. Once a catheter is placed into the epidural space, a continuous infusion can be maintained for several days. Generally, the epidural route uses a combination of local anesthetics and opioids for pain relief [17]. The combinations are more efficient than a single type of drug used alone. Common local anesthetics include lidocaine, bupivacaine, ropivacaine, and chloroprocaine. Common opioids include morphine, fentanyl, sufentanil, and meperidine. These drugs are injected in relatively small doses. Occasionally, other agents like clonidine or ketamine may be used.

During some surgeries, such as gynecological surgery (e.g., hysterectomy), orthopedic surgery (e.g., hip replacement), general surgery (e.g., laparotomy) and vascular surgery (e.g., open aortic aneurysm repair), the anesthetist may use epidural analgesia in addition to general anesthesia, which may reduce the patient's requirement for opioid analgesics. The dose required for anesthesia is much higher than that required for analgesia. For postoperative analgesia, analgesics are given into the epidural space for a few days after surgery, provided a catheter has been inserted. With the use of a patient-controlled epidural analgesia (PCEA) infusion pump, a patient may be given the ability to control postsurgical pain medications administered via the epidural route. Injection of analgesics and steroids into the epidural space may improve some types of back pain. Epidural techniques are most suitable for analgesia for the chest, abdomen, pelvis or legs. They are much less suitable for analgesia for the neck or arms and are not possible for the head.

This route is not recommended for older patients suffering from certain CNS disorders like multiple sclerosis, or if they have heart-valve problems such as aortic stenosis. A scar tissue formation from previous spinal surgery can potentially cause disruption in the distribution of the medication. A Tuohy needle is used for epidural administration. This needle is specially designed for locating the epidural space safely. Real-time observation (ultrasound or image guided) of needle insertion and advancing needle is becoming a common practice.

Intra-articular Route

Intra-articular injection involves an injection or infusion into the synovial sacs of accessible joints. Antibiotics, lidocaine and anti-inflammatory drugs, like corticosteroids, can be administered into joints for the treatment of infections, pain, inflammation, or other problems resulting from inflammatory diseases (e.g., rheumatoid arthritis or trauma). Some agents are administered in single injections

and some (e.g., antibiotics) via continuous infusion. Intra-articular injections are usually administered in the knee, ankle, wrist, elbow, shoulder, phalangeal, sternoclavicular, and acromioclavicular joints. If the joint is deformed by any disease process (e.g., rheumatoid arthritis or trauma), it can be more difficult to enter the synovial sacs and inject the drugs.

Usually, the intra-articular route is used when only one or two joints are involved. A sterile, 19–25 gauge, stainless steel needle attached to a syringe is usually used in this route of administration. Usually, 19–24 G is used for the knee and shoulder; and 20–25 G is used for the wrist, ankle and elbow. The entry of the needle should be at the point where the synovial cavity is most superficial and free of large vessels and nerves. The synovial fluid should be first aspirated to ensure that the needle is within the joint space. Then, the syringe is changed, and one containing the drug(s) to be injected is attached, and the drug is administered. A threat following intra-articular injection, called iatrogenic infection, may result in destruction of the joint. Administration of corticosteroids is particularly troublesome because, if a serious infection occurs, then detection may be delayed due to the suppression of the local inflammatory response. Therefore, destruction of the joint and the cartilage may occur before the identification of a complicating infection.

Intra-abdominal or Intra-peritoneal Route

An intra-abdominal administration involves an injection or infusion directly into the peritoneal cavity via a needle or indwelling catheter or directly into an abdominal organ, such as the liver, kidney, or bladder. This route is used to treat local or widespread intra-abdominal diseases due to microbial infections or tumors. The route is also utilized to remove various toxic substances from the abdomen when severe renal failure prohibits excretion (e.g., peritoneal dialysis). Sometimes, radio opaque agents are used via the intra-abdominal route to determine the structure of various vascular or lymphatic systems in older patients. Drugs injected into the intra-peritoneal space are usually absorbed into the vascular compartment, and under certain pathological conditions, they can introduce uncontrolled risk of toxicity or therapeutic failure. Usually, a 20–25 gauge stainless steel needle is inserted for intra-abdominal administration. Larger diameter needles (16–18 G) are typically used to provide a tissue core for histological assessment.

The intra-abdominal route of administration can cause abdominal infection (peritonitis) and hemorrhage. The source of infection may be extrinsic (e.g., from skin or contaminated drugs or infusates) or intrinsic (e.g., from puncture of the bowel). The risk of infection is more with an indwelling catheter, instead of a single injection using a sterile needle. The chance of inducing hemorrhage is usually related to the size of the needle used, the anatomical site selected for injection, the skill of the technician, and any tendencies of the patient to bleed (i.e., coagulation

problems). If hemorrhage occurs, it may be difficult to control and may require surgical intervention and repair.

Intracardiac Route

Intracardiac injections involve delivering drugs directly into chambers of the heart or the cardiac muscle. This route is only used under unusual circumstances and in certain emergency situations, such as cardiac arrest, in which drugs may have to reach the myocardium immediately. Usually, a beveled, 18- to 22 gauge, 4–6 inches long, stainless steel needle is used. In emergency cardiothoracic procedure, a 22 G needle is inserted into the left ventricle, preferably the atrium [18]. This route involves the risk of damaging the heart muscle, coronary arteries, or the conducting system due to trauma of needle or drug. Occasionally, hemorrhage into the myocardium or pericardium may result, leading to infarction or pericardial tamponade (constriction of the cardiac blood vessels). If extra-cardiac structures (e.g., lung) are accidentally punctured, a pneumothorax may result and breathing may be impaired.

Intraocular Route

The intraocular route consists of injections of drug products directly into the various chambers of the eye. Four types of injections are given to the eyes, including (i) injection or irrigation directly into the anterior chamber of the eye; (ii) injection directly into the vitreous cavity of the eye (intravitreal); (iii) injection around the posterior segment of the globe (retrobulbar); and (iv) subconjunctival. Subconjunctival and retrobulbar injections are not considered *intra*ocular. They are administered beneath the conjunctiva, thus the medication diffuses through the limbus and sclera and into the eye. Intraocular transport and diffusion are poor, thus absorption of drugs into the eye is difficult. This route is usually employed to treat infections and inflammatory diseases of the eye which are not effectively treated by topical or systemic drug administration. Infection is always a threat in intraocular drug delivery and complications (e.g., optic nerve damage, hemorrhage, retinal detachment, retinal necrosis, cataracts) can occur. The volume of injection is strictly restricted to no more than 0.1–0.2 mL. Selection of the type of intraocular injection depends on the disease present and the exact location of that disease within the eye.

Generally, a 25–32 G, 0.5–1 inch long, stainless steel needle, is used for intra-ocular delivery. A volume of fluid equal to that to be injected must be removed before instillation. Great care must be taken not to inject or damage the lens of seniors, as this may result in cataract formation. During intra-ocular injection, great care must be taken to not detach the retina or to not injure the optic nerve.

Vascular Access Devices

Repeated injections over time can cause discomfort and pain to older patients; thus devices can be used to provide continued access and to reduce pain associated with administration. The use of indwelling polymer catheters reduces the need for multiple punctures during IV therapy. The choice of catheters depends on several factors, including the purpose of infusion, length of time of the infusion and the condition and availability of the veins. Several devices are used for venous access, including peripheral insertion devices, midline, and central venous access devices.

Peripheral insertion devices: The most common method of accessing the venous system is through the insertion of a needle or flexible catheter to a peripheral vein through venipuncture (technique that allows a needle or catheter into a vein). In peripheral IV therapy, medications and various solutions can be administered through over-the-needle catheter IV catheters. The metal stylet is used to pierce the skin and enter the vein, and the plastic or polymer catheter is inserted into the skin and the metal stylet is removed. IV catheters are available in different sizes. The lumen size is measured as odd numbers (winged infusion needle), for example, 19, 21, 23 and catheter size is designated by even numbers. The most common adult catheter sizes are 18, 20 and 22. Catheter lengths are usually ¾–2 inches.

Midline infusion devices: Midline catheters are inserted near the antecubital fossa and terminate in the vasculature, right before axilla [14]. These catheters are usually 4–6 inches long and used for patients who need moderate term parenteral therapy or have limited peripheral access.

Central venous access devices: A flexible catheter is placed into one of the patient's large veins with the tip of the catheter placed in either the superior vena cava or the right atrium in central venous access devices. They are used when the patient's peripheral venous access is not available or adequate for the duration or type of IV therapy required. The central veins are often necessary for irritating medications such as chemotherapeutics or TPN or for infusing hypertonic solutions. Central venous catheters can be classified into four major categories:

(a) Single or multi-lumen catheters are inserted into the superior vena cava or right atrium. They can have one, two or three lumens which can be used in simultaneous infusion of fluids or medications or blood products. Due to the risk of complications, multi-lumen catheters are used only in hospitalized patients and for short-term therapy.
(b) Peripherally inserted central venous catheters (PICCs) are long-line catheters that are used for patients who need venous access for intermediate to long term therapy at home or hospital. PICC lines are small in diameter, so they are very useful for older patients.
(c) Tunneled central venous catheters are used for long, permanent IV therapy. They may have one or several lumens and are implanted by surgical procedure.

(d) Implanted access ports are surgically placed within the chest and into a central vein that can be accessed when needed. They are very useful for cancer therapy where the self-sealing septum or port allows repeated use without any external tubing between treatments.

Infusion Techniques: Methods and Devices

Infusion techniques are commonly used for older patients in order to deliver a continuous supply of drugs. In this technique, an accurate dosage and an appropriate drug delivery technology (e.g. infusion) are needed to obtain precise and safe dose delivery of a medicine in venous or arterial administration. Various infusion methods such as gravity infusion technique, positive pressure infusion technique as well as other highly specialized types of infusion equipment are important for seniors who have frequent needs for infusion in nursing homes, hospitals, as well as in home care.

The factors influencing the required dosing accuracy are a patient's status, the type and amount of fluid to be infused, and the infusion equipment used. The flow of the infusion can be affected by resistance in the channel of the piercing spike, resistance in the tubing, resistance in the connector pieces, speed of drop formation, variability of the delivery pressure, and physicochemical characteristics of the solution.

Gravity Infusion

Gravity infusion is very common for older patients. The accuracy of the dosage and the infusion rate requirements are low for this type of infusion (±50 %). This technique is based on the hydrostatic pressure differential between the patient and the infusion container. The rate of fluid administration can be modified or accelerated by compressing the container or by increasing the internal pressure of the container.

The rate of the infusion is a critical factor for gravity infusion and is mainly regulated by means of the roller clamp in most hospital settings. Most standard infusion sets are designed to deliver approximately 20 drops/min (equivalent to 1 mL/min). Specialized roller clamps can provide drop rates of 60 drops/min. Tubing independent flow regulators can provide improved dose accuracy and flow rates that range from 3–200 mL/h. These units are utilized for infusion solutions, which are carrier solutions for drugs that need to be administered at a specific concentration for longer durations. An ideal flow regulator can provide the desired flow rate irrespective of changes in the infusion height and patient activities.

Pressure Infusion

Pressure infusion is used for older adults during IV administrations using infusion or transfusion bags. A pressure cuff with an inflation bulb can be used (similar to blood pressure measurement) to apply pressure. A pressure of up to a maximum of 300 mmHg can be applied on a regular infusion bag. Different types of positive pressure infusion equipment are used when the dosage accuracy is required; or when an increased rate of infusion is needed; or when a constant rate of delivery during long-term infusions is preferred. Different applications and administrations may have different infusion rates and pressure infusion rates may vary from 1 and >1000 mL/h (e.g., shock therapy in intensive care) for adult patients. Syringe pumps are pressure infusion devices and can provide a very accurate administration of drugs. It administers the content of one or more syringes while simultaneously using precision linear drive.

Smart Pumps

Many intravenous medications are high-alert medications and therefore they can cause harm if an error occurs during administration [19]. Smart pumps are computerized infusion devices with dose-error reduction software designed to avoid and reduce IV programming errors, as well as other errors associated with infusions administered to patients. They can reduce administration errors associated with miscalculated doses. Smart pumps can also store dosing guidelines in them which can be organization-specific. They produce real-time alerts and stops to allow clinicians to recognize programming errors when attempts are made to program doses outside of the established safe dose range. Smart pumps can be programmed to include customized drug libraries as well as lists of IV medications and their concentrations. The device can guide the user to choose a medication from the drug library, confirm the selection, input a volume to be infused, and input an infusion rate or dose for seniors. They can check manual calculations to ensure that the selected dosing formula is appropriate to the medication and the patient (e.g. mcg/kg/h vs. mcg/kg/min) [20]. For all medications selected from the library, the keypad entry of an infusion rate in milliliters will automatically calculate the equivalent dose in units, milligrams or micrograms. Another advantage of these devices is the availability of programming data captured when practitioners program or use the pumps. Analysis of this information can lead to quality improvement efforts concerning errors in patient care.

Patient-Controlled Analgesia

Patient-controlled analgesia (PCA) is one of the most common methods for providing postoperative analgesia in older patients, and it is done by delivering analgesic drugs (e.g. opioids) via a programmable infusion pump. PCA lessens the time between start of pain and treatment (analgesia) as it is delivered via preexisting IV line into the patient (activation automatically pumps the dose). The prescribed analgesic is preloaded into the PCA and programmed per the physician's order for amount and interval between doses. It stops delivering the drug to the patient if the patient tries to self-administer an excessive dose. Older patients who use PCAs report better analgesia and lower pain scores than those patients who have to request analgesia from the nursing staff when they are in pain.

Disposable Infusion Pumps

For nonelectric disposable pumps, mechanical restriction within the flow path regulates the speed of pressurized fluid. The pressure on the fluid can be exerted by a variety of mechanisms including a stretched elastomer, compressed spring, pressure produced during a chemical reaction and pressure delivered from a cartridge of pressurized gas. The restriction of flow in all disposable pumps is produced by narrow-bore tubing. Tubing diameter is also important for the device's flow rate. Therefore, flow restrictors are usually made of materials in which the dimensions don't change with temperature to maintain accuracy. Glass capillary flow restrictors are typically used for devices infusing at a rate of 0.5–10 mL/h; a polymer is typically used for flow restrictors of pumps infusing at rates of 50–250 mL/h.

Elastomeric infusion pumps are disposable devices, where the pressure on the fluid is generated by the force of a stretched elastomer. They are usually used for administering liquid drugs (e.g. anesthetics, cytotoxics or antibiotics). Elastomeric pumps are known for their reliability and accurate flow rate. They are maintenance-free and run independently without any electronics. Elastomeric pumps operate with a driving pressure of 260–520 mmHg and infuse at rates of 0.5–500 mL/h. Depending on the size of the pump, the drug inside the pump can be delivered over a timeframe varying between one to seven days. This type of pump is ideal for older patients who may require a high level of mobility.

In a negative-pressure pump, a driving force is generated from the pressure difference across two sides of the pump's low-pressure chamber wall, with one side being at very low pressure (inside a vacuum chamber) and another side being at atmospheric pressure. A pressure on the movable wall plunger is generated by the large pressure difference between its two sides, causing it to move and compress the fluid in the drug containing chamber during the delivery of infusion.

Self-injection of Parenterals for Older Patients

There are many injectable drugs currently on the market or in the drug development phase that require repeated dose administration during the day or week and therefore, are preferred for self-administration. Self-administration medical devices require easy-to-use systems that encourage patients to comply with a dosing regimen. The convenience of a portable device and the reliability of delivering the required dose make it a very useful choice for subcutaneous delivery; especially when older patients are transferred from hospital to homecare, self-administration devices for injectable drugs can be beneficial. The need for patient self-injection for many chronic diseases (e.g. rheumatoid arthritis, multiple sclerosis and diabetes) and specific therapeutic areas (e.g. anti-dote) are being enabled by the use of insulin pumps, auto injectors, patch injectors and pen injectors.

Insulin Pumps

Insulin pumps are small computerized devices that can deliver insulin over the course of 24 h. The dose can be delivered (1) as a steady measured and continuous dose (the "basal" insulin); (2) as a surge ("bolus") dose, at a patient's direction, around mealtime to control the rise in blood glucose after a meal; or (3) as corrective or supplemental doses, such as, if the patient has high blood glucose levels before a meal, then, a correction or supplemental bolus of insulin has to be programmed to bring it back to target range. Such insulin pumps can also overcome the dawn phenomenon, where the pump can be programmed to change basal rates throughout the night to meet changing insulin needs.

Doses are delivered through a flexible plastic catheter which is inserted through the skin and into the fatty tissue and is secured in place. Insulin pumps are preferred by the older population as this is a continuous system of insulin delivery as opposed to injections. Often, patients can program different amounts of insulin at different times of the day and night. It was observed that the quality of life (QOL) in type 1 and insulin-requiring type 2 diabetes patients is improved using pumps. Sometimes, insulin pumps come with convenient built-in Continuous Glucose Monitoring (CGM), where CGM measures glucose levels in real-time throughout the day and night. The insulin pump with CGM can detect and notify the patients if glucose is reaching a high or low limit. Seniors can have better control of their diabetes with these new systems with frequent updates on their glucose levels right on their insulin pump screen. Examples of currently available insulin pumps on the market are OneTouch® Ping® (Animas), Vibe™ (Animas), Accu-Chek Spirit Combo® (Roche), Asante Snap (Asante Solutions), Paradigm Revel (Medtronic), OmniPod (Insulet), Dana Diabecare R and Diabecare IIS (Sooil USA), t:slim, t:flex and t:slim G4 (Tandem diabetes).

Auto Injectors

Auto injectors are medical devices that are extremely useful for delivering single drug doses. They are easy to use and are intended for self-administration. It is usually administered into the thigh or the buttocks, and the depth of the injection can be adjusted or fixed. Generally, they are spring-loaded systems that reduce the distress associated with self-administration of the needle-based drug delivery device. The needle is fully shielded prior to injection and the passive safety mechanism in the auto injector prevents any accidental injection. Usually, the injection time is just a few seconds.

After activating the auto injector, the syringe needle is automatically inserted into the skin or tissue and the drug is delivered. Some auto injectors have visual or audible indication to confirm that the full dose has been delivered to the patients. Auto injectors may contain glass or polymer syringes. Glass syringes are fragile with higher pressure; thus, more recently, companies have been looking into making auto injector syringes out of polymer e.g. COP syringe PLAJEX® (Terumo®) to prevent this issue.

Epinephrine auto injectors are widely used for the treatment of anaphylaxis and they are very useful for injecting a measured dose or doses of epinephrine (adrenaline). There are many trade names for the epinephrine auto injector device; for e.g., EpiPen, Emerade, Twinject, Adrenaclick, Anapen, Jext, Allerject, and Auvi-Q. Other examples are Rebiject, Rebiject II and Rebidose autoinjectors for Rebif (interferon beta-1a) which is used to treat multiple sclerosis. The Enbrel SureClick autoinjector is a single-use prefilled auto injector which contains one 50-mg dose of Enbrel to treat rheumatoid arthritis. Table 5 shows a list of auto injectors with their name and indications.

Pen Injectors

Pen injectors are commonly used to inject insulin for when the treatment of diabetes requires multiple insulin injections. A large population of older patients is affected by diabetes and insulin pens are very useful for the self-administration of insulin. Pen injectors are composed of an insulin cartridge (integrated or bought separately) and a dial to measure the dose. The needles used in pen injectors are one-time use disposable pen needles. Insulin pens are more convenient and easier to use for repeated accurate dose delivery. In general, recommended injection sites for pen injectors include the abdomen, parts of the buttocks and thigh areas.

Table 5 Different auto injectors available on the global market

Name	Drug	Indication	Device manufacturer	Pharmaceutical company
Simponi®	Golimumab	Rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis	Owen Mumford	Johnson & Johnson
Rebif®	Interferon beta-1a	Multiple sclerosis	BD	EMD Serono
Humira®	Adalimumab	Rheumatoid arthritis, juvenile idiopathic arthritis, psoriatic arthritis, ankylosing spondylitis, adult Crohn's disease, pediatric Crohn's disease, ulcerative colitis, plaque psoriasis, hidradenitis suppurativa	Owen Mumford	Abbvie
Enbrel®	Etanercept	Rheumatoid arthritis, polyarticular juvenile idiopathic arthritis, psoriatic arthritis, ankylosing spondylitis, plaque psoriasis	SHL	Amgen and pfizer
Aranesp®	Darbepoetin alfa	Anemia due to chronic kidney disease	SHL	Amgen
Avonex®	Interferon beta-1a	Multiple sclerosis	SHL	Biogen
Plegridy®	Peginterferon beta-1a	Multiple sclerosis	SHL	Biogen
Rasuvo®	Methotrexate	Active rheumatoid arthritis, active polyarticular juvenile idiopathic arthritis	BD	Medac
Otrexup®	Methotrexate	Rheumatoid arthritis, polyarticular juvenile idiopathic arthritis, psoriasis	Antares Pharma	Antares Pharma/Leo
Benepali®	Etanercept	Rheumatoid arthritis, polyarticular juvenile idiopathic arthritis, psoriatic arthritis, ankylosing spondylitis, plaque psoriasis	SHL	Biogen/Samsung
Sumatriptan®	Sumatriptan	Migraine	SHL	Sun Pharma
Zembrace®	Sumatriptan	Migraine	SHL	Promius/Dr. Reddy's Laboratories
Pegasys®	peginterferon alfa-2a	Chronic hepatitis C	SHL	Roche

(continued)

Table 5 (continued)

Name	Drug	Indication	Device manufacturer	Pharmaceutical company
Trulicity®	Dulaglutide	Type 2 diabetes mellitus	Lilly OEM	Lilly
Taltz®	Ixekizumab	Plaque psoriasis	Lilly OEM	Lilly
Orencia®	Abatacept	Rheumatoid arthritis, polyarticular juvenile idiopathic arthritis	BD	Bristol-Myer Squibb
Praluent®	Alirocumab	Hypercholesterolemia	SHL	Sanofi/Regeneron
Repatha®	Evolocumab	Hypercholesterolemia	SHL	Amgen
Cosentyx®	Secukinumab	Plaque psoriasis, psoriatic arthritis, ankylosing spondylitis	SHL	Novartis

Patch Injectors

Patch injectors can be used for reliable self-administration of high-volume subcutaneous delivery of viscous or sensitive drug products that may require an extended injection time. The injection time may range from a few seconds to several minutes. Patch injectors are usually pre-assembled for patient ease of use and may have passive sharps injury protection needle removal. So far, there is no drug product in the market with a patch injector.

Controlled Release Delivery of Parenterals for Older Patients

Parenteral drug delivery with intravenous, subcutaneous or intramuscular injection can gain easy access to systemic circulation with rapid drug distribution and/or absorption. For drugs with a very short biologic half-life, the maintenance of constant plasma levels is a challenge. For tissue regeneration therapy, the in vivo half-life of some cytokines are sometimes limited to only a few minutes after injection, far from sufficient to exert pharmacological effects. Continuous intravenous infusion has been known to maintain a constant and sustained drug level within a therapeutic concentration range for effective treatment in aging adults. However, this often requires hospitalization and close medical supervision of the patient. Pharmaceutical companies have recently been focusing on controlled release drug delivery systems like microspheres, liposomes, gels, suspensions, in situ forming implants, lipophilic solutions, solid lipid nanoparticles (SLN); and drug eluting stents which are utilized to provide sustained, targeted, and controlled drug delivery to the patients with less dosing frequency. Sustained release formulations reduce the dosing frequency to patients, which can benefit aging adults, who may forget to take their medications. They provide long therapeutic effects, maximizing the efficacy–dose relationship, decreasing adverse side effects. Moreover, these systems can enhance patient compliance by alleviating pain during administration and reducing costs of parenteral drug treatment for seniors. Examples of applications for prolonged release parenteral delivery for older adults include: hormone therapy, protein therapy, infection treatments (antibiotics and antifungals), cancer therapy, orthopedic surgery, postoperative pain treatment, chronic pain treatment, vaccination/immunization, treatment of CNS disorders, and immunosuppression. They mostly use the concept of parenteral depot system where long acting parenteral drug formulation are designed to provide slow, constant, sustained action. Brief description of the controlled release dosage forms are given in next few paragraphs. Table 6 shows different marketed controlled release products and their indications for older patients.

Table 6 Different controlled release drugs available in the global market

Drug	Brand name	Indications	Route of administration	Dosing frequency	Company
Implants					
Leuprolide acetate	Eligard®	Advanced prostrate cancer	Subcutaneous	Every 1–6 months	Sanofi-Aventis
Histrelin acetate	Vantas®	Metastatic prostate cancer	Subcutaneous	Once a year	Endo
Carmustine	GLIADEL® WAFER	high-grade malignant glioma, glioblastoma multiforme	Intracranial	Maximum 8 wafers	Eisai
Goserelin acetate	Zoladex®	Prostrate cancer, breast cancer	Subcutaneous	Every 1–3 months depending on dose	Astra Zeneca
Buserelin acetate	Suprefact® depot	Advanced prostrate cancer	Subcutaneous	Every 2–3 months depending on dose	Sanofi-Aventis
Dexamethasone	Ozurdex®	Non-infectious uveitis, macular edema	Intravitreal	Every 2–3 months	Allergan
Ganciclovir	Vitrasert®	Cytomegalovirus retinitis	Intravitreal	Every 5–8 months	Bausch and Lomb
Fluocinolone acetonide	Retisert®	Uveitis	Intravitreal	Every 30 months	Bausch and Lomb
Microsphere					
Risperidone	Risperidal® Consta®	Schizophrenia, bipolar disorder	Intramuscular	Every 2 weeks	Janssen/Alkermes
Naltrexone	Vivitrol®	Alcohol dependence	Intramuscular	Once a month	Alkermes
Leuprolide acetate	Lupron Depot®	Advanced prostate cancer	Intramuscular	Every 1–3 months	Abbott

(continued)

Table 6 (continued)

Drug	Brand name	Indications	Route of administration	Dosing frequency	Company
Octreotide acetate	Santostatin® LAR depot, injectable suspension	Acromegaly, metastatic carcinoid tumor	Subcutaneous	Every 2–4 weeks	Novartis (Sandoz, abbott)
Triptorelin pamoate	Treslar™ LA	Advanced prostate cancer	Intramuscular	Every 1–6 months	Watson Pharma/Debiopharm
Exenatide	Bydureon	Type 2 diabetes	Subcutaneous	Once a week	AstraZeneca
Injectable drug suspension					
Medroxyprogesterone acetate	Depo-Provera®	Hormone therapy	Intramuscular	Every 3 months	Pfizer
Medroxyprogesterone acetate	Depo-subq provera 104®	Hormone therapy	Subcutaneous	Every 3 months	Pfizer
Paliperidone palmitate	Invega Sustenna®	Schizophrenia	Intramuscular	Once a month	Janssen
Olanzapine	Zyprexa Relprevv®	Schizophrenia	Intramuscular	Every 2–4 weeks	Eli Lilly
Methylprednisolone acetate	Depo Medrol®	Anti-inflammatory	Intramuscular, intra-articular, soft tissue or intralesional injection	1–6 months	Pfizer
Triptorelin pamoate	TRELSTAR®	Advance prostrate cancer	Intramuscular	4–24 weeks	Actavis
Betamethasone	CELESTONE® SOLUSPAN®	Anti-inflammatory	Intramuscular	3 days to once a week	Merck
Aripiprazole	ABILIFY MAINTENA®	Schizophrenia	Intramuscular	Once a month	Otsuka

(continued)

Table 6 (continued)

Drug	Brand name	Indications	Route of administration	Dosing frequency	Company
Oil based injections					
Pipothiazine palmitate	Piportil® depot	Schizophrenia	Intramuscular	Every 4 weeks	Sanofi-Aventis
Flupenthixol decanoate	Fluanxol® depot	Schizophrenia	Intramuscular	Every 2–4 weeks	Lundbeck
Zuclopenthixol decanoate	Clopixol® depot	Schizophrenia	Intramuscular	Every 2–4 weeks	Lundbeck
Fluphenazine decanoate	Fluphenazine decanoate	Schizophrenia	Intramuscular	Every 2–4 weeks	APP Pharm
Fluphenazine decanoate	Modecate®	Schizophrenia	Intramuscular	Every 2–5 weeks	BMS/Sanofi
Haloperidol decanoate	Haldol decanoate	Schizophrenia	Intramuscular	Once a month	Ortho-McNeil
Testosterone cypionate	Depo-testosterone®	Hormone therapy	Intramuscular	Every 2-4 weeks	Pfizer
Testosterone enanthate	Delatestryl®	Hormone therapy	Intramuscular	Every 2–4 weeks	Endo
Estradiol valerate	Delestrogen®	Hormone therapy	Intramuscular	Every 4 weeks	Monarch Pharma
Estradiol cypionate	Depo-Estradiol®	Hormone therapy	Subcutaneous	Every 3–4 weeks	Pfizer
Liposome					
Cytarabine	DepoCyt®	Anticancer, meningitis	Intrathecal	Every 2–4 weeks	Pacira Pharmaceuticals
Morphine sulphate	DepoDur®	Pain	Epidural	Discontinued	Pacira Pharmaceuticals

(continued)

Table 6 (continued)

Drug	Brand name	Indications	Route of administration	Dosing frequency	Company
Doxorubicin hydrochloride	DOXIL®	Overian cancer, AIDS-related Kaposi's sarcoma, multiple myeloma	Intravenous	Every 4 weeks	Janssen
Daunorubicin	Daunoxome®	Kaposi's sarcoma	Intravenous	Every 2 weeks	Galen Limited/Almac Pharma
Verteporfin	Visudyne®	Age-related macular degeneration, pathologic myopia or presumed ocular histoplasmosis	Ocular	After 3 months if needed	Bausch and Lomb

Injectable Suspensions

Injectable suspensions are dispersed, heterogeneous systems consisting of insoluble drug molecules and excipients that need to be resuspended or redispersed in either aqueous or vegetable oil vehicles before administering to the patient. Subcutaneous or intramuscular delivery of a drug in aqueous or oil suspension results in depot formation. Depot can act as a drug reservoir and slowly release the drug over a period of time after the dissolution of the drug particle in the subcutaneous tissue.

Injectable Emulsions

Common types of parenteral drug delivery emulsions include (1) water in oil emulsions (W/O) used in sustained release of steroids and vaccines by intramuscular injection and (2) oil in water (O/W) or lipid emulsions administered by a variety of parenteral routes (for example subcutaneous, intramuscular and intra-arterial). Oil in water (O/W) emulsions are mainly injected intravenously in parenteral nutrition applications for older patients. Emulsions are used for sustained release and drug targeting as well as to solubilize drugs with low aqueous solubility, stabilize labile drugs or reducing toxicity.

Microspheres and Micro Particles

Microspheres are used for the sustained release of drugs for prolonged systemic therapeutic effects after subcutaneous (SC) or intramuscular (IM) administration in seniors. They are reservoir type systems in which a micron size core material/internal phase (solid, liquid or gas as drug, cell, microorganism, proteins or peptides, enzymes, hormones etc.) is enclosed in a thin layer of a shell wall forming material (usually a polymer). Micro particles are made of biodegradable polymers that have been extensively investigated for controlled release delivery systems in over the last three decades. For parenteral delivery, micro particles smaller than 125 μm are preferred.

Liposomes

Liposomes are extensively used as carriers for numerous cosmetics as well as investigational and commercial pharmaceutical drug delivery applications. They are small, spherical, bilayer phospholipid vesicles ranging from 30 nm to micrometers. They are biocompatible, biodegradable, have low toxicity, have an ability to be

used for both hydrophilic and lipophilic drugs, and can be used for site-specific drug delivery to tumor tissues. Liposomes are utilized in decreasing drug toxicity, increasing stability of drugs and/or targeting specific cells (for e.g. tumor or cancer cells) in ailing seniors.

Niosomes

Niosomes are highly ordered vesicular structures with a bilayer membrane made up of non-ionic surfactant with or without incorporation of cholesterol. They are stable and act as a depot for short-acting peptide drugs for patients.

Implants

Implant systems are designated for chronic therapy, such as hormone replacement therapy and chemical castration in the treatment of prostate cancer. Parenteral implants can be highly viscous liquids, semisolid, or solid formulations which may be injected with a needle and/or device. Example of solid implant is Vantas® (Endo Pharmaceutical) which is made with steroid hormones (histrelin acetate) in small, slowly absorbed pellets to prolong their effect in relieving the symptoms of prostate cancer in aging adults.

In Situ Forming Implants

In situ forming implants are based on drug-containing polymers in semi-solid or solution forms, which after entering into the body, undergo physicochemical changes to form a unit implant for controlled drug delivery. In situ forming microparticle (ISM) systems offer a new encapsulation technique that provide prolonged release of a drug along with much greater ease of preparation and administration than conventional microparticles and surgically implanted systems. They have low risk of dose-dumping, are capable of being modulated to exhibit varying release patterns, are reproducible, easily applicable and well-tolerated compared with classically surgical implants. Various intramuscular or subcutaneous controlled drug delivery systems in the form of implants or microparticles have been developed based on biodegradable polymers.

Home-Use Parenteral Kits for Older Patients

Home-use parenteral kits are very useful for older adults as they do not need to visit the hospital and can take the medication by themselves or supported by a care giver. It is cost-saving as the physician and administration fees are not needed each time the drug is required to be administered. These kits contain all the necessary components for its use and administration in a patient's home. Examples of home use kits are Xyntha® (antihemophilic factor, recombinant), BeneFIX (Coagulation Factor IX (Recombinant)), NovoSeven® RT (coagulation factor VIIa (Recombinant)) etc. Emergency parenteral kits are similar in packaging. Patients always carry these as they may need it at any time. Some examples of emergency kits are glucagon emergency kits for low blood sugar (glucagon for injection [rDNA origin]), naloxone rescue kits, kits for Addison's disease (intra-muscular injection of hydrocortisone) etc.

Miscellaneous Uses of Parenteral Route for Older Patients

There are a few other important applications for the parenteral route for older adults including total parenteral nutrition, delivery of vaccines and radioactive agents. They are briefly discussed below.

Geriatric Nutrition

The prevalence of malnutrition is a common issue in seniors and the risk of developing secondary malnutrition is very high. It is estimated that 85 % of older adults living in their own houses present at least one disease that could be improved with appropriate nutrition treatment. There are various reasons for malnutrition. One of them is age-related changes in taste. Older people experience increased sensitivity to bitterness and decreased sensitivity to sweetness, thus they lose interest in consuming certain foods. The assessment of diagnosing malnutrition in older adults is not easy. A useful indicator is a weight loss from baseline or the development of anorexia. Weight loss of more than five percent of total body weight, or five pounds in one month, or more than ten percent, or ten pounds in six months is significant. To combat this issue, parenteral nutrition (PN) bypasses the normal digestion in the stomach and bowel. It is a special liquid food mixture given into the blood through an intravenous (IV) catheter in the chest or arm. The mixture contains proteins, carbohydrates (sugars), fats, vitamins and minerals (such as calcium). Both nutritional screening and nutritional intervention have recently been suggested as suitable cost-effective tools in appropriately selecting older patients at risk for malnutrition. Although artificial feeding may be prescribed for home

patients, it is mainly used in hospitals and nursing homes. Nutritional support has different objectives, depending on the clinical situation; including main part of treatment (e.g. in diabetes mellitus therapy), improving/preventing the onset of illnesses (e.g. cardiac failure), avoiding/managing malnutrition (e.g. stroke sequels) and controlling clinical parameters (e.g. serum cholesterol, blood pressure values). This can be done either through central veins such as the subclavia (central parenteral nutrition, CPN) or through peripheral veins such as the basilica (peripheral parenteral nutrition, PPN). CPN permits nutritional repletion, whereas PPN does not. The term 'total' added to parenteral nutrition implies that nutrition support given solely by this route guarantees nutritional repletion. PN may supply all types of macro and micronutrients, guaranteeing gastrointestinal (GI) rest and maintaining an appropriate nutritive status. PN is known for its intravenous nutrient load, bypassing the GI tract and liver. These fall into three groups: mechanical (post-catheter pneumothorax), infectious (catheter sepsis) and metabolic (electrolyte disturbances, glycaemia, serum urea). Although the patient's age should never be a definite factor to rule out PN, it is well known that the following PN-associated complications will increase in the geriatric population. The most common complications associated with catheter placement include infection, clogging (occlusion), and breakage. Thrombosis (blood clot) of a blood vessel around an intravenous catheter is another potential complication with intravenous therapy as well as intravenous nutrition. For seniors, hyperglycaemia, uraemia and electrolyte disturbances are more frequent; fluid overload associated with cardiac failure risk is always present; respiratory failure and CO_2 retention are possible; and, due to their depressed immunology response, the presence of a catheter sepsis risk is always prevalent. Although prolonged PN is rarely supplied to the older patients, when it is done, both metabolic (mainly bone and liver diseases) and psychological complications may affect the older patients more than younger adults. For all of the reasons mentioned, PN should be used only in specific clinical settings; when there is no possibility of using the GI tract, and when PN is supplied for a limited period of time (pancreatitis, abdominal trauma). In addition, close PN monitoring and follow-up to detect and treat complications early should be done for older patients.

Vaccines

Vaccine are very important for the general health of the older adults population as they are at higher risk of complications from numerous preventable infectious diseases that may cause significant illness and even death in unvaccinated seniors. In addition, seniors may be using immunosuppressant drugs for treatment of autoimmune diseases or from surgical complications that will also suppress their ability to prevent common infections or illnesses. Vaccines are administered through parenteral delivery, mostly by subcutaneous, intradermal or intramuscular injections. It is essential for seniors to review and maintain a sufficient vaccination status, especially if they may not have been vaccinated as a child. Moreover, new

vaccinations may now be available, immunity may have faded for old vaccines, and most importantly, seniors are more susceptible to serious and possibly life-threatening infections. A few vaccines like the flu vaccine, pneumococcal vaccine, shingles vaccine, and tetanus-diphtheria-pertussis vaccine (Tdap) can reduce the chances of infections in older populations. There are various recommended vaccines for older adults that can prevent Influenza (Flu), Shingles (Herpes Zoster), Diphtheria, Tetanus, Pertussis (Whooping Cough), and Pneumococcal disease (Pneumonia). Due to the nature of these vaccines, vaccination is mainly delivered through parenteral delivery. They are discussed briefly in the following sections.

An annual influenza vaccination for older adults—with or without underlying high-risk conditions such as, heart disease or diabetes—is helpful as well as necessary, since immunity is short-lived and vaccine manufacturers include new strains every year to make it more effective. During recent flu seasons, between 80 and 90 % of flu-related deaths have occurred in people 65 years and older [21]. The seasonal flu vaccine can protect seniors against influenza viruses which can be prevalent during the flu season. Traditional flu vaccines (called "trivalent" vaccines) are made to protect against three flu viruses; an influenza A (H1N1) virus, an influenza A (H3N2) virus, and an influenza B virus. Quadrivalent vaccines can protect against the same viruses as the trivalent vaccine and an additional B virus [21].

Pneumonia causes significant illness in seniors and is responsible for 60,000 deaths each year. Patients older than 65 who have previously been vaccinated, can get a one-time repeat vaccination, if 5 years or more have elapsed since the original shot and if they were younger than 65 at the time of their primary vaccination. There are currently 2 types of pneumococcal vaccines available for older adults; pneumococcal conjugate vaccine (PCV13 or Prevnar 13®) and pneumococcal polysaccharide vaccine (PPSV23 or Pneumovax®). PCV13 is recommended for all adults 65 years or older, and with certain risk factors. PPSV is recommended for all adults who are 65 years or older who are at high risk for pneumococcal disease. Seniors who have not previously received PCV13 should receive a dose of PCV13 first, followed 6 to 12 months later by a dose of PPSV23. If any senior has already received one or more doses of PPSV23, the dose of PCV13 should be given at least one year after the most recent dose of PPSV23. Seniors who are taking a drug or treatment that lowers the body's resistance of infection, such as long-term steroids, certain cancer drugs, radiation therapy, or who are smokers or have asthma should take one dose of PPSV23.

Shingles is a very painful, contagious blistering rash that can lead to even more severe complications. The injectable vaccine, Zostavax, is recommended for one-time administration to most adults age 60 or older by the Centers for Disease Control and Prevention [22]. The vaccine may decrease the risk of having shingles by about 50 %, or at least minimize its severity. The shingles vaccine can be administered to seniors regardless of whether they recall having had chickenpox, which is caused by the same virus as shingles. Protection from the shingles vaccine

lasts about 5 years. In adults vaccinated at age 60 years or older, protection from the vaccine decreases within the first 5 years after vaccination.

Tetanus-Diphtheria-Pertussis (Tdap) is important for older people as they need to replace one of the series of tetanus vaccines. It contains the same components as the tetanus-diphtheria vaccine with the addition of the pertussis component. More and more seniors are getting pertussis, or whooping cough, possibly due to fading immunity, thus providers may administer the Tdap vaccine to a person 65 years or older as it is immunogenic and would provide protection.

Diagnostic Agents Including Diagnostic Radiopharmaceuticals

Diagnostic agents can be given by parenteral delivery through a needle or catheter (plastic tube) placed in a vein. Radiopharmaceuticals are used as diagnostic markers through several different imaging technologies, such as X-rays, CT scans, or MRIs. Diagnostic agents are used to create images of specific body parts, including the kidneys, head, lungs, breast, gallbladder, heart, or blood vessels. For older patients, such diagnostic imaging technologies are frequently used.

Conclusion

The percentage of people aged 65 years and over is continuously increasing due to the invention of new medications and drug delivery. Older adults are a major user group for prescribed medications and this predominance will continue to increase in coming decades. Precise drug delivery and medication management are very complex and challenging for the elderly population as they are exposed to several chronic disease conditions. They also experience age-related changes and limitations which need to be reflected in their medication management strategies. Parenteral drug delivery can deliver precise doses to seniors. The frequency of administration has diminished with the advancement in long-acting injections and implants. Moreover, with the continuous advancement in biotechnology and DNA recombinant mechanisms, protein and peptide macromolecules have emerged as promising therapeutic agents in recent years. The demand for efficient drug delivery methods for biotechnology drugs is continuously increasing due to their susceptibility to denaturation and degradation, short half-lives and, therefore, poor oral bioavailability. Parenteral administration can help optimize drug release profiles for biologics by directly delivering the drug to blood circulation. Substantial progress has also been made in parenteral delivery technologies through innovative devices and needle types that significantly reduce the administration burden of parenteral delivery. Thus, the parenteral route of administration will continue to play a pivotal

role in the treatment of older patients for precise drug delivery, drug targeting to specific tissues or organs and for prolonged therapeutic effects.

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Inhalation and Nasal Formulations

Jolyon Mitchell

Abstract The efficient delivery of inhaled medications via either the oral or nasal route is challenging because of the need to bypass defenses that have evolved to protect the human respiratory tract. The situation is exacerbated when treating the older patient, as there are limitations associated with diminished manual dexterity and cognitive function that may ultimately require the medication be given with the assistance of a caregiver. This chapter first examines the aging respiratory tract, including the likelihood of diseases affecting patency of the airway through the nose and airways of the lungs. The formulations currently available to treat respiratory disease in the older patient are then examined in some detail. Since the device component is a critical part of the inhaler, each of the major classes of delivery device is reviewed, paying attention to the advantages and limitations from the perspective of the older patient. Finally, prospects for development of inhaled medication-based therapy in the near future are considered. Throughout, emphasis is placed on the role of the caregiver as well as the perspective of the patient, given that in many instances, caregiver support will be needed to ensure efficient medication delivery and maintenance of adherence to the prescribed therapy.

Keywords Inhaler · Add-on devices · Oral delivery · Nasal delivery · Obstructive lung disease

Introduction

It is becoming increasingly recognized that just as infants and children are not miniature adults in terms of their response to pharmaceutical therapies in general, so the older adult (defined here loosely as a person of pensionable age) cannot

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S. Stegemann (ed.), *Developing Drug Products in an Aging Society*,
AAPS Advances in the Pharmaceutical Sciences Series 24,
DOI 10.1007/978-3-319-43099-7_19

necessarily be treated in an identical way in terms of dosing regimen to the younger adult population [1–4]. This trend, taken to its extreme, leads toward individualized therapy, a process that is gaining traction for certain diseases such as several types of cancer, in which a genetic component can be established as part of the root cause of the disease [5, 6]. More general concerns, such as the large intrinsic variability associated with fact that older patients tend to live in a multi-morbid state and are therefore at risk of polypharmacy are discussed elsewhere in this book. The nature of inhalation therapy has additional complexity beyond that associated with ingesting a pill or receiving an injection of medication. In particular, the lungs, as the target organ for topical delivery or as the gateway to other organs for systemic delivery of medications, are defended from foreign particles entering and depositing therein by a variety of means. These include mucociliary clearance, macrophage envelopment as well as the presence of a progressively narrowing pathway from the nares or mouth that the particles must follow if they are to reach their target zone [7–9].

A patient-by-patient individualistic approach to formulation of medicines to treat the two major chronic diseases involving the airways of the lungs (asthma and chronic obstructive pulmonary disease (COPD)) is not yet viable. Both diseases have a multiplicity of causes, including environmental factors [10, 11]. Many genes are involved in asthma, but the disease pathways have not yet been clarified at the genetic level, and there is also an environmental component to this disease [12]. COPD is also multifaceted, having components of chronic bronchitis, emphysema, and in some patients, there is also an asthmatic element [13]. In contrast, a simpler genetic linkage is apparent in cystic fibrosis (CF), as this disease is caused by mutations in a gene that produces a protein, called CFTR [14]. The CFTR protein controls the flow of sodium and chloride ions as well as water in and out of the cells of organs, in particular the lungs and pancreas. Here, for pulmonary therapy, dornase alfa (Pulmozyme® Genentech, San Francisco, USA) is indicated for delivery by nebulization [15]. This active pharmaceutical ingredient (API) is a highly purified solution of recombinant human deoxyribonuclease (rhDNase), an enzyme which selectively cleaves DNA. It hydrolyzes the DNA present in sputum/mucus of CF patients and reduces viscosity in the lungs, thereby promoting improved clearance of secretions. However, CF is primarily a young person's disease. Nevertheless, current life expectancies are increasing year by year as the result of better bronchial hygiene techniques combined with such medications, and the median age is currently approaching the early 40s, based on the registry maintained by the US-based Cystic Fibrosis Foundation [16]. So there is the realistic prospect that treatment of the older adult with this disease may become more commonplace in the foreseeable future. For this reason, information pertinent to the delivery of inhaled formulations to treat CF is included in this chapter.

A critical concern when considering the delivery of medication by either the oral or nasal routes to older patients is the appreciation that in many cases they have

reduced or even absent physical and/or mental faculties that make the delivery of the medication difficult [17]. Unfortunately, tests readily administered in daily practice to detect age-related deterioration may not accurately predict optimal use of inhaler devices [18].

In contrast to other forms of drug delivery, such as via the transdermal or oral-gastrointestinal routes, and with the exception of most nebulizing systems, inhalers have to be actuated in order to create the aqueous droplets or dry powder particles as an aerosol cloud that can be inhaled. It is important to appreciate that an aerosol is by nature, always an unstable system [19]. The time to deliver the medication following creation of the aerosol therefore becomes critical for maintaining medication delivery efficacy to the place of action in the respiratory tract. This consideration is especially important with pressurized metered-dose inhalers (pMDI), where ideal technique for use is difficult to achieve [20]. Furthermore, in the case of asthma, there is clinical evidence of reduced disease stability if patient coordination is less than ideal [21]. Thus, the ability to coordinate actuation of the inhaler with the ideal onset of inhalation, should be taken into account when prescribing an inhalation device that must be operated in this way [22]. In the case of most DPIs, the patient initiates aerosol formation by the action of inhaling, so coordination is relatively unimportant. However, delivery efficacy will suffer if the patient cannot inhale with sufficient force to generate the aerosol as intended, noting that the amount of force required is based on the inhaler resistance to airflow through the pathway conveying the powder to the patient [22]. For these reasons, this chapter is as much concerned about the means of medication delivery (i.e., the device component) as it is about the formulations themselves.

Particle size is an important parameter to consider when describing how inhaled aerosols behave when inhaled. The relationship between aerodynamic diameter (used as the size scale when describing aerosol transport processes) and physical size as measured by a microscope, takes into account variations in particle density from that of water and also shape from those properties of a perfect sphere [19]. Much effort has been devoted to the development of formulations and associated delivery devices to optimize the portion of the label claim dose that is comprised as so-called “fine particles” ≤ca. 5 μm aerodynamic diameter. There is also interest in formulating with a significant portion of the dose as so-called “extra-fine” particles with sizes ≤ca. 1 μm aerodynamic diameter. In general, particles larger than about 5 μm in aerodynamic diameter are deposited onto surfaces in the upper airway by a combination of processes, including turbulence and to a lesser extent sedimentation due to gravity [23]. On the other hand, extra-fine particles penetrate efficiently to the distal airways leading to the alveolar sacs, where they may deposit or remain suspended until being exhaled. A breath-hold at the end of inhalation is often advised to optimize deposition of such particles [24]. However, in the older patient having limited cognitive ability, it has to be recognized that a forced breathing maneuver of this type may be difficult for the patient to achieve, as it requires

a conscious effort to do so. Furthermore, it should be noted that breath-holding is counterproductive in treating dyspnea, a particularly troublesome symptom commonly encountered in patients having COPD [25].

Finally, when considering the inhalation route rather than other ways of delivering medication to the lungs, it is important to note that delivery of the label claim dose is complicated by the need for the medication in aerosol form to pass through the upper airway. This route may be either via the nasopharynx or oropharynx depending whether the patient is inhaling through the nose or mouth, respectively. Control and mitigation of such losses has long been a goal of formulators by ensuring that the aerodynamic particle size distribution of the emitted aerosol is such that its fine particle fraction is optimized. However, the actual outcome is also critically dependent upon the way in which the patient inhales their medication [26]. In contrast, deposition of droplets from nasal sprays for topical delivery is simpler in execution, as the medication is delivered directly to the tissues lining the nasal cavity. Here, the main concern becomes one of avoiding emission of fine particles that might penetrate beyond the nasopharynx to enter the airways of the lungs [27]. Such lung-deposited particles may have an adverse effect to that intended, and the license for the nasal-delivered product will likely not include more distal medication delivery. For this reason, in products indicated for nasal use, formulators design for much larger particle formation, typically in the range from ca. 40 to 250 μm diameter [28].

The Respiratory Tract in the Older Person

The human respiratory tract, like other parts of the body, is subject to normal changes as a result of the aging process. There are four process that gradually take place: (1) decrease in motor (intercostal and accessory muscle) power; (2) decrease in elastic recoil of lung tissue; (3) stiffening of the chest wall; and (4) decrease in the size of the intervertebral spaces [29]. Dynamic lung volume and capacity both decrease progressively with increasing age; this process is largely caused by a decrease in the motor power of the accessory muscles for breathing and decreased expansion of the chest wall. These changes are evident clinically as reductions in clinical markers of lung performance, one of these being forced expiratory volume in 1 s (FEV_1), as shown by the uppermost curve of Fig. 1 for the normal adult. The smaller airways that are without cartilaginous support are kept patent by the elastic tissue surrounding them and the subatmospheric intra-pleural pressure, and airway stability is supported by the presence of lung surfactant [30]. The decreasing intervertebral spaces may account for some of the 10 % decrease in total lung capacity between ages 20 and 70 [31], but reduction is muscle motor power may also be partly responsible [29].

Apart from the enhanced risk of developing neoplasms in the respiratory tract [32] (not within the scope of this chapter), tobacco smoking has a major deleterious

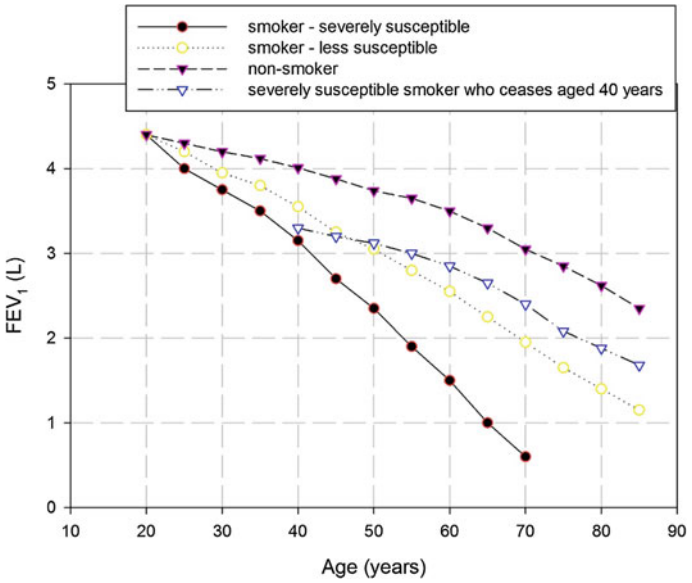

Fig. 1 Lung function deterioration based on forced expiratory volume in 1-s (FEV_1) with age in adult life

effect on this aging process, by a combination of inducing inflammation of the airway endothelium resulting in bronchoconstriction, increased mucus secretion (often becoming purulent as the result of chronic bacterial infection), and small airway remodeling associated with emphysema. These changes, referred to collectively as COPD, manifest themselves as chronic bronchitis accompanied by "smoker's cough" as the person affected attempts to clear secretions. In later stages, dyspnoea becomes a noticeable symptom as the capacity for gas exchange in the alveoli becomes increasingly impaired as the result of progressive emphysema [33]. In 2012, it was reported that approximately 15 % of U.S. adults aged 40–79 have lung obstruction, with about one-third of those having moderate or worse obstruction [34]. COPD is therefore likely to be the major respiratory disease in the older patient whose symptoms can be treatable by inhaled medications. The lowermost curve of Fig. 1 illustrates the more rapid decline in FEV_1 in the severely susceptible individual to the point at which premature death occurs, usually as the result of an acute exacerbation of symptoms brought about by a respiratory tract infection episode. The middle curve in Fig. 1 illustrates a similar but less dramatic decline in lung function for the less susceptible smoker. Importantly, giving up smoking, although not returning lung function to the nonsmoker level, results in the age-related decline becoming closer to that of a nonsmoker [35] (transition curve identified by the open triangles in Fig. 1, beginning at age 40 at which point a hypothetical individual ceases smoking altogether). It therefore follows that smoking cessation should be the highest priority in the management of COPD, augmented by topical inhaled medications where appropriate [36].

COPD may also be accompanied by asthma in some older patients [37], or asthma may be present alone [38]. In contrast with the processes associated with COPD that are irreversible, asthma generally manifests as intermittent and reversible airway obstruction caused by underlying inflammatory disease of the smooth muscles lining the airways combined with excessive mucus production [39]. The goals of therapy in the older patient with COPD are multidisciplinary with the following aims (a) treat and prevent chronic symptoms, (b) decrease emergency room and patient floor hospital visits; optimize and maintain physical activity; (c) optimize pulmonary function with minimized risk of adverse effects of medication [40]. The use of mucolytics and anticholinergic bronchodilators to clear secretions and maintain airway patency respectively is widespread, augmented by the use of antibiotics (inhaled/oral/injected) when airway infections occur to avoid exacerbations.

Asthma is a heterogeneous disease, having many different causes, including, allergic and nonallergic forms. It may arise in the older patient as late onset disease, and also in fixed airflow limitation where airway remodeling has taken place. Asthma may also be associated with obesity [41, 42]. Asthma and asthma-COPD syndrome are also likely to be widespread in the older population, and like COPD alone, is managed by the use of orally inhaled medications, except in the most serious disease states in which oral ICS and oral or injected theophylline may also be given [39, 43].

In contrast with these chronic diseases affecting the lungs, nasal conditions manageable by topically inhaled medications are relatively minor in nature; the most prevalent being allergic rhinitis (seasonal and nonseasonal forms) resulting from inflammation of the soft tissues lining the nasal cavity [44]. The symptoms are chronic nasal congestion with mucus production. Rhinitis may or may not be accompanied with polyposis, in which abnormal but benign growths arise mainly from the mucous membranes of the nose and paranasal sinuses [45]. Rhinitis with or without polyp formation is managed with ICS. Polyps can also easily be removed by endoscopic surgery, especially if they become large enough to obstruct nasal breathing significantly, and/or interfere with the sense of smell.

The Formulations

Bronchodilators and Inhaled Corticosteroids (ICS)

Currently, the vast majority of prescribed medications for inhalation via oral delivery to the older patient are indicated for the treatment of asthma and COPD. The former disease is thought to be the result of lifelong genetic atopy [10]. Asthma is often acquired in childhood, but can appear later as adult-onset disease [46, 47], and may also be associated with COPD [42]. COPD is also prevalent in the adult population as one consequence of tobacco smoking [31]. Rarer conditions treated

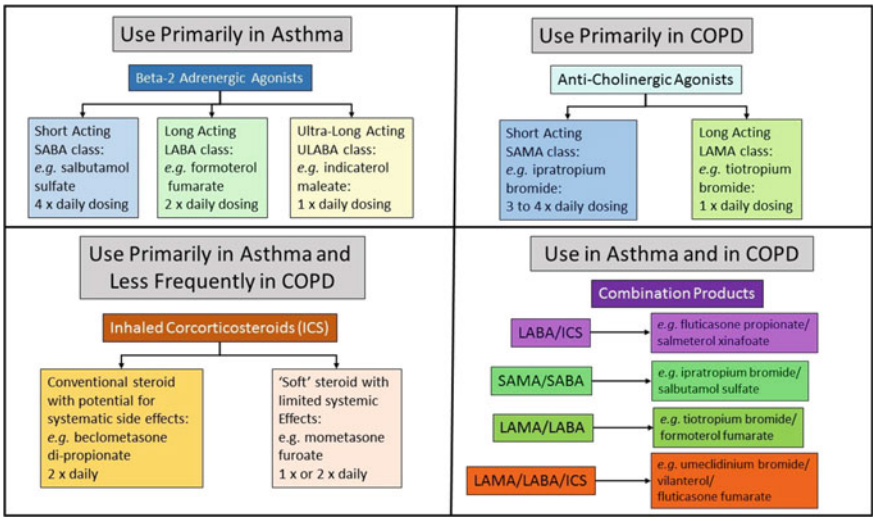

Fig. 2 Inhaled formulations to treat asthma and/or COPD: increasingly these formulations are being used in combination with longer acting APIs

orally by inhaled medications include CF and alpha-1 anti-trypsin deficiency (AAD) [14, 48]. At the present time, there are no curative drugs for any of these conditions, although gene therapy-based interventions offer some promise with AAD and CF [49, 50]. Two actions are undertaken by the principal inhaled medications in asthma and COPD (Fig. 2)

1. Brochodilatation of the constricted smooth muscle tissue lining the airways with beta-2 adrenergic agonists and anticholinergics [51];
2. anti-inflammatory action with ICS in order to control the underlying disease via interaction with the glucocorticoid receptors, also distributed throughout the lungs [51].

Opening up the airways is accomplished in asthma by stimulating the beta-2 adrenergic sympathomimetic receptors that are distributed throughout the airways. This process can be extremely rapid, taking place in a few minutes [52] and providing a conscious sensation of relief of dyspnea [53]; hence this class of drugs is therefore often referred to as "rescue" medications. In order to assist patients to recognize these medications from the so-called "controller" class, mentioned later, their mouthpiece actuators are often, but unfortunately not always, color-coded blue. Beta-2 adrenergic agonists were originally only available in short-acting (SABA) forms, initially with compounds such as isoproterenol and terbutalene, which replaced earlier compounds such as epinephrine, which had to be delivered by injection [54].

Salbutamol in either base or sulfate forms is readily available from several pharmaceutical companies nowadays in pMDI, dry powder inhaler (DPI) formats. This compound is also obtainable as ampoules for nebulization, with the API formulated in physiologically normal saline solution [55]. Adverse side effects include tremor [56] and increased pulse rate [57]. However, cardiac effects are less common with current medications in this class as their alpha and beta-1 receptor affinities are weaker than their predecessors [51]. Although rapid in action, a significant limitation has been their short-term action (i.e., 6-h), necessitating multiple treatment sessions a day, with the consequent inconvenience to the user. Therefore, in the past 10–15 years, the focus has moved to the development of longer acting drugs (the so-called long-acting beta agonist (LABA) class), examples being formoterol fumarate and salmeterol xinafoate. These days, LABAs are almost always administered as part of a combination, most usually with an ICS for asthma and COPD treatment [58] or long-acting muscarinic agonist (LAMA) solely for COPD therapy [59]. The use of combination therapy has the added advantage to the patient of avoiding the need to carry two different inhalers, a potentially important consideration for the older user with poor memory. Monotherapy with LABA alone (salmeterol xinafoate) in asthma resulted in increased mortality [60], resulting in the FDA imposing a "black box" warning on formulations containing salmeterol xinafoate and formoterol fumarate in 2005 [61]. More recently, formulators have developed so-called "ultra LABAs" (ULABAs), such as indacaterol maleate, which can be administered as infrequently as on a daily basis in the treatment of COPD [62] and asthma [63]. This drive toward daily dosing, albeit often at increased price per dose, is important in the context of treating the older patient, since it is easier to time therapy with an event that occurs each day, such as a particular meal [64]. There are also fewer opportunities to make mistakes when taking the medication, but this advantage is to some extent, offset by the potentially more serious consequences of a missed dose when a longer interval exists between successive therapies.

The anticholinergic formulations (Fig. 2) have historically been the mainstay for bronchodilatation in the context of COPD management [65]. This class of medication functions by blocking the parasympatholitic muscarinic receptor subtype M_3, preventing acetylcholine from activating the receptor, and thereby inhibiting bronchoconstriction [51]. The muscarinic receptors are also widely located in smooth muscle tissue lining the airways of the lungs, with perhaps greater density in the central rather peripheral airways [66]. The development of this class has paralleled that of the beta-2 adrenergic family, in that the first compound licensed (ipratropium bromide) was a relatively short-acting compound (SAMA), whereas the latest licensed products, such as tioptropium bromide and umeclidinium bromide, are both longer acting (LAMA) agents [67]. For many years, SAMAs have been available for administration by either pMDI or by ampoule using a nebulizer [51]. The SAMA/SABA Combivent® (Boehringer Ingelheim Ingelheim am Rhein, Germany) was one of the first combination formulations including a SAMA to be licensed, based on clinical data indicating that a synergistic effect was evident in some COPD patients when the combination was given simultaneously, rather than separately [68]. The newer single-component LAMA, tiotropium bromide, is also

available in either DPI format (Spiriva®, Boehringer Ingelheim) [69] or as a solution to be used with the Respimat® soft mist inhaler (SMI) in asthma [70] or COPD [71]. One study involving 57 patients with COPD (male:female ratio of 52:5, mean age of 73.6 ± 7.1 years) has found a patient preference for the SMI version compared with the DPI format, even though clinical efficacy of either delivery formats was determined as being equivalent [72]. Nowadays, however, the focus of formulation development for treatment of COPD is also based on the use of combination LAMA/LABA agents [59]. Examples are umeclidinium bromide/vilanterol trifenatate, (Anoro® Ellipta®; GSK plc. UK) [73], and glycopyrronium bromide/indacaterol (Breezehaler®; Novartis Pharma, Swizerland) [74]. Both of these LAMA/LABA combination formulations are currently both available only in DPI format. LAMA/LABA combinations are becoming increasingly important as first-line therapy in COPD, as it is realized that this disease may be combined with asthma in some older patients, making it advantageous to treat both classes of receptor simultaneously [43, 75].

The ICS formulations have quite different function to either of the bronchodilator inhaled medication classes, in that their pharmacological action is to suppress the inflammatory response by binding to the glucocorticoid intracellular receptors [51]. ICS medications treat the underlying disease rather than its symptoms, and they therefore commonly referred to as "controller" medications. There is a large body of clinical literature in support of ICS therapy for asthma, except in cases where the symptoms are very mild (need for SABA < twice a month, and no risk for exacerbations, including none in the past year) [76]. The use of ICS as monotherapy to treat COPD is less clear [77], since the net effect of treatment with this class of medication for such patients has been considered as being detrimental in view of the observed increased episodes of pneumonia associated with such agents [78, 79]. Despite this lack of clear evidence of a benefit, it is interesting to note that at the turn of this century, 40 to 50 percent of patients with COPD in the US were receiving ICS either alone, or in combination with a bronchodilator [80]. The situation is unlikely to have changed much since, especially as an ICS is present in several widely used combination formulations. The most likely reason for the preference for prescribing ICS in COPD is the recognition by clinicians that this disease can have an asthmatic component [43], and therefore such treatment fulfills the desire to offer the patient maximal therapy. Furthermore, there is some evidence in terms of improving long-term survival, in favor of treating COPD patients with combination ICS/LABA formulations [81].

In asthma, the time of action of ICS in terms of eliciting a discernable response in terms of improved lung function is much lengthier than that observed with the inhalation of bronchodilator-based rescue medication [82]. As a consequence, to be effective, ICS therapy needs to be sustained [83]. Although much of the evidence has thus far come from asthma therapy, it is reasonable to suppose that a similar consideration applies in the treatment of COPD, especially where an asthmatic component is present. In summary, it has to be recognized that inhaling an ICS product is not associated with an immediate relief sensation, as is the case with bronchodilators [84]. There is therefore an increased tendency for nonadherence

with a consequent increased risk of adverse events [85], most likely arising from the perception by the patient that the "medicine has had no effect" [86]. One of the drivers for the development of combination LABA/ICS products, and most recently a triple combination LAMA/LABA/ICS formulation, has been the realization that the risk of failing to take necessary ICS therapy will be reduced if the ICS component is administered at the same time as the bronchodilator, since relief of bronchoconstriction (from the LABA component) will be sensed as "the medicine has worked" [87].

Other Orally Inhaled Medications

Mucus secretion-controlling medications (mucolytics) are widely prescribed for delivery by nebulization to patients with CF [15, 88] and COPD [89]. Their role is to reduce the viscosity of the mucus plugs obstructing the airways so that they can eventually be expectorated. In the case of COPD, mucolytics do not affect the rate of lung function decline, but they do not seem to have any significant adverse effects [89]. They should therefore be considered in: (a) patients with more severe COPD who have frequent or prolonged exacerbations; (b) those who are repeatedly admitted to hospital; (c) in those patients with frequent exacerbations who are unable to take a LAMA such as tiotropium bromide or an ICS [89]. There is a role for mucolytics in the loosening and removal of secretions in COPD, particularly when they become purulent as the result of an infection causing an exacerbation of the disease. Medications falling into this category include acetylcysteine, a general purpose mucolytic. The role of mucolytics can be enhanced with mechanical aids for bronchial hygiene, particularly those that function by providing oscillating positive expiratory pressure waves (OPEP) to vibrate the airways rapidly when the patient makes a forceful exhalation [90]. While OPEP does not yet have definitively proof of superiority to other methods of airway clearance strategies, there is no clear evidence that these devices are inferior [90]. Ultimately, the correct choice may therefore be an airway clearance strategy that is cost effective, and as important, is also preferred by the patient so that adherence to therapy, which can be lengthy to be effective, can be at the very least encouraged. A variety of such OPEP devices are on the market (Table 1), offering slightly different modalities of pressure–time waveforms.

Taking the Aerobika® OPEP aid (Trudell Medical International/Monaghan Medical Corp.) as an example, this device provides a continuum of pressure oscillations that begin at low intensity at the beginning of each exhalation, rapidly reaching a maximum and then decreasing toward the end for maximum effect (Fig. 3).

There are also five flow resistance settings that can be selected, depending upon patient need for increased or decreased maximum oscillatory mechanical force. The Aerobika® OPEP device can be used in the home environment either alone by so-called "huff-coughing" during the exhalation phase of each breathing cycle

Table 1 Selected Mechanical Devices for OPEP Bronchial Hygiene Therapy

Name	Manufacturer	Comments
RC-Cornet®	R. Cegla Ltd., Eye, Suffolk, UK	See: http://www.cegla-ltd.com/; offers choice of small, continuous pressure pulses or slowly increasing pressure with rapid drop-off
aCapella®	Smiths Medical Watford, Herts, UK	See: http://www.smiths-medical.com/catalog/bronchial-hygiene/acapella/acapella.html; different units for 3 s therapy at low <15 L/min or high >15 L/min flow rate use
Aerobika®	Trudell Medical International, London, ON, Canada	See: http://www.trudellmed.com/consumer-health/aerobika-oscillating-pep; Oscillations start at the beginning of each exhalation and continue through the end for maximum effect; adjustable pressure of oscillations
Lung Flute®	Medical Acoustics LLC, Buffalo, NY, USA	See: http://www.ddmed.com/products/images/Medical%20Acoustics/Therapeutic%20Lung%20Flute%20Brochure%20-%20Final.pdf; A low frequency wave is generated at the mouth by exhaling through a mouthpiece over a laminar surface (reed) located inside the tubular device body

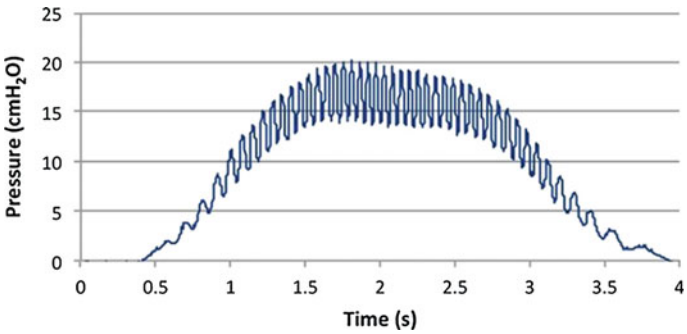

Fig. 3 Oscillating pressure waveform with Aerobika® OPEP aid continues throughout entire exhalation phase of each breathing cycle when this device is used to assist in mucous secretion clearance from the airways of the lungs (reproduced with permission from Trudell Medical International)

(Fig. 4a), or in conjunction with the AeroEclipse-XL® BAN/portable compressor (Fig. 4b), where the nebulizer supplies medication to assist bronchodilation during inhalation phase [91].

In subjects, some with COPD and others with bronchiectasis, three weeks of OPEP therapy using the Aerobika® device alone, the aid was well tolerated and there was improved dyspnoea, quality of life, exercise capacity and ease in bringing up sputum [92].

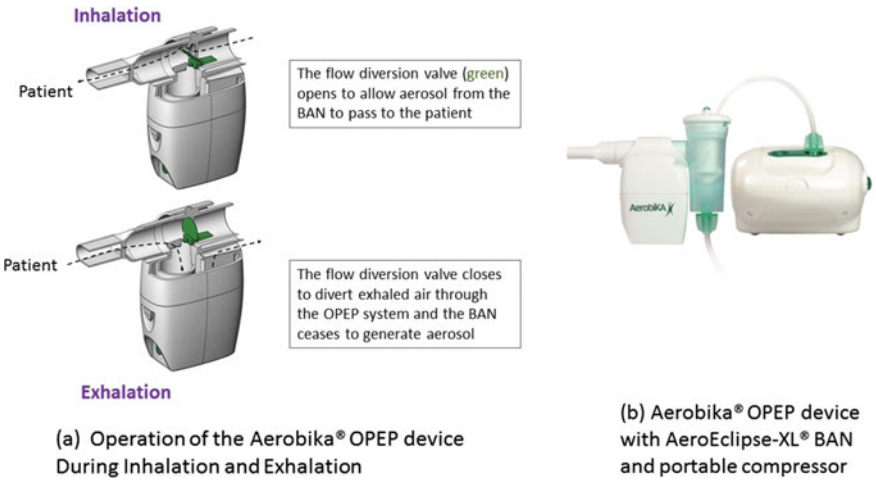

Fig. 4 Bronchial hygiene by Aerobika® oscillating positive expiratory pressure (OPEP) device is an important component in clearing mucus secretions that could otherwise impede access to the airways in subsequent bronchodilator-based therapy (reproduced with permission from Trudell Medical International). **a** Operation of the Aerobika® POEP device during inhalation and exhalation. **b** Aerobika® OPEP device with AeroEclipse-XL® BAN and portable compressor

Inhaled antibiotic medications are frequently prescribed for the treatment of infections in the lungs especially in associations with exacerbations in COPD [93]. Such medications are delivered almost always via a nebulizer, although there are a few DPI products in development to treat non-CF bronchiectasis [94]. In some instances, for example the treatment of *Pseudomonas aeruginosa* in either CF or bronchiectasis, the antibiotic is indicated for delivery by a specific inhalation device [95]. An example is the Turbospin™ DPI for the delivery of colistimethate sodium (Colomycin®) manufactured in single-dose capsules by Forest Europe Pharmaceuticals, London, UK (now part of Actavis Corp.). However, some antibiotics are licensed for delivery by more than one type of device, an example in the US marketplace being dornase alfa (Pulmozyme®) for mucus management in CF, which can be delivered via one of the following pneumatic jet nebulizers:

(a) either the LC® Jet+ or PARIBABY™ nebulizer with PRONEB® portable compressor (PARI GmbH, Germany);
(b) the durable Sidestream® nebulizer (Philips Healthcare, Netherlands), with either their Porta-Neb® portable compressor or the Mobilaire® compressor (Invacare Corp., Elyria, OH, USA);
(c) the Hudson T Up-Draft II® nebulizer (Hudson RCI-Teleflex Corp., Morrisville CT, USA) or Acorn II® nebulizer (Marquest Medical Products Inc., Englewood, CO, USA) with the Pulmo-Aide® compressor (DeVilbiss Healthcare, Somerset, PA, USA.

Pulmozyme has also recently been licensed in the US for delivery by the e-Rapid® vibrating membrane nebulizer system (PARI GmbH).

The prophylactic treatment and management of viral infections such as influenza in the elderly patient is possible by means of DPI delivery with the neuroaminidase inhibitor zanamivir (marketed as the product Relenza®; GSK plc) [96]. This API is formulated as a dry powder and packaged in four 5 mg blisters on a Rotadisk® cartridge for inhalation via the Diskhaler® DPI. Unfortunately, however, this medication is not indicated for patients with either asthma or COPD, as there is the risk of induced bronchospasm in such individuals [97]. For the many older patients with these chronic conditions there is therefore an urgent unmet need to develop other antiviral products without the potential risk of this adverse side effect.

So far all the formulations described have been indicated for topical delivery to the lungs. However, the alveolar sacs where gas exchange takes place, are heavily vascularized with capillaries, and the large surface area available (ca. 75 m^2 in the adult lungs [98]) offers the prospect of delivering inhaled medications of a size targeted to reach the distal airways [99] so that rapid uptake into the bloodstream can take place to convey the API to a distant location where therapy is desired [8, 100]. Inhaled insulin is currently the only product in this category licensed since June 2014 in the USA for the treatment of types-1 and -2 diabetes using the Afrezza® DPI (Mannkind Corp., Danbury, CT, USA) [101]. The porous insulin encapsulated microspheres have mean diameters in the range 2–3 μm [102], making them highly capable of reaching the distal lung. However, in the context of treating the older patient, it should be noted that use of this API can induce bronchospasm, and is therefore contraindicated in patients with chronic obstructive conditions, in particular asthma and COPD. It is early days to determine how popular this treatment modality will become, especially given the ready availability of needle-free pen injection systems to treat diabetes [103]. However, its arrival as a commercially available product (and its predecessor, Exubera® [104] inhaled insulin (Inhale Therapeutics, San Carlos, CA, USA) that was withdrawn for economic reasons by Pfizer Inc. in 2007), represent landmarks in that it has been demonstrated that the inhalation route is capable of being used as the gateway to reach internal organs.

Nasal Formulations

Currently, most formulations developed for the two classes of commercially available nasal delivery devices (nasal pressurized metered-dose inhaler (N-pMDI) and nasal spray pump) are ICS. These medications are indicated to relieve underlying inflammatory disease associated with allergic rhinitis (both seasonal and permanent forms of the condition) [105, 106] as well as nasal polyposis [107]. The US-licensed QNASL®40 nonaqueous nasal spray solution containing 40 μg beclometasone dipropionate per actuation (Fig. 5a; TEVA Respiratory LLC, Sellersville, PA, USA) is an example of the N-pMDI delivery approach.

In the context of delivering this class of medication to the older person, it is important to note that glaucoma, cataracts, and increased intraocular pressure may

Fig. 5 Delivery devices for inhalation via the nasal route of administration. **a** QNASL® image courtesy of teva respiratory, LLC. **b** Flonase is a registered trademark of GSK plc

be associated either with intranasal corticosteroid use [108] or with anticholinergic sprays to treat rhinorrhea [109].

Although proper insertion of the nose piece into the nostril should prevent blowback of medication droplets with the possibility of eye contact, patients with a change in vision or with a history of increased intraocular pressure, glaucoma, and/or cataracts should be closely monitored for deterioration in these symptoms.

The widely available product Flonase® aqueous nasal spray containing 50 μg fluticasone propionate (Fig. 5b; GSK plc, UK) is an example of the approach utilizing a nasal spray pump. Similar precautions to the use of an N-pMDI apply with the use of this type of actuation system. However, there is less risk of ocular exposure, since there is no propellant expansion phase and the droplets are emitted at ambient pressure in a directed stream when the user actuates the spray pump.

An antiviral medication (FluMist®, Medimmune, Gaithersburg, MD, USA) is available as a nasal spray, but is currently indicated in the USA only for children, adolescents, and adults, ages 2 through 49 years. The low upper age limit which excludes users in the age range covered by this chapter, appears to be related more to the age range of the subjects enrolled in the clinical trials required for the product registration, than by any physiological restriction related to age. However, it should be noted that patients with diabetes, heart, lung, and kidney conditions are specifically excluded, so that many older patients would likely be ineligible for this medication on the basis of their preexisting conditions.

Medication Delivery Devices

Oral Delivery by Inhalation—Overview

Table 2 illustrates the major classes of oral inhaled products that are currently available for providing therapy to the older adult. Examples of each of the oral inhaler classes are provided in Fig. 6. It should be noted that these illustrated

Table 2 The major classes of inhalers for oral administration of inhaled formulations and their suitability for the older patient

Administration route	Oral				
Inhaler class	pMDI	pMDI + VHC	DPI	SMI	Nebulizer
Suitability for the older patient	√	√√√	√	√√	√√√
Suitability via a caregiver	√√	√√√(with facemask)	√	√√	√√√(with facemask)

Notes √ = less suitable; √√ = suitable; √√√ = more suitable; pMDI = pressurized metered-dose inhaler; VHC = valved holding chamber; DPI = dry powder inhaler; SMI = soft mist inhaler [i.e., Respimat® device (Boehringer-Ingelheim)]
Nebulizer could be pneumatic jet/vibrating mesh/membrane/ultrasonic

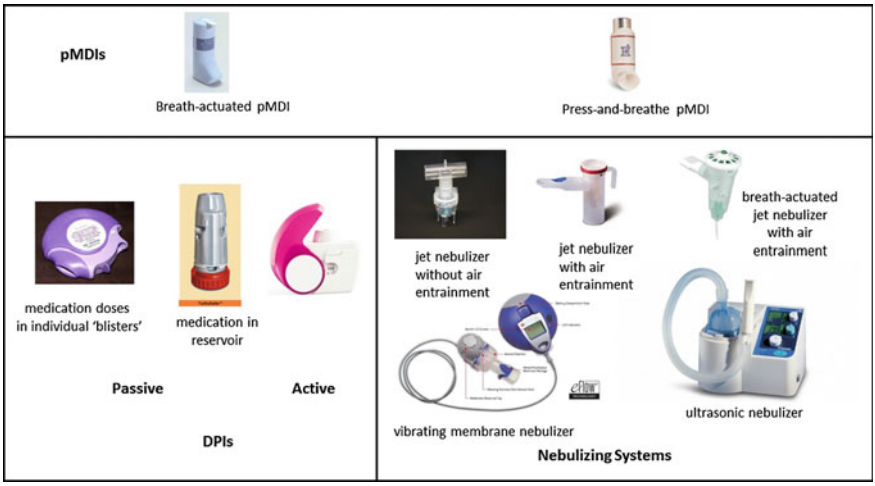

Fig. 6 Selected Examples of orally inhaled products capable of being used by the older patient

devices represent only a small fraction of the inhaled medication products that are available for use with the older patient.

The descriptions of each inhaler class that follow are not intended to provide detailed information about their operation and clinical performance; the reader can find such information in a number of authoritative reviews on the subject [110–113]. Rather the focus is on the appropriateness of the different device configurations for use by the older patient or caregiver, taking into consideration the scope for use in terms of variety of medications which are currently licensed in Europe and North America.

Pressurized Metered-Dose Inhalers and Valved Holding Chamber (VHC) Add-on Devices

pMDIs are still the widest prescribed class of inhaler in North America for the treatment of the commonly encountered chronic obstructive lung diseases, in particular asthma and COPD [114]. However, in Europe and to some extent in Canada, DPIs have become an increasingly popular choice for adults [115], and the trend is likely to continue as the result of the introduction of so-called "active" DPIs. In an active DPI, the aerosolization process is taken out of the hands of the patient by being linked either mechanically or electronically to the inhalation maneuver itself [116].

pMDIs (and the related N-pMDI class) contain their own energy source for dispersing the medication as an aerosol by virtue of the liquid propellant (these days either in the form of 134a or 227 hydrofluoroalkane) retained in the canister under pressure at room ambient conditions [117]. The canister is often supplied to the patient in a package separate from its plastic actuator mouthpiece. The patient/caregiver first inserts the canister so that the valve stem enters the receptacle provided at the base of the actuator. After preparing the inhaler for use, a process that may involve shaking the assembled unit several times as prescribed by the manufacturer, he or she cradles the assembly in one hand, with the index finger supporting the base and the thumb located in the concave distal end of the canister that projects slightly from the actuator body. The mouthpiece is located with its exit facing directly into the open mouth (open mouth technique) or with the lips sealed over this exit (closed mouth technique). During actuation, the aliquot of propellant together with one or more APIs and excipient(s) (if the latter are present) that have been retained in the metering chamber which forms part of the actuation mechanism, is exposed to ambient atmospheric pressure by movement downward past the metering valve. Whereupon the propellant rapidly flash evaporates, greatly expanding in volume [118, 119]. This process results in simultaneous dispersion of the API as discrete particles or droplets if a co-solvent, most usually ethanol, is present in small proportions in order to retain the API in solution within the canister [120]. In the latter case, the ethanol being volatile at room ambient temperature, rapidly evaporates to leave a suspension of dry particles [120]. All these processes take place within milliseconds after the inhaler is actuated. At this stage, unless the patient inhales the aerosol cloud, it will rapidly disperse due to mixing with surrounding air and to some extent gravity-induced sedimentation of the larger particles. The so-called "closed mouth" technique, whereby the patient forms a spacer-like chamber by closing the lips over the actuator mouthpiece immediately before inhaler actuation [121], is intended to present such dispersion. However, the forward momentum imparted to the particles by propellant flashing results in the largest of them (typically >10 μm diameter) impacting on the mucosal lining located at the back of the oral cavity. Such unwanted deposition can have adverse consequences, with oral thrush (candidiasis) and dysphonia being reported when ICS are inhaled as controller medication to treat underlying inflammatory disease in

asthma [122]. Use of a VHC (see below) avoids such side effects. The "open mouth" technique [121], requires that the patient inhales immediately upon inhaler actuation to avoid large loss of medication due to dispersion to the surroundings if the patient mistakenly exhales. Even if the patient inhales correctly, as with the closed mouth technique, much of the dose contained as coarser particles will deposit in the oropharynx with the undesirable side effects already mentioned. From the foregoing, it is evident that perfect coordination of pMDI actuation with inhalation is difficult to achieve even by younger adults [123], and it is self-evident that the likelihood of success in older patients diminishes with declining cognitive function [124].

It should also be borne in mind that many of the major clinical guidelines for the topical treatment of obstructive lung diseases by the inhalation route [39, 43, 47, 76] recommend that a pMDI should ideally be used with a VHC add-on device. The primary purpose of a VHC is to conserve the aerosol so that the patient does not have to time the onset of inhalation precisely with inhaler actuation [125]. The VHC also acts as a spacing device by placing the actuator orifice of the pMDI further away from the patient. Open tube spacers are also available for this purpose. However, these do not have a means of retaining the medication aerosol once emitted from the actuator of the pMDI. There is therefore the significant risk of the aerosol being dispersed if the patient either delays inhalation or worse, exhales instead of inhaling at the appropriate time. On the other hand, VHCs operate by virtue of having a one-way valve that connects the aerosol chamber to the patient interface (mouthpiece, as shown in Fig. 7a) or facemask (as illustrated by Fig. 7b) [126]. It is likely that many older users will be able to cope with a VHC with mouthpiece as the patient interface. However, if there is deterioration in manual dexterity, for example as the result of Parkinsonism, or in cognitive function as the

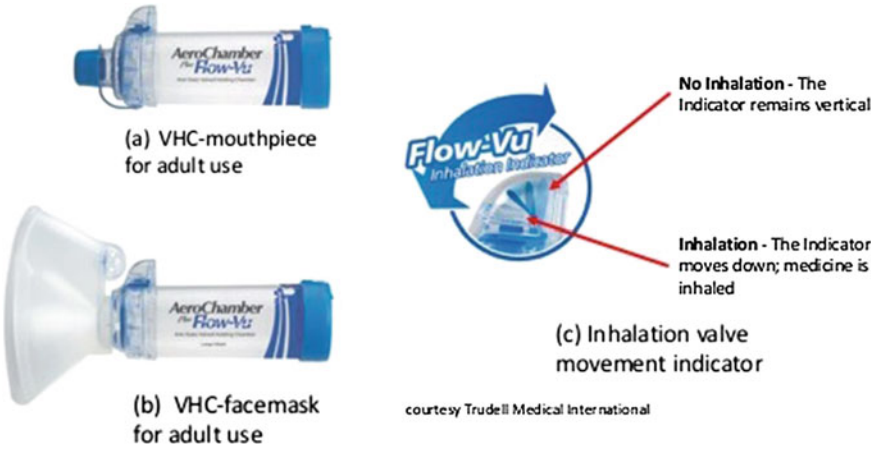

Fig. 7 VHC options and example of an inhalation valve movement indicator to provide user/caregiver knowledge when patient inhales their medication (reproduced with permission from Trudell Medical International). **a** VHC-mouthpiece for adult use. **b** VHC-facemask for adult use. **c** Inhalation valve movement indicator

result of an Alzheimer-like condition, the caregiver should consider the use of the alternative facemask as the patient interface. Some designs of VHC have a facemask option for adult use under such circumstances [127].

In use, the pMDI is attached to the distal end of the chamber after preparing both inhaler and VHC in accordance with manufacturer instructions. The patient then either closes the lips over the mouthpiece or the caregiver places the facemask over the lips and nose of the patient, and actuates the pMDI. When the patient next inhales, the valve opens and the aerosol is transferred via the patient interface to the respiratory tract. Since the VHC also removes the coarser particles from the aerosol emitted from the inhaler by impaction to the interior walls [125], the inhaled aerosol consists almost entirely of particles fine enough to pass through the naso- or oropharynx to reach the airways of the lungs where the receptors for the API are located. In this way, side effects, such as oral candidiasis and dysphonia are avoided, as are potentially undesirable side effects caused by gastrointestinal absorption of deposited API in the upper airway [128]. Surface electrostatic charges accumulated during manufacture, storage, and patient handling of VHCs produced from nonconducting materials can result in greatly reduced medication delivery. It is important to note that such behavior will not be evident to the user, regardless of their age [129]. Some manufacturers in recent years have responded by using conducting, metallic antistatic materials in the construction of VHCs [130]. However, the advent of transparent and charge dissipative polymers has restored the ability for the caregiver to see the aerosol as it is formed when the pMDI is actuated. The use of antistatic materials also avoids the need to prewash the device with mild detergent before use to minimize electrostatic charges. Washing therefore needs only to be undertaken as advised by the manufacturer as part of regular maintenance for hygienic reasons [129].

VHCs incorporating an inhalation valve movement indicator (Fig. 7c), such as is present with the AeroChamber Plus® family of VHCs (Trudell Medical International, London, ON, Canada/Monaghan Medical Corp., Plattsburgh, NY, USA) are an important consideration for medication delivery to the older patient using a facemask as interface [131]. Such an indicator provides feedback, enabling the caregiver to be sure when the patient inhales, that medication has been transferred, by knowing that the valve has opened [123]. This verification of correct function is essential, because any leakages between facemask and face may result in failure of the valve to open and the medication aerosol to enter the facemask, since pathways for ambient air ingress via leaks to the patient's face have lower flow resistance [132].

There are a number of aspects to consider in relation to the older patient receiving therapy by pMDI, when considering this relatively complex chain of events compared with swallowing a pill containing medication (Table 3):

1. Can the patient depress the thumb in the downward direction with sufficient force to actuate the inhaler [133]? There are mechanical aids to assist those with arthritic or other motor limitations in the hands, one example being the LeverHaler™ device (Birdsong Medical Inc., Cleveland Ohio, USA), illustrated

Table 3 Considerations when delivering inhaled medication by pMDI to the older person

	Consideration	Action
1	Has the patient adequate cognitive ability to coordinate actuation with inhalation?	Consider adding a VHC even with patients having excellent technique, because performance can deteriorate over time
2	Has the patient the mechanical strength to actuate the inhaler?	Consider recommending an aid to provide additional mechanical advantage, especially if the patient has arthritis
3	Can the patient use a mouthpiece to inhale?	A pMDI-VHC-facemask is the best solution for patients with limited cognitive ability or with inadequate motor control, as with Parkinsonism
4	Should the medication be given by caregiver?	Provide training for the caregiver in correct preparation of the inhaler and VHC, fitting of the facemask, and actuation of the pMDI
5	Has the pMDI a dose counter or indicator?	Consider prescribing one that has this important feedback aid. Diary cards to count doses are generally impractical for older patients
6	Is there a concern about ocular exposure?	If the patient has glaucoma, consider ensuring that anticholinergics are taken via SMI or VHC with mouthpiece/tight-fitting facemask
7	Should the experience of the patient with the inhaler be reviewed?	Yes. Training should be given before initial use to either the patient if he or she can operate the inhaler, or to the caregiver, if not. Periodic (regular) review of technique accompanied by retraining should be repeated on a regular basis, as there is strong evidence that learnings are lost over time and therefore need to be reinforced

in Fig. 8a and which is suitable for most pMDI products. A similar lever-based system called MDIEase® (Fig. 8b) was developed in 1999 by Boehringer Ingelheim Pharmaceuticals Inc., (Ridgefield, Connecticut, USA) for use with their pMDI products, Atrovent® (ipratropium bromide anticholinergic) and Combivent® (ipratropium bromide/salbutamol sulfate anticholinergic/beta-2 adrenergic agonist) which are indicated primarily for the treatment of COPD. However, the future availability of this aid may be uncertain, with the advent by this pharmaceutical company of SMI-based (Respimat®) as their mainstream alternative to pMDI therapy.

2. Can the patient coordinate the onset of inhalation with inhaler actuation [134]? This consideration assumes that he or she is not already using the preferred method of aerosol delivery via a VHC already described under such circumstances, otherwise much of the aerosolized medication will be lost due to dispersion and mixing with the surrounding air, even if the patient breath-holds for less than a fraction of a second. Furthermore, if he or she exhales, the dispersion process will be worsened, as described previously when an open tube spacer is used. Realistically, the most likely scenario is that perfect timing cannot be reliably achieved, but if there is any doubt, the degree of patient coordination can readily be

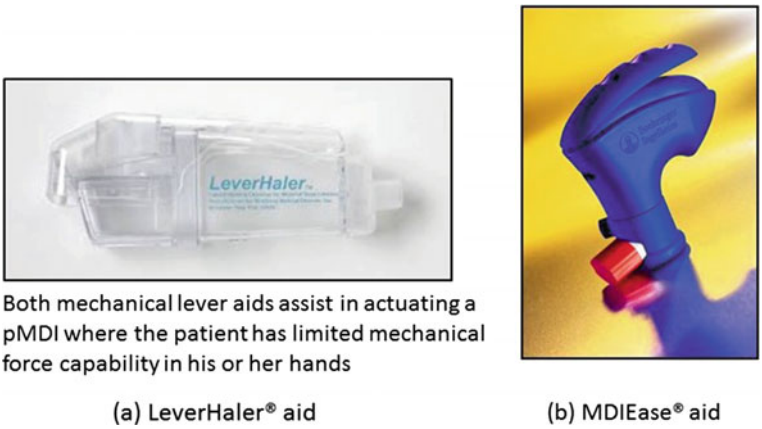

Fig. 8 Selected Mechanical aids for pMDI operation; **a** image courtesy of Birdsong Medical Inc and **b** image courtesy of Boehringer Ingelheim Pharmaceuticals Inc.

checked using a standardized procedure making use of video-recorded demonstrations of their method [135]. Nevertheless, there is ample evidence that perfect inhaler coordination, even after training, is difficult to achieve, and that typically patients rapidly regress to poor technique [123, 136]. On the other hand, if a high quality VHC is used, the aerosol formed at actuation of the inhaler will be retained for sufficient time (up to 10 s or more) for the fine particle portion of dose to be inhaled eventually. Under these circumstances, almost all of the fine particle dose is able to reach the receptors in the airways of the lungs associated with airway opening and moderation of underlying inflammatory disease. When selecting a VHC (and there are many devices that are claimed by their manufacturers as being suitable with all types of pMDI), there are some further considerations specifically for the older patient that ought to be taken into account [137]:

(a) Does the patient have the ability to use a mouthpiece by himself or herself, or should the medication be delivered by facemask with the help of a caregiver?
(b) In the latter case, is there a visual aid that tells the caregiver when the patient has inhaled and the valve of the VHC has opened to allow the aerosol to be inhaled?
(c) Are the instructions for use sufficiently clear that the patient/caregiver, who may have poor vision, can read and understand them (pictograms can be very helpful to achieve this goal)

3. Is the pMDI almost empty or empty of medication? Most currently marketed inhalers in the US marketplace come equipped with a dose counter or indicator, following guidance issued by the FDA to this effect [138]. Regrettably, this clarity of regulatory guidance is less explicit for Europe. However, there is increasing acceptance by manufacturers of the need for such an indicator to be

provided as a patient-feedback aid with newer launched pMDI products. In the case of the older patient, the caregiver should make certain that the prescription for the pMDI-delivered medication is refilled well in advance of being fully consumed to avoid the potential for a lack of rescue bronchodilator medication in the event of a sudden exacerbation of asthma and/or COPD. It is also important to note that the once common practice of dropping the canister into a bowl of water to check if it floats as a sign that it is near to empty or empty, is to be discouraged because it is inaccurate. There is also the risk of water ingress into the canister with consequent deterioration of the formulation contained therein [139].

4. Finally, the avoidance of ocular exposure to anticholinergic medications used extensively in therapy for COPD and related conditions would be a wise precaution, even though the link between pMDI therapy and this condition is uncertain [140, 141]. Clearly, the "open mouth" technique using the pMDI alone is inadvisable under these circumstances because the aerosol plume is unconfined and can be exhaled into the eyes. Here, the use of a VHC-mouthpiece to deliver the anticholinergic therapy could be advantageous, in addition to the benefits already described for this type of add-on device. Care will be needed to ensure that the seal to the face is airtight before inhaler actuation as described above, if a facemask is present. The facemask should be left in place until all the medication has been inhaled, so that an indicator to visualize inhalation valve movement would also be useful to assist the caregiver in this respect [131].

Dry Powder Inhalers

DPIs as an inhaler class are far more diverse in construction and operation than pMDIs (Fig. 9) [141–146], making it difficult to generalize when exploring issues of pertinence for the older patient. Importantly, though, all DPIs marketed in Europe and North America have some form of dose counter to provide the patient or caregiver with information needed to time refilling of the prescription before the inhaler is exhausted. Each manufacturer, in an endeavor to retain proprietary rights through patent protection, has evolved their own solution to the basic processes of (a) storing the medication in powder form before use; (b) inserting it into the delivery device; (c) operating the device to disperse the powder; (d) deliver the resulting aerosol as fine particles to the lungs of the patient as efficiently as possible.

DPIs can be primarily classified as either having bulk powder storage in a reservoir (i.e., Turbuhaler®, AstraZeneca, Sweden) or operating with individual doses of medication. In the latter situation, these DPIs can be subclassified into those in which the powder is either stored in separate capsules (i.e., HandiHaler®, Boehringer-Ingelheim, Germany) or in separate blisters in a strip whose components can be mechanically separated to expose the dose in each blister immediately before use (i.e., Diskus®, Ellipta®, GlaxoSmithKline, UK). If the medication is

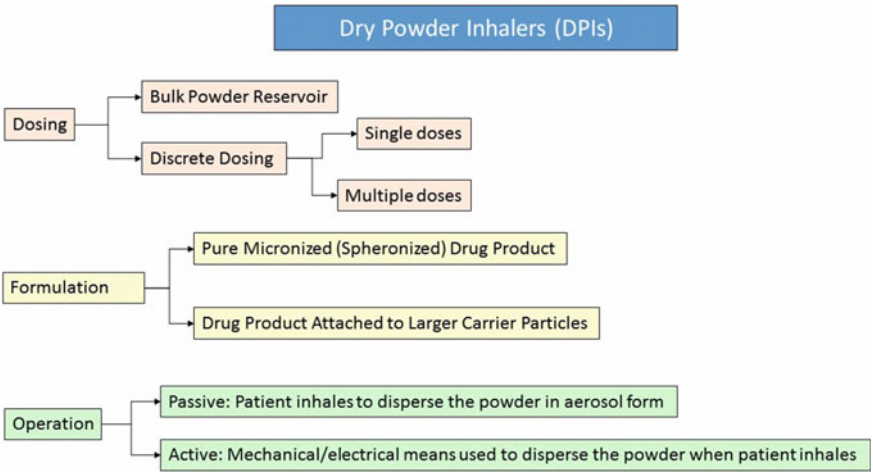

Fig. 9 Taxonomy of DPI systems; their dosing, formulation types, and operation

retained in capsules, then each is loaded individually (i.e., as with the HandiHaler® DPI, Boehringer-Ingelheim, Germany; Twister®, Aptar Pharma, France; Rotahaler®, GlaxoSmithKline, UK). Other DPI designs have proprietary cartridges containing multiple doses that are used one at a time [i.e., Novolizer® inhaler, Allmirall-Sofotec Pharma, Germany (now part of AstraZeneca)]. The medication-containing powders themselves may be fabricated as pure drug substance in the form of microspheres in the optimum size range close to 5 μm diameter, as is the case for formulations used with the Turbuhaler® DPI [146]. More commonly, however, significantly larger carrier particles (typically "tomahawk"-shaped crystals of lactose), to which the drug particles are bonded by van der Waals forces, are used in DPI formulations [146]. The action of inhaling generates airflow that lofts the carrier crystals, and at the same time shear in the airflow velocity profile in the immediate vicinity of each particle provides the energy that detaches the micron-sized drug particles from the carrier crystals. Inhaled lactose is sensed as a sweet taste by some users, but has no physiological action in connection with lung disease mitigation.

Although this class of inhaler is popular, before prescribing a DPI to an older patient or their caregiver, it behooves the clinician to consider several issues related to their effective use [134] (Table 4)

1. Can the patient develop enough power to provide the airflow necessary to disperse the powder as the manufacturer intended? DPIs have a wide range of flow resistance, from the high resistance associated with the HandiHaler® at ($0.049\ kPa^{0.5}/(l\ min^{-1})$) to the low resistance of the Cyclohaler® (TEVA, Netherlands) at $0.0189\ kPa^{0.5}/(l\ min^{-1})$, as examples. In the case of a low resistance DPI, de-aggregation and the resulting dispersion of the drug are both highly dependent upon the inhalation flow rate profile achieved by the patient,

Table 4 considerations when delivering inhaled medication by DPI to the older person

	Consideration	Action
1	Has the patient adequate cognitive ability to coordinate actuation with a strong inhalation?	Consider the patient for therapy by pMDI-VHC or nebulizer if not. A firm inhalation maneuver is essential if the powdered formulation is to be dispersed properly and detached from carrier crystals, if present
2	Can the patient use a mouthpiece to inhale?	Consider the patient for therapy by pMDI-VHC or nebulizer if not. DPIs in general, are not supplied with a facemask, as the user is expected to couple their inhalation flow to the mouthpiece of the device to provide the energy needed to disperse the powder as an effective aerosol
3	Has the patient adequate manual dexterity to open single-dose packages for DPI use?	If not, consider a multi-dose DPI with integral dosing, where the need to manipulate single doses is avoided altogether
4	Should the medication be given by caregiver?	In the event that the patient has arthritis in the hands, but can otherwise coordinate the actuation/inhalation process, provide training for the caregiver in correct preparation of the inhaler. focusing on timing actuation of the inhaler with inhalation
5	Is the operation of the inhaler intuitive?	If a patient is used to a particular DPI, it is probably best for him or her to remain with it, provided they demonstrate correct operation. In the case of a first time user, consider inhalers where the instructions for use are simple, clear and require the least opportunity for mistakes
6	Is there a concern about ocular exposure?	If the patient has glaucoma, consider ensuring that anticholinergics are taken via either SMI or pMDI-VHC with mouthpiece or tight-fitting facemask
7	Should the experience of the patient with the inhaler be reviewed?	Yes. Training should be given before initial use to either the patient if he or she can operate the inhaler, or to the caregiver, if not. Periodic (regular) review of technique accompanied by retraining should be repeated on a regular basis, as there is strong evidence that learnings are lost over time and therefore need to be reinforced

because the role of resistance-induced turbulence as an agent for both processes is relatively unimportant [145]. It follows that with medium or high resistance DPIs, the dependency of these aerosol formation processes on patient flow rate is reduced by the presence of significant turbulence as part of the flow characteristics of such devices. Under such circumstances, medication delivery is likely to

be relatively unaffected even if the patient is unable to achieve the required peak inspiratory flow rate (PIFR) [145]. However, when considering the special needs of the older patient, if severe obstructive disease is present, combined with poor tone of the muscles involved with inhalation, the individual may not be capable of generating an adequate PIFR in the short time available (at most a few seconds) per inhalation even with such a DPI [134, 147]. Under such circumstances, a lower than ideal inspiratory effort may therefore result in insufficient drug deposition in the lung and excessive deposition in the oropharynx [148]. This adverse outcome may lead to the unpleasant sensation of mouth dryness and in consequence adversely affect medication adherence [134]. Under such circumstances, therapy by either pMDI or nebulizer should be considered.

2. Can the patient use a mouthpiece? Currently available DPIs are intended for patients who can use this form of interface, largely because it is less easy to focus the inhalation flow rate via a facemask to provide the necessary force to disperse and deliver the aerosol cloud efficiently. Unusually, however, several years ago Bisgaard described a prototype device for automatically actuating a Turbuhaler® DPI (Astra Zeneca, Mohlndahl, Sweden) into a non-electrostatic VHC of his own design from which the patient inhales via a facemask [149]. Although developed for pediatric use, such an aid could, in principle, be fitted with an adult-sized facemask. Realistically, however, its relative complexity compared with the more conventional pMDI-VHC use is unlikely to lead to commercialization in the foreseeable future. Furthermore, the use of a mouthpiece rather than a facemask has the advantage that ocular exposure to anticholinergic-containing aerosols, with consequent risk of glaucoma, can be avoided. If the patient needs to use a facemask, it therefore follows that an alternative inhaler class should be sought, either in the pMDI + VHC or nebulizer group, even if this situation means a further search is needed to find the most suitable drug product or combination of drug products to treat their condition.
3. Does the inhaler require a degree of manual dexterity to load the medication into the DPI? Opening a blister pack that contains the medication capsules is reported as one of the most difficult aspects of DPI use for elderly patients [146]. This consideration is especially important with single capsule designs that have to be maneuvered into the correct location for the inhaler to operate correctly. It should go without saying, but when using a single-dose design of DPI, the patient should be capable of knowing that the capsule containing the medication is intended for inhalation and not ingestion orally [150]. However, it can be difficult to distinguish DPI capsules from those intended for oral delivery of medication by the gastrointestinal route. This is one advantage of multi-dose DPIs, such as the Diskus® and Ellipta® inhalers (GSK Plc), in which the powder blisters are integral within the inhaler and do not have to be loaded individually by the patient.
4. Is the operation of the inhaler intuitive, or does the patient require skill at understanding a series of instructions both to prepare and maintain the inhaler. Taking the Turbuhaler® device as an example and not as the only DPI associated

with user handling errors [136], its operation can be bewildering, particularly to the new user. Common mistakes when using this particular inhaler have been reported as including failure to turn the base fully in both directions and failure to keep the device upright until loaded [151]. The patient can also easily forget which direction to twist the reservoir to load a dose and then remember to return it to its initial condition in preparation for the next dose delivery.

5. Has the patient the cognitive ability to remember to inhale as instructed? It is notable that in assessments of patient errors with this class of inhaler, exhalation instead of inhalation has been reported as being a common mistake [151]. Careful instruction may help [152]. However, if the cognitive ability of the patient is limited, it is likely that he or she will receive more benefit from nebulizer therapy [134] (see below), where tidal breathing is all that is required to receive the medication efficaciously.

There are currently no restrictions on the prescribing of a DPI-based formulation to an older patient with asthma, COPD or a combination of both, except when clearly contraindicated for a particular drug class because of the risk of adverse side effects. However, it is good clinical practice to undertake pulmonary function testing (spirometry) [153] at the start of treatment to establish capability through measures such as FEV_1 and peak inspiratory flow rate, following the appropriate guidelines on management of bronchoconstrictive disease [39, 43, 47, 76]. Such testing with equipment in the physician's office should be repeated at regular intervals, thereby taking into account the very real prospect that pulmonary function is declining with time [154], even with adherence to the prescribed therapy, this being the most likely scenario with COPD progression being associated with acute exacerbation phases of increasing severity [155].

Soft Mist Inhaler (SMI)

Currently the Respimat® SMI developed by Boehringer Ingelheim Pharma GmbH & Co. KG (Ingelheim-am-Rhein, Germany) is the only device in this inhaler class (Fig. 10a) [156]. It is a hybrid between a pMDI, which it resembles both in its appearance and in the way it is used, and a nebulizer, because it emits a low-velocity mist droplets containing the single or combination of APIs in aqueous solution. Upon actuation, this device forces the liquid medication through narrow orifices located in the proprietary Uniblock unit such that the merging streams collide. The Uniblock itself consists of a filter structure that includes two very fine outlet channels, built on a silicon wafer. Approximately 1000 identical micrometer-sized circular nozzles are produced simultaneously with high precision to complete its construction. The nozzle is optimized to produce a high proportion of the dose as fine particles <5.8 μm in aerodynamic diameter by the time that the medication reaches the oropharynx of the patient following a slow inhalation. The manufacturer

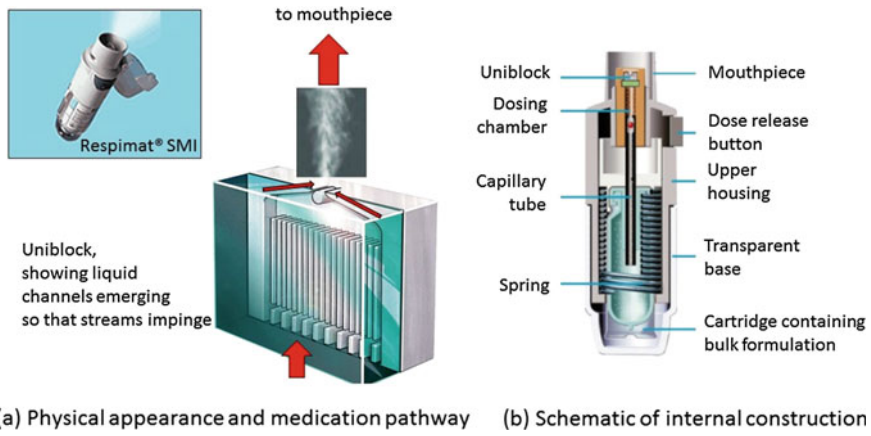

Fig. 10 Respimat®, a registered trademark of Boehringer Ingelheim Pharmaceuticals, Inc., SMI Showing Uniblock liquid feed arrangement to create aerosol containing medication in aqueous droplets moving with low-velocity profile at point of inhalation. **a** Physical appearance and mediation pathway. **b** Schematic of internal construction

claims that between 50 and 60 % of the medication inhaled reaches receptors located in the airways of the lungs. This compares with only about 30 % for most press-and-breathe pMDIs. In consequence, Brand et al. have observed using gamma scintigraphic analysis of radiolabelled aerosols inhaled via either Respimat SMI or press-and-breathe pMDI, that the former provides higher lung deposition in COPD patients with poor inhaler technique [157]; a factor of potential importance for the older user. However, despite these measurements of enhanced particle deposition, the evidence for improved clinical outcomes compared with other inhalers is less clear, at least in COPD [158].

The avoidance of eye contact with the emitted droplets with consequent risk of enhancing narrow angle glaucoma, is an important advantage of the SMI compared with nebulizing systems that are often used to deliver anticholinergics via a face-mask to the older patient with COPD and related conditions.

Although this SMI shares the dose-metering characteristics of pMDIs, it does not require propellant to create and disperse the aerosol cloud, and therefore it is unnecessary to use an add-on device such as a VHC to reduce droplet velocities. This inhaler is important when considering the options for delivering inhaled medications to the older patient because it is the vehicle that has been chosen to deliver tiotropium bromide (Spiriva®), one of the new generation of long-acting muscarinic agonists (LAMAs) for the relief of bronchoconstriction associated with COPD [159]. The Respimat® SMI has also been developed to deliver the two-component combination product, Combivent® [160], which contains the older short-acting anticholinergic (SAMA), ipratropium bromide, together with salbutamol sulfate as the short-acting beta-2 adrenergic agonist (SABA) component for COPD therapy, and has replaced the original pMDI-based formulation of the same name [161]. The number of products delivered using this SMI has recently

Table 5 Considerations when delivering inhaled medication by SMI to the older person

	Consideration	Action
1	Has the patient adequate cognitive ability and manual dexterity to operate the inhaler correctly?	Consider caregiver training and support if not. Otherwise, the patient may be better treated either by pMDI-VHC-facemask or nebulizer
2	Can the patient use a mouthpiece to inhale?	Consider the patient for therapy by pMDI-VHC or nebulizer if not. Currently, the Respimat® SMI does not come equipped with an adult-sized facemask
3	Should the experience of the patient with the inhaler be reviewed?	Yes. Training should be given before initial use to either the patient if he or she can operate the inhaler, or to the caregiver, if not. Periodic (regular) review of technique accompanied by retraining should be repeated on a regular basis, as there is strong evidence that learnings are lost over time and therefore need to be reinforced

increased to include a new LABA, olodaterol as the product Striverdi® Respimat® [162], further improving the options to treat acute exacerbations of COPD, including chronic bronchitis and/or emphysema.

Care is needed to ensure that the older patient or caregiver has both the cognitive and manipulative ability to prepare and operate the SMI correctly (Table 5), as with other inhaler classes already mentioned. A 180° twist of the device base is first needed to compress the spring (Fig. 10b), thereby drawing a metered dose of drug solution through the capillary tube to the dosing chamber. Operation of this mechanism requires a degree of manual dexterity, as the spring itself requires significant force to complete its compression to the "ready-for-use" position. However, once this operation has been completed, depressing the dose release button located at the side of the inhaler is a comparatively easy procedure, so that the power stored in the compressed spring moves the capillary tube into the dosing chamber to release the medication cloud as a low-velocity aerosol from the mouthpiece.

The lack of an option to deliver the medication via an adult-sized facemask might preclude prescribing this inhaler to the patient requiring this form of interface. However, the manufacturer has recently been exploring the use of a facemask interface via a VHC for pediatric use [163], so there may be the prospect for an adult version to be available in the future. For the time being, though, in the case where the patient is incapable of using this interface, the caregiver will need first to prepare the inhaler, second to insert the mouthpiece between the lips of the patient and finally, time actuation to the onset of inhalation by carefully observing the tidal breathing of the patient.

Nebulizer Systems

Nebulizers are a common way to deliver inhaled therapy to the older population requiring such medication, largely because the traditional pneumatic devices are low cost, and some of the formulations used to treat chronic obstructive lung diseases are only available for delivery by this route [164]. The solutions or suspensions containing one or more APIs for nebulization are usually packaged in single-dose disposable containers (e.g., glass vials or blow-fill-sealed (BFS) ampoules) to preserve sterility without the use of potentially toxic preservatives that would be probably required for repeated use of containers for multi-dose aqueous formulations [165]. The physiological benefits in terms of inhaled therapy outcomes of pMDIs and the older pneumatic nebulizers are virtually equivalent [166, 167], so the choice of device is often based on clinician and/or patient preference, rather than clear superiority of one approach over the other form of therapy. Nebulizers, like pMDI-VHC combinations are available with either a mouthpiece or facemask as patient interface. Overall, this class of oral inhaled medication delivery device has the widest array of formulations available, for example [51]:

1. beta-2 adrenergic agonists and anticholinergic bronchodilators are used to treat chronic obstructive lung diseases;
2. corticosteroids have a central role in the management of underlying inflammatory disease in asthma, and more controversially in COPD;
3. antibiotics and mucolytic agents are therapies for cystic fibrosis and bronchiectasis;
4. pulmonary vasodilators are used to manage pulmonary hypertension;
5. there is the prospect that older patients with non-respiratory diseases may benefit from systemic aerosol delivery of drugs, for example opiates for the relief of breakthrough pain in cancer.

In contrast with the previously described inhaler classes that deliver each dose as a bolus during one inhalation taking a second or two, the more commonly used small volume nebulizer can deliver several mL of the formulation to the tidally breathing patient during a treatment period which can typically last for 5–20 min [164]. Larger volume nebulizers which can contain as much as 240-mL of formulation as in the HEART® (High Output Extended Aerosol Respiratory Therapy) nebulizer (Westmed Inc., Tucson, AZ, USA) are used, particularly in the USA, to deliver bronchodilator medication for extended periods (several hours at a time) in the treatment of severe asthma exacerbations in the hospital emergency room situation [168, 169]. McPeck et al. [170] have shown that medication delivery to the patient, expressed as inhaled mass over time, is similar for large volume nebulization (HEART system) compared with intermittently filled small volume pneumatic nebulizers of the type described next in this chapter. Large volume nebulizer use permits the redistribution of healthcare personnel and may therefore reduce the costs of therapy in this particular intensive setting [170].

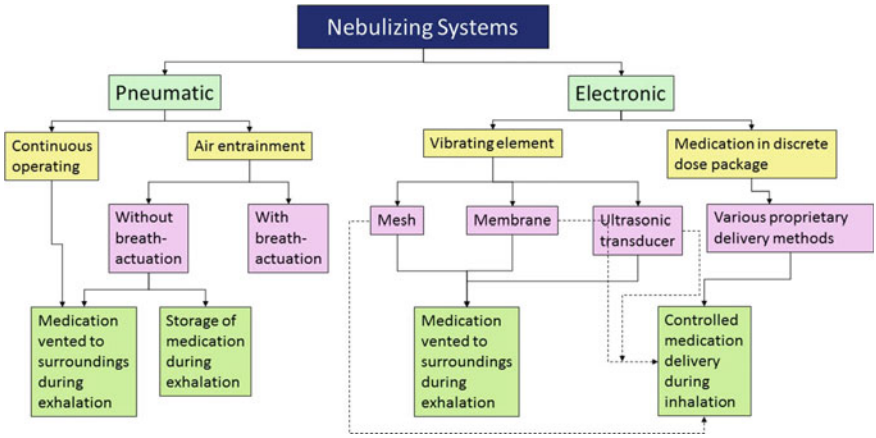

Fig. 11 The various types of nebulizing system can be divided into two major classes, pneumatically operated and electronically operated devices

There are two major subcategories of nebulizers (Fig. 11); those termed pneumatic because they require a compressed gas supply, usually air or medical grade oxygen, to operate [164], and electronically operated systems of various types, including ultrasonic- and vibrating mesh/membrane-based devices [164, 171]. The electronic nebulizer categories operate with their own in-built power source and are therefore more expensive than pneumatic nebulizers. However, they can be more readily adapted as custom devices for the delivery of particular medications, based on both clinical requirements (dosing, etc.) and the delivered droplet size distribution that it is desired the patient receives [172]. In general, vibrating mesh/membrane nebulizers are more efficient than most jet nebulizers and can therefore potentially provide higher drug doses to patients [171].

Pneumatic nebulizers can be further subdivided into continuous, breath enhanced, medication conserving (reservoir) and fully breath-actuated designs [164]. Continuous devices, as their name implies, deliver the medication at a constant rate, irrespective of whether the patient is inhaling or exhaling (Fig. 12a). The Airlife® Misty-Fast™ device (CareFusion Inc., San Diego, CA, USA) is an example in this category. Breath-enhanced nebulizers increase the medication output by drawing the inhaled airflow through a venturi to create a pressure drop in the vicinity where the medication liquid is atomized into an aerosol (Fig. 12b). An example of this type of nebulizer is the LC-Plus®device (PARI GmbH, Starnberg, Germany). Medication-conserving nebulizer systems have a means of storing the aerosol created from a continuous nebulizer during the exhalation phase of each breathing cycle, ready for the next inhalation (Fig. 12c). This can be as simple as a reservoir bag and one-way valve in the mouthpiece connector to direct the aerosol either to the bag or patient; apart from their relative complexity, medication is inevitably lost to the walls of the bag by processes such as inertial impaction and gravitational sedimentation.

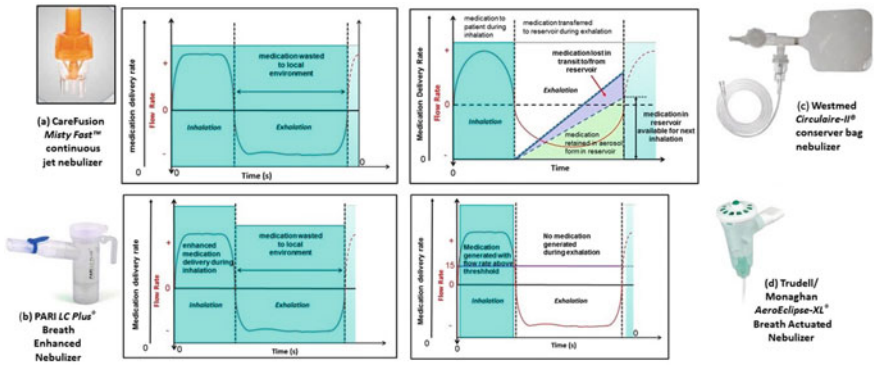

Fig. 12 The four types of pneumatic nebulizer and their function with use, showing an idealized adult tidal breathing pattern having inspiratory/expiratory time ratio of 1:2; **a** image courtesy of Becton-Dickinson & Co., **b** image courtesy of PARI Respiratory Inc., **c** image courtesy of Westmed Inc., **d** image courtesy of Trudell Medical International

The Circulaire-II® nebulizer (Westmed, Tucson, AZ, USA) is an example device in this category. Although conserving the aerosol during the exhalation phase of each breathing cycle would at first sight appear to improve overall medication delivery efficiency, Rau observed the lowest output from this type of device in an in vitro comparison of the different types of pneumatic nebulizer for the delivery of a widely prescribed salbutamol (albuterol) SABA solution. He speculated that losses of medication to the walls of the conserver bag may be the underlying cause [173]. Finally, the fully breath-actuated nebulizer (BAN) has the attributes of a breath-enhanced nebulizer, but also contains a mechanism that allows atomization of the liquid medication only when the patient inhales with the flow rate in excess of a well-defined limit (Fig. 12d). The AeroEclipse-II® BAN (Trudell Medical International, London, ON, Canada/Monaghan Medical Corporation, Plattsburgh, NY, USA) is currently the only device in this class. A BAN avoids medication wastage as well as preventing contamination of the local environment [111, 174]. In the just referred to comparison undertaken by Rau [173], the BAN delivered the most medication, but took slightly longer to do so than the other classes of device, because the solution was conserved during exhalation phases. However, in a more recent in vitro study comparing the BAN with breath-actuated nebulizers and simulating breathing patterns associated with COPD, the medication conserved in the BAN remained available in the liquid reservoir for aerosolization during subsequent inhalation phases [175], an attribute that could be important when nebulizing relatively expensive drug products.

Electronic nebulizers are also available in several formats based on the method of aerosol generation [172]. These include vibrating mesh, membrane, and ultrasonic systems, with the option for even more sophisticated forms of aerosol delivery using proprietary technology to release the aerosol droplets from blister packaging

containing a unit dose of medication [176]. A product in this class is in development for the delivery of nicotine as a smoking cessation aid [177]. This development is highly pertinent in the support of the significant number of patients with COPD but who have not yet terminated the smoking habit [178].

The commercialization of a specially designed version of the vibrating membrane nebulizer (eFlow CS, PARI GmbH, Starnberg Germany) for the older patient at home is also an important advance, as it marks the recognition that this population find it difficult to load conventional nebulizers with ampoules containing the medication, as well as to cope with connecting up the equipment to the compressor and routine maintenance. Using a human factors approach, as advocated in guidance by the FDA [179], the following features were introduced [180]

(a) an improved ampoule that can only be inserted into the nebulizer in one way
(b) an enlarged and simplified medication cap that reduces the ampoule opening torque and provides a better grip for the user to manipulate when loading the medication after for cleaning after use;
(c) a sideways nebulizer access opening for improved aerosol-head assembly for cleaning;
(d) a more robust interface for the connection cord adapter to the compressor unit.

As with pneumatic devices, the patient typically inhales the medication directly from a vibrating mesh/membrane nebulizer using either a mouthpiece or facemask by tidal breathing rather than with a forced maneuver such as a long, slow inhalation. The advantages of electronic systems are (a) reduced wastage of medication left behind in the reservoir associated with pneumatic devices; (b) the possibility of controlling medication delivery to take place during a predetermined part of the inhalation portion of the breathing cycle [172]. However, ultrasonic nebulizers cannot be used to deliver suspension formulations containing micron-sized particles efficiently, since the solid drug-containing particles are not readily entrained in the only slightly larger aqueous droplets generated by such devices [181, 182]. Plugging of vibrating mesh/membrane nebulizers by the largest suspended particles in some such formulations may also be an issue. Another drawback is the relatively high cost of electronic systems compared with pneumatic nebulizers; this consideration can be important for the older patient who is either on a limited income or without medical insurance, remembering that a home compressor need only be purchased once even if the nebulizer is replaced on a regular (i.e., monthly) basis.

The most expensive, nebulizing systems make use of microprocessor technology first to "learn" the tidal breathing pattern of the patient and then to time medication delivery to coincide with the optimum portion of the inhalation flow profile [183]. One system available in Europe (APIXNEB®, Vectura plc, Gemünden/Wohra, Germany), can even take over the breathing of the patient in order to optimize fully the timing and therefore the lung deposition profile of the inhaled medication delivered from a vibrating mesh electronic nebulizer [184]. Despite the variety of nebulizing systems that are available or in the pipeline, their common denominator

is their capability to generate aqueous-based aerosols containing one or more APIs. However, the likelihood of such sophisticated devices coming into general use is unlikely in the foreseeable future, because of their relatively high cost compared with more conventional nebulizers. Nevertheless, where the cost is affordable, the possibility of combining such systems with telemedicine in order for the prescribing physician to assess both adherence and the disease state of patients remotely in their homes, has the potential to become more important [185]. Nevertheless, the relevance of such an advance for the management of the older patient is self-evident, given that the need for travel to the clinical facility for periodic assessment would be greatly reduced [186].

Despite evidence that other forms of inhaled aerosol therapy (principally pMDI/VHC) are less demanding upon resources [187], nebulizers are widely used as the first-line device for delivering micrometer-sized inhaled medications to the airways of the lungs of patients in the hospital environment, both in the emergency room and on the in-patient floors [188]. Under these circumstances, the pneumatic devices are normally intended for single patient, single use as disposable items, and are operated with air or medical oxygen supplied at relatively high pressure (usually 50 psig, 345 kPa). Helium–oxygen mixtures (Heliox) are also used in the intensive care setting in conjunction with nebulizer-based inhaled therapy for bronchodilator therapy, because the lower density of such gas mixtures compared with the density of air or oxygen improves the transport and deposition efficiency of the aerosolized medication particles in the airways of the lungs [189]. In contrast, in the home environment where compressed gases (whether air, oxygen or Heliox) are usually unavailable, pneumatic nebulizers are typically operated with compressed air delivered by means of either a portable or table-top compressor [164]. It should be noted that the reduced operating pressures associated with portable compressors [typically in the range 20–30 psig (138–207 kPa) compared with hospital-supplied compressed air or oxygen delivered at 50 psig (345 kPa)], will likely result in an inhaled aerosol that comprises coarser droplets [164], unless the nebulizer design has been optimized for home compressor use [190]. Generally, nebulizers indicated for home-based therapy are reusable by the patient for which they have been prescribed.

Although many of the medications deliverable by the other oral inhaler formats can be inhaled from any nebulizer, there are some drug products that have been registered for use with a named device. An example is the use of the Respigard-II® pneumatic nebulizer (CareFusion Inc., Colorado, USA) as the recommended device for the delivery of pentamidine isethionate, an antimicrobial agent effective in the treatment of *pneumocystis carinii* pneumonia in patients with acquired immunodeficiency syndrome (AIDS) [191]. This nebulizer is constructed with one-way valves and filters to present contamination of the ambient environment with the aerosolized potent medication [164].

The disadvantages cited for nebulizers in the literature are not ones of patient use but rather the need for daily cleaning and longer time required for drug administration compared with other treatment modalities [134]. However, there are several

Table 6 Considerations when delivering inhaled medication by nebulizer to the older person

	Consideration	Action
1	Is there a concern about ocular exposure?	If the patient has glaucoma, consider ensuring that anticholinergics are taken via SMI or pMDI-VHC with mouthpiece or tight-fitting facemask
2	Has the patient adequate cognitive ability and manual dexterity to operate the inhaler correctly?	Consider caregiver training and support if not
3	Can the patient use a mouthpiece to inhale?	Consider the use of a facemask if not. However, be mindful of possible exacerbation of glaucoma with anticholinergics (see (1) above)
4	Does the medication require a specific nebulizer(s) for delivery	If so, choose either that nebulizer or one of the choices available. Medication delivery efficiency could be compromised if another nebulizer is used
5	Is the medication expensive?	Consider a breath-actuated pneumatic nebulizer or a vibrating mesh/membrane device, remembering that the latter are more expensive and may not disperse medications formulated as suspensions efficiently. Breath-actuated nebulizers do not waste medication if the patient removes the mouthpiece/facemask during therapy
6	Should the experience of the patient with the nebulizer-compressor system to be used in the home setting be reviewed?	Yes. Training should be given before initial use to either the patient if he or she can operate the inhaler, or to the caregiver, if not. This training should include cleaning and maintenance of the nebulizer to ensure continued hygienic operation. Period (regular) review of this information, accompanied by retraining should be considered on a regular basis, as there is strong evidence that learnings are lost over time and therefore need to be reinforced

factors that are worthwhile to consider when prescribing the use of a nebulizing system for the older patient (Table 6):

1. Almost all currently marketed nebulizers can be used with either a mouthpiece or facemask as the patient interface [192]. However, if the latter is prescribed, it is important to realize that unless the nebulizer is fully breath actuated, there is the risk that medication droplets that are vented to the surroundings when the patient exhales, have the potential to come into contact with the eyes. In the case of formulations that contain an anticholinergic medication, there is therefore the risk of causing or exacerbating narrow-eye glaucoma [109].

2. The breathing pattern of the patient affects the amount of aerosol reaching and therefore capable of depositing in the lungs [193]. Based on in vitro data using simulation of a range of different breathing patterns, the patient should be encouraged to use a slow tidal breathing pattern with an occasional deep breath, thereby improving aerosol penetration and deposition in the lungs [194].
3. Where the patient is unsupervised during treatment, as can be the case particularly in a nursing home with limited availability of staff to supervise the administration of treatment, there is always the possibility that he or she will take out the mouthpiece to have a conversation or for some other nontherapy-related purpose. Under these circumstances, an unknown quantity of medication will be lost unless a fully breath-actuated design is chosen.
4. Regular maintenance of all types of nebulizer is a further consideration if the patient at home does not have the capability to undertake cleaning and disinfection as per the manufacturer instructions [51]. Under such circumstances, the caregiver must be instructed to take over this role which is essential if microbial contamination and possible reinfection of the patient are not to occur.

Nasal Inhaled Medication Delivery Devices

The suitability of the two major classes of devices indicated for nasal delivery of inhaled medication is summarized in Table 7.

Considerations for using either of the two classes of delivery device with the older patient are summarized in Table 8.

N-pMDIs

N-pMDIs, as a class of inhaler, are similar in operation to conventional pMDIs intended for oral delivery, except that the nose piece is located at an acute angle to the axis of the inhaler body such that it can be inserted readily into the nostril before actuation (Fig. 12a) [195]. As far as the older user of this class of inhaler is concerned, propellant expansion provides a source of energy to help disperse the droplets into the nasal cavity, so the need to coincide actuation with a rapid sniff, while manually plugging the other nostril, is less critical compared with the case

Table 7 The major classes of inhalers for nasal administration and their suitability for the older patient

Administration route	Nasal	
Inhaler class	N-pMDI	Nasal spray
Suitability for the older patient	√	√√
Suitability via a caregiver	√	√√

Notes √ = less suitable; √√ = suitable; N-pMDI = nasal pressurized metered-dose inhaler
Nasal sprays are unpressurized and medication is delivered by mechanical action through a pump that forms part of the device

Table 8 Considerations when delivering inhaled medication by nasal delivery device to the older person

	Consideration	Action
1	Is the patient concerned about the sensation associated with plume expansion when using a N-pMDI	If so, an aqueous spray pump is an alternative device
2	Has the patient adequate cognitive ability and manual dexterity to operate the inhaler correctly?	Consider caregiver training and support if not
3	Should the experience of the patient with the inhaler be reviewed?	Yes. Training should be given before initial use to either the patient if he or she can operate the inhaler, or to the caregiver, if not. Periodic (regular) review of technique accompanied by retraining should be repeated on a regular basis, as there is strong evidence that learnings are lost over time and therefore need to be reinforced

when receiving medication therapy via droplets emitted from an aqueous nasal spray pump.

In use, the patient is usually instructed to follow these steps:

(a) Exhale slowly, keeping the head upright.
(b) Holding the N-pMDI as shown in Fig. 13a in one hand, use a finger of the other (free) hand to close the nostril on the side not receiving the medication.
(c) Press down on the canister and at the same time begin inhaling through the nose.
(d) Repeat the process for delivery of the medication to the other nostril.

Finally, the patient is instructed not to sneeze or blow the nose immediately after using the inhaler [196]. The action of sniffing simultaneously with inhaler actuation assists in moving the droplet stream further within the nasal cavity. The degree of coordination needed to carry out the sequence of steps just outlined may be quite

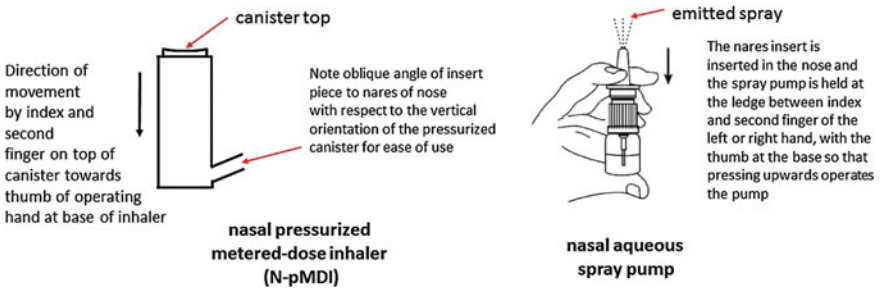

Fig. 13 Operation of the two types of nasal inhaled products

difficult for some older patients with cognitive difficulties to master, making it necessary for the caregiver to administer the medication.

The N-pMDI as an inhaler class was once in widespread use. However, this type of inhaler has fallen out of favor compared with aqueous nasal spray pump technology (see below) because Montreal Protocol for the elimination of chlorofluorocarbons (CFC) as propellants did not provide a "medical use" exception for the use of N-pMDIs to treat allergic rhinitis [197]. Nevertheless, the avoidance of preservatives such as benzalkonium chloride, needed in spray pump-based formulations that adversely affect the nasal mucosa [198], is resulting a reemergence of the N-pMDI inhaler [197]. There is also no need for a spacer or VHC, since the nose piece is inserted inside each of the nostrils (effectively mimicking the "closed mouth" technique with an oral pMDI), and rapid impaction of the droplet stream on nearby mucosal surfaces in the interior of the nasal cavity is the desirable outcome therapeutically. From the perspective of delivering medications to the older patient with limited cognitive ability or manual dexterity, it is notable that this class of inhaler is not currently available with a nasal facemask. Such a feature would be useful for a caregiver to provide therapy via the nasal route, much as is done when delivering aerosol-based therapy orally via a pMDI-VHC-facemask combination. It would therefore seem to be a reasonable goal for a manufacturer to develop a suitable nasal facemask, perhaps based on the type used when providing continuous positive airway pressure (CPAP) in the treatment of sleep apnoea.

Currently, efforts are being directed at delivering the medication topically to coat surfaces in the anterior of the nasal cavity as a stream in the approximate size range from 25 to 200 μm diameter [199]. This size range is relatively coarse compared with those needed for oral delivery to the lungs to the nasal cavity, but finer droplets might migrate beyond the nasopharynx via the posterior of the nasal cavity to reach the lungs. Such a situation is an undesirable outcome given that many nasal preparations are not licensed for lung delivery [200, 201].

Of particular concern to the older user whose nasal mucosa may be more delicate, is the fact that N-pMDI-generated aerosols have been criticized as being too forceful compared with the droplet sprays emitted from aqueous spray pumps [202]. Whereas this may have been the case with products using the now obsolete CFC propellants [203], a recently undertaken study comparing the emission of aerosols from an HFA propellant-based nasal aerosol spray delivering the ICS, ciclesonide, to that from an aqueous spray pump delivering the same API (Omnaris®, Sunovion Pharmaceuticals Inc., Marlborough, MA, USA), has shown that the force of the emitted N-pMDI aerosol is less than that of the spray [204]. Nevertheless, some patients, regardless of age, dislike the sensation experienced when the droplet plume is emitted from the nose piece as the propellant rapidly expands. Under such circumstances, it behooves the prescribing clinician to consider an aqueous nasal spray pump, if a suitable formulation is available, in the interest of avoiding the likelihood of nonadherence.

N-pMDIs are primarily used for the delivery of inhaled corticosteroids for the treatment of a variety of conditions, in particular seasonal allergic rhinitis and nasal polyposis [197, 202]. In the future there is the tantalizing prospect of using the nasal route to administer medications systemically [205, 206], including to the brain via the olfactory bulb where the blood–brain barrier can be bypassed [207, 208], as well as the delivery of vaccines [206].

Aqueous Nasal Spray Pumps

The types of medication delivered from aqueous nasal spray pumps are wider than those currently provided by N-pMDIs, including "over-the-counter" topical decongestants, antihistamines, mast cell stabilizers (cromoglycates), and physiologically normal saline (0.9 % w/v NaCl as an aqueous solution), as well as medications normally requiring a prescription, such as ICS, anticholinergics and antimicrobial agents [209]. As a result, spray pumps are far more widely available. Droplet sizes are similar to those produced from N-pMDIs.

Aqueous nasal spray pumps differ fundamentally from N-pMDIs in their operation because the user has to provide the energy to atomize the liquid containing the medication by operating a mechanical pump using the open hand to squeeze the moving components toward each other [207, 210–212]. This action forces the liquid medication through the spray orifice where atomization takes place at the distal end that, like the nose piece of the N-pMDI, is inserted into one of the nostrils at a time to deliver the medication, while blocking the other nostril. In use, the patient is usually instructed as follows [196]:

(a) tilt the head forward slightly, at the same time breathing out slowly;
(b) Next, holding the pump bottle with the thumb at its base and the index and middle fingers on top (Fig. 13b), use a finger on the other (free) hand to close the nostril on the side not receiving the medicine;
(c) Squeeze the pump to actuate the spray, at the same time inhaling through the nose;
(d) Repeat the process for delivery of the medication to the other nostril.

Finally, as with N-pMDI use, the patient is instructed to try not to sneeze or blow the nose immediately after using the spray. As with N-pMDIs, the action of sniffing simultaneously with pump actuation assists in moving the droplet stream well within the nasal cavity. Again, the degree of coordination may be difficult for some older patients with cognitive difficulties, making it necessary for the caregiver to administer the medication. Furthermore, the manual dexterity required to operate the spray pump and at the same time plug the nostril not receiving medication may be a difficult or impossible task for a patient with arthritis or motor disability in the hands. Finally, aqueous nasal spray pumps are not normally supplied with a nasal facemask as the patient interface.

Future Developments with Inhaled Therapy

Currently, there are few developments across the development of the different forms of oral inhaled therapy that are targeted specifically at the older patient. Concerning asthma therapy, Lavorini has commented that since it is likely that in the future inhaled bronchodilators and ICS will remain the cornerstone of disease management, development of inhaler devices may become more important than new formulations [22]. Unfortunately, no currently available treatments reduce the progression of COPD, or suppress the inflammation in small airways and lung parenchyma [213]. However, several new APIs that target the inflammatory process are now in clinical development [214, 215], and offer the prospect of improved management of the underlying disease process, if not providing an outright cure. It is highly likely that new forms of DPI will continue to appear on the market, especially in Europe where their use is most popular. However, at the present time, there is little evidence that the specific needs are being met for the older patient who might have limited inspiratory force and/or manual and cognitive ability to use this form of inhaler.

Possibly the most significant development that is having and will continue to impact the therapeutic experience is the arrival of lower cost generic products given that many innovator company patents have recently expired or are about to expire [216]. An example is the combination LABA/ICS product Advair®/Seretide® (GSK) that is now off-patent and contains three different dosage strengths of fluticasone propionate with the same strength of salmeterol xinafoate. This product is indicated for the treatment of asthma (GSK plc), and in treating airflow obstruction and reducing exacerbations in patients with COPD. A generic version is now available in some European countries from Cipla Pharmaceuticals, India [217]. Meanwhile, GSK has moved to a new drug delivery platform, based on their Ellipta® DPI, from which LABA/ICS (Breo™ Ellipta, containing the APIs vilanterol trifenatate and fluticasone furoate) and LABA/LAMA (Anoro™ Ellipta®, containing vilanterol trifenatate and umeclidinium bromide as APIs) combination products can be delivered to treat asthma and COPD, respectively [218, 219]. At least one clinical study comparing this new platform with the use of a more conventional DPI (Breezehaler®, Novartis Pharma, Basel, Switzerland), with older adult inhaler-naïve Japanese patients has shown that the Ellipta® device appears to be easier to use by this age group [220].

The decision to move the older patient to a newer DPI platform will likely be an economic one, since there is increasing recognition by stakeholders that a successful clinical outcome is determined as much by the choice of the appropriate inhaler device as by the drugs that go in them [219]. Apart from the prospect of accessing newer and longer acting drugs, current DPI delivery systems are highly effective, provided that the patient can generate sufficient force to disperse the dry powder into aerosol form during inhalation [219]. In this connection, it is worth being aware that high resistance DPIs tend to produce greater deposition of the inhaled aerosol deeper in the lungs than those with a lower resistance [219].

However, the clinical significance of this observation is not yet known [221]. If the patient is unable to generate an adequate inspiratory force, he or she will likely have to move to receive therapy by pMDI-, SMI- or nebulizer-based delivery platforms. Under such circumstances, the newer LABA/LABA/ICS formulations will in general not be accessible, since they are currently only available in DPI format.

Although the Respimat® SMI is proprietary to Boehringer Ingelheim Pharma GmbH & Co. KG, Germany, and therefore offered with only a limited range of their products that are focused on delivering therapy to patients with COPD, their newer LABA/LAMA combination product (olodaterol/tiotropium bromide) has recently been approved [222]. The likelihood of a rival SMI being licensed in the near future is remote, given the patent protection currently afforded the Respimat® SMI [223] as the innovator delivery system in this class.

The prospects of pMDI-based technology developing with a specific focus on meeting the needs of the older patient appear also to be remote. There is the possibility that alternative breath-actuated pMDIs to the Autohaler™ (3 M Drug Delivery Systems, St. Paul, MN, USA) that is presently licensed for use with only one SABA (pirbuterol acetate) may appear to administer additional APIs. However, the prospect for developments with this class of inhaler to administer the present formulation classes is more likely to focus on improving the patient experience with add-on devices, in particular VHCs, to assist the patient receive their medication as effectively as possible from press-and-breathe-based products. It is worth noting that newer breath-actuated pMDI technology is in the offing. However, such products are aimed at delivering APIs for new indications, such as the delivery of dihydroergotamine (DHE) via the Tempo® low-velocity breath-actuated inhaler for migraine management [224], rather than for treating the "classic" chronic obstructive lung diseases that are common in old age.

Nebulizer-based therapy is gradually moving toward the adoption of breath-actuated and/or high-efficiency electronic devices because the amount of medication that is delivered to the patient can be better quantified than with the more traditional continuous or breath-enhanced systems [225]. In terms of topical therapy, there have been some interesting recent developments with the formulation of antibiotics using liposome-based technology as a vehicle for controlled slow release of the API. So far, two products (Pulmaquin® and Lipoquin®, Aradigm Corp., Hayward, CA, USA), each containing ciprofloxacin for treatment of bronchiectasis (often but not always associated with COPD), and in infections of *P. aeruginosa* in CF patients, respectively, are in phase 2 and phase 3 clinical trials, respectively [226]. Arikace™ (Insmed Corp., Bridgewater, MJ, USA) has recently completed phase 3 clinical trials, and is a liposomal formulation for nebulization, that contains amikacin as antibiotic and is indicated to be delivered to CF patients for treatment of nontuberculous mycobacteria colonization of the lungs solely via the e-Flow® vibrating membrane nebulizer (PARI GmbH, Germany) [227]. In terms of systemic delivery, as proof of principle, the AeroEclipse® BAN has been evaluated for the delivery of a liposomal formulation of the highly potent opiate, fentanyl for the relief of breakthrough pain in cancer [228]. However, to the best of knowledge of the author, this development has not been pursued to

commercialization. A newer version of this nebulizer (AeroEclipse®-II has recently been evaluated in a clinical trial with adults as a candidate for the replacement of the obsolete Wright nebulizer in the delivery of methacholine for bronchial challenge in the diagnosis of reversible bronchoconstrictive disease [229]. In the foreseeable future, the versatility and variety of nebulizing systems are likely to continue to make them the most popular platform for the development of the new biochemical agents such as siRNA that are in the research pipeline for the delivery of vectors to treat various forms of cancer [230, 231].

Nasal delivery products are likely to remain confined to the treatment of various forms of rhinitis in the near future with an increasing number of generic formulations becoming available [232]. Further out, there is the prospect of an increasing variety of molecular entities being delivered via this route of entry, including peptides and vaccines [207]. In addition, there is the highly attractive prospect of delivering medication via the nasal route to target the olfactory bulb where there is the prospect of bypassing the blood–brain barrier [233]. Devices are presently in development to deliver anti-migraine medication, as well as to address neurodegenerative conditions such as Parkinsonism and Alzheimer disease via this route. However, the challenges are severe, not least because of the difficulty of selectively delivering the medication to the target [234], but also in terms of assessing the hoped-for clinical benefits [235]. Nevertheless, from the perspective of the older patient, such developments, if successful, will represent major advances in disease mitigation by means of inhaled therapy.

Acknowledgments The author wishes to acknowledge the help and advice from former colleagues at Trudell Medical International, London, Canada.

Financial Disclosure The author is a self-employed consultant in the field of inhalation therapy and has received no funds in support of this work. He was from 1994 until 2013 a full time employee of Trudell Medical International.

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Ophthalmic Drug Development and the Elderly

Patrick Hughes and Sesha Neervannan

Abstract As the global elderly population has gone up, so has age-related ocular conditions and diseases. The eye is a highly protected organ and has natural barriers that pose substantial challenges to drug delivery. In addition, since most drugs are directly applied to the eye, patient compliance, especially in the elderly, poses significant additional challenges. This chapter highlights the key anatomical and physiological barriers both in the anterior segment and posterior segments of the eye, as well as key strategies employed by drug development scientists to overcome patient compliance issues. Optimization of conventional topical medications as well as novel strategies for sustained delivery and thorough judicious use of devices are needed for effective treatment of these conditions.

Keywords Ocular disease · Drug delivery barriers · Anterior segment disease · Posterior segment disease · Pre-corneal · Corneal · Ocular bioavailability · Passive transcorneal flux · Viscosifier · Prodrugs · Suspensions · Ointments · Emulsions · Microelectromechanical systems

Ocular Diseases in the Aging Population

The economic and health costs of ocular diseases are staggering. It is estimated that there are 156 million blind and 356 million visually impaired individuals, discounting uncorrected refractive error, worldwide [1]. There are over 100,000 blind from glaucoma in the US alone representing about 10 % of the blinded population [2]. This translates to a very high economic cost: 19 billion in US dollars lost to blindness and 23 billion lost to visual impairment worldwide [3]. The monetary cost in the US alone includes an annual federal cost of 5.4 billion [4]. The direct health care burden is also highly onerous with over 10 million physician visits per year.

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S. Stegemann (ed.), *Developing Drug Products in an Aging Society*,
AAPS Advances in the Pharmaceutical Sciences Series 24,
DOI 10.1007/978-3-319-43099-7_20

Ophthalmic disease can happen at any age, but disproportionately affects the aging population. As has been shown, the treatment burden is heavy and as a society we are not getting any younger. The percentage of people over age 65, when a lot of visual impairment starts, is increasing rapidly and will be twice what it is today in 50 years [5]. Visual impairment will be an even greater burden on society in the future. Clearly, there is a great need for medications to mitigate ophthalmic disease and reduce the overall health care burden.

Diseases of the anterior segments of the eye include infection and inflammation, glaucoma and dry eye amongst others. Glaucoma itself is a group of progressive neuropathies that lead to blindness and is estimated to affect 79.6 million people worldwide by 2020 [5, 6]. Elevated intraocular pressure (IOP) is a risk factor for primary open angle glaucoma. For IOP lowering agents and other diseases of the anterior segment topical ocular delivery is the route of choice. However, because of the difficulties to administering drops by the elderly, compliance with the treatment regimens is very low.

Diseases of the posterior segment are also significant in the elderly population. Age-related macular degeneration is the leading cause of blindness in the western world for people over 65 with an estimated 11 to 28 % of the population effected [7, 8]. Diabetic retinopathy affects to some extent 80 % of diabetics of greater than 20 years duration [9]. We are fortunate that pharmacologic intervention for many posterior segment diseases is on the horizon. From diabetic macular edema to age-related macular degeneration, new drug substances are being developed and older drugs being repurposed to mitigate these diseases. However, a persistent problem is delivering drugs at therapeutic concentrations to their intended site of action, and for the desired duration. The posterior segment is exquisitely protected from external influences, including therapeutic agents; and unlike anterior segment diseases, topical delivery is ineffective. New modes of administration are required for treating posterior segment disease.

To effectively manage ocular disease in the elderly, the mode of administration must be chosen with a route in mind and should be optimized for the particular demographic. With an increasing elderly population and new pharmacology being developed to address ophthalmic diseases, there is a need for the pharmaceutical scientist to develop formulations that can effectively deliver drugs to the appropriate site of action. The anatomy and physiology of the eye naturally divide the issue of ocular drug delivery into two separate challenges: anterior segment delivery and posterior segment delivery. The anterior segment of the eye comprises of the ocular surface and conjunctiva, cornea, aqueous humor, iris–ciliary body and lens. The posterior segment is made up of the uveal tract, vitreous, retina, and choroid. The constraints and strategies to deliver drugs to these two segments differ greatly and will be treated separately in this chapter.

Anterior Segment Ocular Drug Delivery

Constraints With Anterior Segment Delivery

For ophthalmic conditions, traditional therapy includes topical administration. There are numerous advantages to topical over systemic therapy for treating ocular disorders. First, topical drops may offer higher ocular bioavailability to the anterior segment of the eye relative to systemic administration. Hence, topical administration inherently results in fewer systemic adverse events. That's not to say bioavailability is high with topical administration as demonstrated below.

The key goals for developing topical ophthalmic formulations include:

- Minimizing toxic side effects while maximizing drug bioavailability: Topical administration delivers drugs directly to the eye; however, off-target effects can cause both local and systemic toxicities. This can be compounded in the elderly with concomitant medications and comorbidities.
- Ensuring tolerability and patient acceptance: Formulation factors can greatly affect tolerability and ease of use for patients. These issues are critical in the elderly—as the biggest reasons for noncompliance, which approaches 50 %, are: difficulty in administration into the eye, discomfort, stinging, and redness [10, 11].
- A consistent and stable dosage form is also required, ideally having a minimal shelf life at room temperature of 2 years.
- And finally, the formulation must prevent contamination with pathogens as infections of the eye can be sight threatening.

The topical ocular route of administration is the preferred route of dosing for ocular delivery. It is noninvasive and has a relative ease of administration. Unfortunately, bioavailability is low, even to the anterior chamber with small molecules. The barriers to productive topical absorption of drugs into the anterior chamber can be pre-corneal or corneal.

In the pre-corneal space most of the applied dose is immediately lost through nasolacrimal drainage. The cul-de-sac has a volume of about 7–9 μL at rest, but can transiently accommodate up to 30 μL [13]. A typical drop is 35–50 μL. After topical administration to the cul-de-sac the majority of this is lost through nasolacrimal drainage as the volume is normalized. Blinking further drives the drug into the nasolacrimal duct. This drug is not only lost therapeutically, but becomes available for systemic absorption across the nasal mucosa. Dilution due to tear turnover, lacrimation, protein binding, and conjunctival absorption further diminish bioavailability. Pre-corneal half-life is on the order of minutes, in fact, clearance can be so fast that it is often only the first few blinks that spreads drug over the tear film for productive absorption [12–14].

Corneal factors also play a major role in bioavailability. The cornea is considered a tri-laminate structure relative to mass transfer: an extremely lipophilic

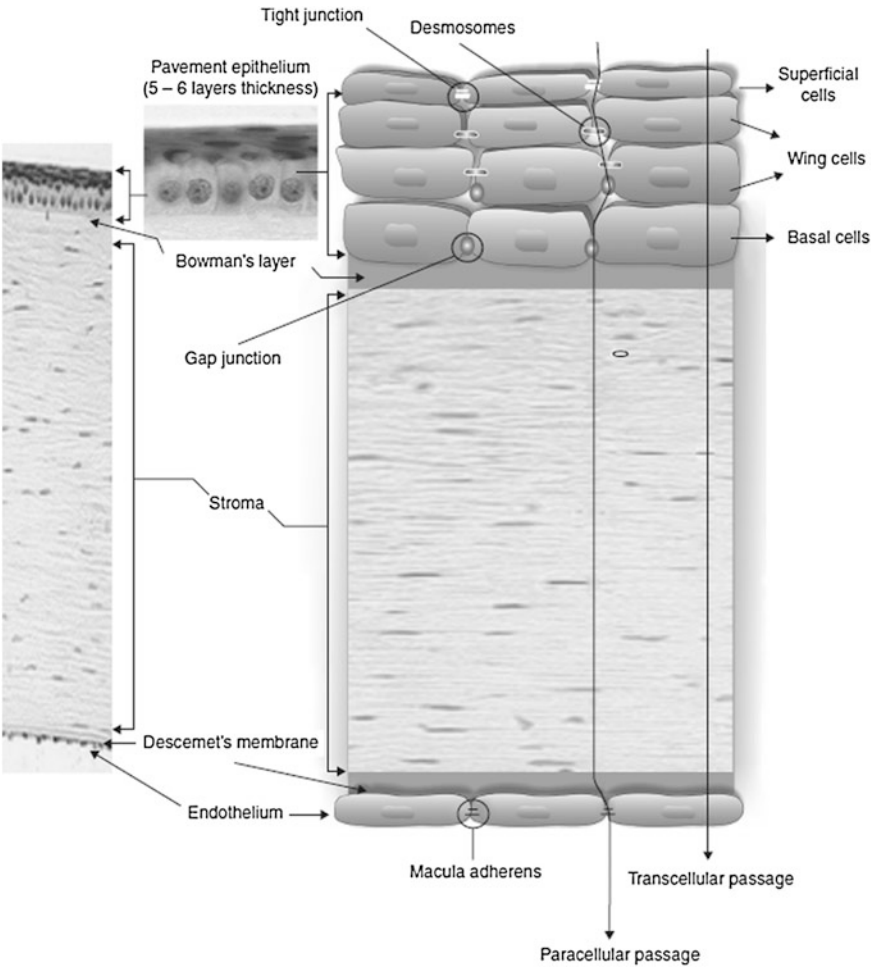

Fig. 1 The cornea and its cellular organization of various transport-limiting layers. The outer superficial epithelial cells, possessing tight junctions, display the tightest monolayer. The inner endothelial cells, displaying macula adherens, are more permeable (reproduced with permission from Barar et al. [15])

epithelium, a hydrophilic stroma, and the endothelium (Fig. 1) [15]. The epithelium has a thickness of 3 to 5 layers characterized by banded tight junctions. Due to the very lipophilic properties, the cornea has a low permeability for hydrophilic drugs. The middle layer, the stroma is composed of 80–90 % water and is acellular. Hydrophilic compounds readily diffuse through the stroma. The inner layer, the endothelium, is a single layer and poses very little barrier to permeation. Because of the tri-laminate nature, drugs must possess sufficient lipophilicity to penetrate the epithelium, but have sufficient aqueous solubility to create a diffusional driving

force in the aqueous tear film and partition into the stroma from the epithelium. Penetration begins to optimize for compounds with a distribution coefficient (log D) of 2 to 4 [16].

The pre-corneal and corneal constraints combined are such that ocular bioavailability from topical drops is very low (1–5 %) [12]. Further rapid elimination occurs from the anterior chamber as a consequence of aqueous humor turnover.

Drugs can also reach the intraocular tissues by the non-corneal route. Access to the aqueous humor and iris can be achieved by the conjunctival/scleral route of absorption. This route is usually most significant for compounds with poor corneal permeability that cannot penetrate the corneal epithelium (e.g., ionized or large molecular weight compounds). Newer studies have shown that the cornea and conjunctiva possess a significant number of transporters. These studies have sought to exploit these transporters for improved ocular drug transport and bioavailability [17]. However, for the most part the formulation scientist will optimize the formulation to enhance the passive transcorneal flux.

Optimizing Topical Formulations

Lipophilic compounds will penetrate from the tear film into the aqueous humor by transcorneal permeation. This is driven by a diffusion process. This leaves the ocular formulator two levers with which to optimize a compounds bioavailability: permeability and solubility.

Increasing corneal permeability of a compound is the first lever the ocular formulation scientist has at their disposal. It has been observed that corneal permeability increases with increasing lipophilicity as measured by the octanol/water distribution coefficient (log D) of the compound up to a log D of 2 to 4 after which it displays a parabolic relationship, decreasing with increasing log D. Beyond a log D of 4, aqueous solubility issues come into play reducing the driving force or the leaving potential of the compound from the epithelium.

The second lever the formulator has to play with is solubility in the tear film or the area under the tear film concentration time curve. Ideally, sufficient solubility to support the clinical dose would be designed into the drug substance. Unfortunately, there is usually no defined final dose nor does a good log D and solubility exist to guide discovery research. Formulations to overcome solubility issues remain a key target. The main ways to accomplish this include adjusting the pH of the formulation around the compounds pKa, using co-solvents and solubilizers and particle size reduction in the case of suspensions.

Consequently, topical formulations must be optimized to possess several key attributes [18–21]:

- Adequate corneal penetration
- Prolonged contact time with corneal tissue (area under the tear film concentration time profile)

- Adequate solubility to achieve target dose
- Simplicity of instillation for the patient
- Nonirritating and comfortable
- Appropriate rheological (flow) properties
- Minimal systemic absorption
- Sterile dosage form

Topical solution formulation factors

The pH values of ophthalmic solutions are adjusted within a range to provide an acceptable shelf life and ocular tolerability. When necessary, they are buffered adequately to maintain stability within this range for greater than 2 years. Fairly low pH formulations can be tolerated depending on the disease being treated. An example is Propine® eye drops with a reported pH range from 2.5 to 3.5. If buffers are required for extreme pHs, their concentration is controlled to be as low as possible (low buffer capacity) so as to avoid affecting the tonicity or pH of the tear film. This enables tears to rapidly bring the pH of the tear film back to the physiological range. Ideally, every product would be buffered to pH 7.2–7.5, the normal physiological pH of tear fluid. Examples of buffer vehicles used:

– Boric acid vehicle: pH of 7.0–8.0
– Isotonic phosphate vehicle: pH ranges from 5.9 to 8
– Citrate buffer vehicles: pH ranges from 5 to 7

Ionization is perhaps the easiest way to solubilize a compound or increase its distribution coefficient. If a molecule has an ionizable group that can be ionized within physiological pH, changing formulation pH may achieve sufficient solubility or conversely lipophilicity.

This strategy of pH optimization was successfully employed in the reformulation of the commercial drug product Alphagan® 0.2 %. Alphagan® 0.2 % has a pH of 6.4. Brimonidine tartrate, the active ingredient in Alphagan 0.2 %, has a pKa of 7.8. Hence, as the formulation pH was increased toward 7.2 there is a dramatic increase in formulation bioavailability due to an increase in the unionized fraction of brimonidine. The ocular bioavailability of the brimonidine formulation adjusted to pH 7.2 and Alphagan® 0.2 %, pH 6.4 was evaluated in New Zealand White rabbits after topical dosing into the cul-de-sac. The 0.2 % brimonidine tartrate, pH 7.2 formulation was 1.4 times more ocularly bioavailable in rabbits than 0.2 % Alphagan® [22].

Viscosifiers can also be utilized to improve a formulation's ocular bioavailability. Viscosifiers serve three important purposes in ophthalmics, first to act as a suspension aid, slowing sedimentation. They can also serve as a demulcent, rewetting the surface of the cornea and they can be used to increase pre-corneal retention time and thereby potentially increase bioavailability. By delaying pre-corneal clearance the area under the tear film concentration time profile is enhanced and ocular bioavailability to the aqueous humor is increased. Increasing formulation viscosity with classical polymers can increase topical bioavailability up to a viscosity of about 100 cps with diminishing returns after about 15 cps [23].

Commonly used viscosifiers include: polyvinyl alcohol, methylcellulose, sodium carboxymethylcellulose (CMC), hydroxypropyl methylcellulose, hydroxyethylcellulose, and carbomers.

Recently, newer viscosifiers have been developed to further increase the bioavailability of topically applied ophthalmic drops. These include gels and in situ gelling systems. Gels can be used to increase pre-corneal retention time. However, gels often have a very porous structure when hydrated and offer very little sustained release. Hence, retention time of the active agent beyond a few hours is minimal. However, given the rapid clearance of topical solutions from the pre-corneal space, even this modest increase in retention can be significant. Gel-forming materials for ophthalmic use include polycarbophil used in DuraSite®. These polymers have been shown to enhance bioavailability over and above standard polymer solutions. The pharmacokinetics of a 2 % ocular solution of azithromycin in Azasite® (DuraSite® vehicle) was evaluated in rabbits. Concentrations of azithromycin peaked at 30 min, however, effective concentrations were maintained for 24 h [24]. Gellan gum (Gelrite®) and xantham gum have been used to increase the pre-corneal retention of topical drops. Both have been used with considerable success. Timoptic XE® (gellan) and Timolol GFS (xanthan gum) allow for once a day dosing of timolol. TobraDex ST™ delivers tobramycin and dexamethasone into the conjunctival sac every four to six hours and also utilizes a xanthan gum vehicle.

Even more complex systems have been used such as Novagali's Novasorb® technology that may further prolong pre-corneal residence time. Novasorb® is a proprietary cationic emulsion that prolongs retention time through binding to the ocular surface rather than viscosification. The positively charged emulsion droplets bind to the negatively charged ocular surface enhancing contact time. The Novasorb® technology is currently used in Retaine® MGD, a lubricating eye drop to mitigate the symptoms of dry eye.

There can be a downside to viscosifiers. The polymers can produce blurring of vision, dry film formation, and crusting in the eye and on the bottle tip. The viscosity enhancements may also make sterile filtration more difficult depending on the rheological characteristics of the formulation. Some polymers may also interact with commonly used preservatives; e.g., CMC may precipitate BAK.

Produgs, solubilizers, and penetration enhancers

Prodrugs have been successfully used to improve the corneal permeability of ophthalmic compounds. In these cases the compounds lipophilicity was transiently increased through prodrug derivatization. Upon permeation of the corneal epithelium, esterases cleave the prodrug back to its more hydrophilic parent. One of the first successful prodrugs was the dipivalyl prodrug of epinephrine (Propine®, Allergan, Inc). The dipivalyl prodrug penetrates the human cornea 17 times more rapidly than epinephrine [25, 26]. This increased bioavailability gives it more efficacy and a lower systemic exposure. Aliphatic esterification has also been successfully used to improve the topical ocular bioavailability of the prostaglandins latanoprost and travoprost.

Surfactants are often added to ophthalmic formulations. Typically, nonionic surfactants at low concentrations are used. These assist in wetting and dispersion of suspension as well as solubilizing the active in solution. Typical surfactants are the polysorbates, tyloxapol, and polyoxyl 40 stearate for example. Surfactants can be irritating and nonionic surfactants are preferred for ophthalmic use. The ocular toxicity of surfactants is generally from most to least; anionic > cationic > nonionic [27]. Care should be taken in formulating ophthalmic preparations with surfactants to use a low enough concentration so as not to cause ocular irritation or other toxicity.

Complexation has also been used to enhance solubility and permeability. Cyclodextrins have been used to improve the topical bioavailability of ocular drugs by enhancing solubility. Cyclodextrins are well known to form inclusion complexes with many drugs, depending on their binding constants to a particular cyclodextrin. These inclusion complexes can greatly increase drug solubility while only minimally impacting release from the complex. EDTA has also been used to chelate calcium on the ocular surface and open up the epithelial tight junctions, thereby improving permeability. It has been shown that 0.5 % EDTA doubled the ocular availability of topical glycerol and cromolyn sodium [28].

Suspensions, ointments, and emulsions

Often drug solubility does not support the intended clinical dose. In these cases a suspension may be employed. Suspensions are also effective in cases where stability of the drug in solution may be limiting to shelf life. For suspension systems ocular bioavailability is related to particle size. The optimal particle size appears to be less than 10 μm [29, 30]. This size minimizes irritation and also provides rapid dissolution to replenish the tear film. The particles in suspensions may also have the added benefit of a delayed pre-corneal clearance. Pred Forte® and TobraDex® R are examples of ocular suspensions. Suspensions pose unique manufacturing and process challenges for ophthalmic dosage forms. Topical ocular medications have a requirement of sterility and need to be essentially free from foreign particulate matter. For drugs or compositions that cannot be terminally sterilized the suspension must be milled and compounded aseptically. Additionally, the milling process cannot materially contribute to foreign particulate matter. Physical stability needs to be addressed as well as chemical stability. In addition to suspension settling and resuspendability, Ostwald ripening and polymorphic form change during processing and upon stability needs to be monitored and controlled.

Ointments can increase ocular contact time, but are difficult to administer and often result in blurring. Several ophthalmic ointments are on the market, examples include Neosporin Ophthalmic (neomycin, polymyxin, and bacitracin zinc ophthalmic ointment), Erythromycin Ophthalmic Ointment, GenTeal® Lubricant Eye Ointment, and Chloromycetin® Ophthalmic Ointment (chloramphenicol). Ophthalmic ointments must be sterile and like suspensions, ointments can be more difficult to manufacture aseptically. Because most ointments are dispensed in multi-dose configurations they also need to be preserved.

Emulsions can be used to improve ocular bioavailability by providing a higher degree of solubilization over solutions and can enhance partitioning. Typically, oil/water emulsions are employed for ophthalmic use rather than water/oil. Restasis® (cyclosporine ophthalmic emulsion) 0.05 % is an example of an ophthalmic emulsion.

Inserts, Implants, and Devices

In an attempt to further improve bioavailability and address the root causes of patient noncompliance, especially in the elderly, several implant and device strategies have been employed.

Pre-corneal inserts

All of the formulation techniques discussed above can only improve bioavailability to a certain extent. To enhance delivery beyond what can be achieved by conventional solubilization, permeability enhancement or pre-corneal retention prolongation, novel drug delivery systems can be employed.

One of the first commercial examples of ocular implants was Ocusert®. Ocusert® is a membrane controlled delivery systems delivering 20 or 40 μg of pilocarpine per hour. Ocusert® allowed for once a week dosing, but suffered from foreign body sensation, expulsion, and difficulty handling. Ocusert did lower IOP, typically no greater than 20 % reduction in open angle glaucoma (OAG) and was discontinued in 2007.

Over the years several other pre-corneal sustained release approaches have been taken ranging from pre-corneal inserts to drug loaded contact lenses. A more current approach has been the use of punctal plugs. QLT Inc. had been evaluating a latanoprost punctal plug in the clinic. The plug is nonbiodegradable and delivers between 44 and 81 μg of latanoprost over 3 months. The system is essentially a punctal plug with hollow lumen to allow for a latanoprost eluting drug core. In one clinical study IOP reduction ranges from 3 to 5.5 mmHg over 3 months, however, retention was initially a problem with these systems with only 75–81 % retention rate of the plug after 8 weeks [31–33]. Like Ocusert®, the punctal plug delivery systems suffer from retention issues or only marginal IOP reduction.

Contact lenses have been used for the delivery of drugs to the eye. Initial efforts involved loading the lens by soaking in a solution of the drug to be administered. In this scenario the drug of interest usually rapidly diffuses from the lens resulting in a burst release without much sustained delivery. Newer technologies involve imbedding drug loaded films or microparticulates into the contact lens. These types of approaches have led to much longer delivery times. However, this approach has not met with clinical or commercial success to date. A more practical issue with contact lenses as delivery vehicles centers on the intended demographics. Many of the glaucoma patients may have difficulty putting lenses in their eye. There is also a

Fig. 2 Amorphex therapeutics, TODDD™, topical ophthalmic drug delivery device (https://amorphextherapeutics.wordpress.com/)

high incidence of dry eye with these patients which could make the contact lens irritate the eye even more.

Amorphex Therapeutics makes use of a modified contact lens design as a pre-corneal insert for drug delivery (Fig. 2, TODDD™, Topical Ophthalmic Drug Delivery Device). The system purports to provide comfort, good retention, and sustained delivery. The soft elastomeric device is curved to rest on scleral conjunctiva. In a study in dogs a latanoprost device lowered IOP 7–10 mm Hg from baseline for up to 16 days [34] (Poster #5073, ARVO 2013). The device is currently in clinical development. There are many similar pre-corneal delivery systems in development that include NODS, BODI, SODI, Dry Drops, Gelfoam, minidiscs, collagen shields amongst others.

Microelectromechanical system (MEMS)

A refillable micropump (Fig. 3, Replenish®) has been developed as an ocular drug delivery device that can be implanted through minimally invasive surgery. The Replenish® pump is comprised of a refillable reservoir, a means of electrolysis and a cannula with check valve. Electrolysis in the reservoir creates hydrogen and oxygen bubbles from water. This creates pressure within the reservoir that, upon exceeding the valve's cracking pressure, allows flow at a controlled rate. Drug solution in the reservoir can then flow out the cannula and into the anterior chamber or posterior chamber, depending on cannula placement. The pump can be programed to delivery precise doses at intervals over months to years. Refilling the pump can occur through an integrated port. The pump has been shown to be well tolerated in clinical studies and offers the possibility of 12 plus month delivery [35].

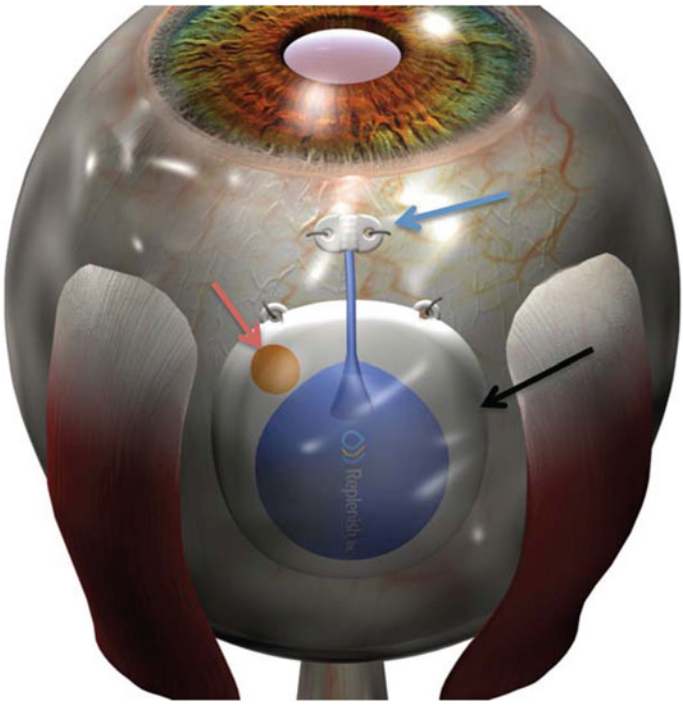

Fig. 3 Schematic representation of the PMP implanted into the subconjunctival space between the superior and lateral rectusmuscles. The *blue arrow* indicates the intraocular cannula at the pars plana location. The *red arrow* indicates the refill port. The *black arrow* indicates the body of the PMP that contains the hermetic sealing package with all electronics, the drug reservoir, and the check valve (used with permission from http://tvstjournal.org/doi/full/10.1167/tvst.3.6.5)

Stents

Several microstents have been developed for IOP reduction. These include the suprachoroidal stents CyPass® Microstent (Transcend Medical) and iStent® (Glaukos). These stents form a permanent connection between the aqueous humor and suprachoroidal space. They are implanted by an *ab interno* process through a minimal corneal incision. In one study the CyPass® Microstent was shown to reduce refractory IOP from an average of 24.5 to 16.8 mmHg [36, 37]. The iStent® Supra by Glaukos is also an *ab intero* device and targets uveoscleral outflow.

AqueSys has developed a flexible stent (Fig. 4) that shunts aqueous humor from the anterior chamber to the subconjunctival space as opposed to the trabecular meshwork and Schlemm's canal. This atypical route can produce lower IOP reductions. The Xen Gel stent is comprised of glutaraldehyde cross-linked gelatin.

Biodegradable delivery systems

Several biodegradable implants have been developed to treat ocular hypertension and glaucoma. Brimonidine DDS is being developed by Allergan PLC as an intravitreal

Fig. 4 The Xen gel stent from AqueSys is a flexible implant that shunts fluid from the anterior chamber to the subconjunctival space (http://www.aquesys.com/xen.aspx)

implant. The implant is a PLGA-based brimonidine eluting implant designed to be neuroprotective. Allergan is also developing an intracameral (IC) implant to treat elevated intraocular pressure, Bimatoprost PF IC DDS. The implant is administered by a preloaded single-use applicator system by direct injection into the intracameral space. Bimatoprost PF IC DDS has been evaluated in a Phase 1/2 clinical trial in open angle glaucoma and ocular hypertensive patients [38].

Topical ophthalmic dispensers

Another major concern with the adequate treatment of an elderly patient for an ocular condition is patient compliance—either with missing a dose or having trouble with the instillation [39]. Oftentimes, elderly patients also do not feel comfortable with self-dispensing and need help from others. Simple physical aspects such as opening the cap, squeezing the dispenser to accurately instill a drop into the eye can be major problems for an elderly patient [40]. The causes for this are severalfold and include several patient-centric issues. These include the decrease in manual dexterity in the elderly, decline in memory, and the complexity of dosing regimen, especially for patients that may be on multiple medications.

Ocular drug development needs to consider all the above aspects while developing a product. Many efforts are underway to improve the accuracy of dosing into the eye (cups, mist) as well as simple changes such as keeping the color of the cap consistent for certain medications and treatments (e.g., AAO stipulates certain color caps for various glaucoma treatments such as purple cap for all prostaglandin analogs) makes it easy for the patient to accurately dose the appropriate medication.

Some of the newer ophthalmic dispensers that have been in development include the VeriDose® Ophthalmic Dispenser (Mystic Pharma), the OptiMyst® handheld nebulizer, the COMOD® (UrsaPharm), Aptar's Ophthalmic Squeeze Dispenser, the MedInstill®, and the Aeropump (Fig. 5). The VeriDose® system features an ergonomic system that utilizes cartridges with unit dose type packaging for accurate delivery and features a dose counter to assist compliance. The COMOD® stands for COntinuous MOno Dose. The device is an airless pump which enables the delivery of sterile preservative-free product. Aptar Pharma's Ophthalmic Squeeze Dispenser (OSD) is a multi-dose device designed for unpreserved eye drops. The system is designed to fit the standard dropper bottle shape to ensure user acceptance. All these offer the potential for multi-dose preservative-free solutions, ease and accuracy of

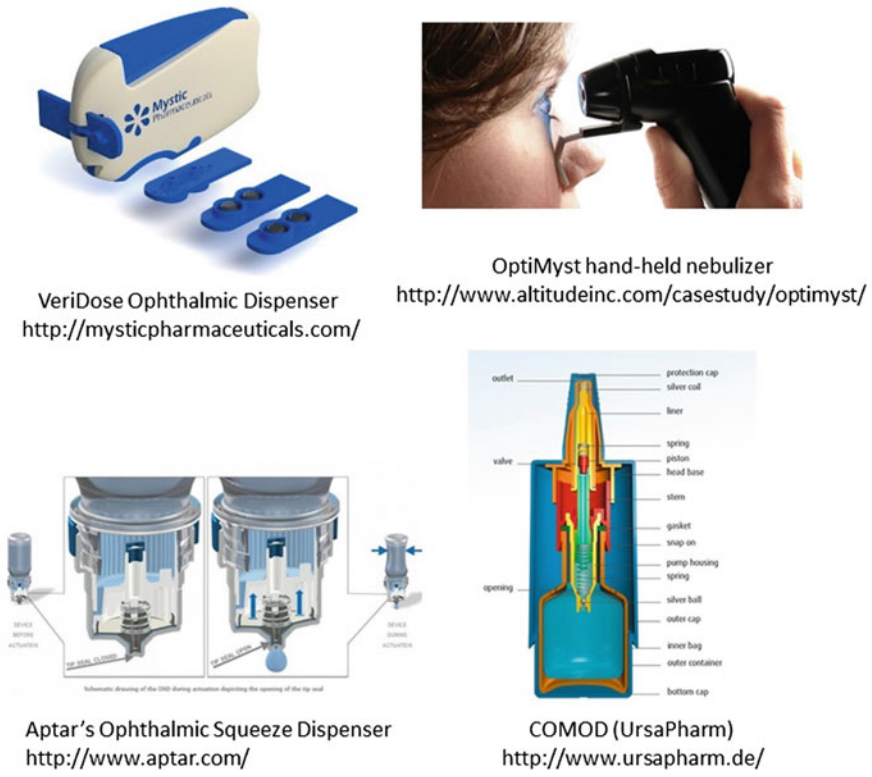

Fig. 5 Various ophthalmic dispensers that are in development

administration, and in some cases improved ergonomics and the potential to monitor compliance.

Posterior Segment Delivery

As stated earlier vitreoretinal diseases are the leading cause of blindness in the western world, especially the aging population [3]. This includes glaucoma, ARMD and DME, amongst others. If someone lives long enough they will probably experience posterior segment disease. Unfortunately, anatomic and physiologic constraints limit the ability to treat the posterior segment, especially with macromolecules. While traditional methods for treating retinal diseases involved systemic or topical delivery, effective treatment in the future will require more direct administration such as intravitreal injections or sustained release.

The anatomy and physiology of the eye pose significant barriers for topical ocular delivery to the posterior structures. As stated earlier about 1–5 % of a topical

administered drop reaches the aqueous humor. Penetration into the posterior segment from the anterior chamber with diffusion to the macula is highly unlikely. Much of the literature describing topical delivery to the retina involves research on rodents or rabbits where vitreous volumes and diffusional path lengths are much smaller than humans. Additionally, pharmacokinetic studies from topical delivery targeting the back of the eye often report measures for the entire vitreous or retina. The mean values reported are in fact the results of very high anterior concentrations and low to insignificant concentrations in the macular region. This grossly overestimates the success of this route of administration.

Systemic penetration of drugs into the posterior segment of the eye is restricted by the blood retinal barriers. The blood–retinal barrier is anatomically separated into an inner and outer blood barriers, the endothelial cells of the retinal vasculature and the retinal pigmented epithelium, respectively [41]. Very lipophilic compounds may gain entry into the vitreous via penetration of the blood retinal barriers. However, most drugs used in the treatment of posterior segment disorders are not able to penetrate the blood retinal barriers and systemic administration of these drugs is extremely inefficient. The result is a requirement to administer extremely large doses systemically to achieve therapeutic posterior segment concentrations. For most drugs therapeutic levels in the posterior segment of the eye can only be achieved by local drug administration such as multiple intravitreal or periocular injections. Direct intravitreal injection is currently being used for the administration of drugs such as Macugen® (pegaptanib), Avastin® (bevacizumab injection), Lucentis® (ranibizumab injection), and Eylea® (aflibercept).

The vitreal half-life of macromolecules is significantly greater than small molecules. Lucentis® and Avastin® have vitreal half-lives in the rabbit of 2.9 days and 4.3 days (M.W. 48 and 149 KDa), respectively [42, 43]. The vitreal half-life of Lucentis® in humans has been estimated to be approximately 9 days [43]. This allows for prolonged residence time, however, these agents still must be injected once every 4–8 weeks to maintain effect. Doses are relatively high to allow the compounds half-life to drive the duration of effect. This puts a heavy burden on providers and patients leading to potential poor patient compliance. There is also an increased risk of adverse events associated with the frequent intravitreal injections as well as the high peak to trough ratio of drug concentration associated with this type of pulsed dosing.

Most compounds in the small molecule range, about 500 Da, have half-lives of less than 10 h [44]. What is surprising is how fast most small are molecules cleared, indicating clearance across the blood retinal barrier. Exceptions were triamcinolone acetonide where its clearance was governed by its own intrinsic dissolution and foscarnate, a charged highly soluble compound. As molecular weight increases there is a shift to longer half-lives that correlate with MW. This corresponds to a shift in clearance from transretinal clearance to diffusion to the anterior chamber. This was evidenced by the change in the retina/vitreous and aqueous humor/vitreous concentration ratios of the drug at steady state [44]. As MW increases past 1000 Da the aqueous to vitreous concentration ratio approaches and exceeds 1 and the retina to vitreous ratio drops below indicating the compound is being cleared out of the anterior chamber. Unfortunately, the vitreous half-life as a function of

molecular weight only increases to a finite limit. Because of this, sustained delivery systems are required for delivery drugs for extended duration.

Sustained release drug delivery systems offer several benefits for posterior segment delivery. Therapeutic efficacy can be improved, maintaining drug at the site of action, minimizing high peak concentrations and minimizing subtherapeutic troughs. Through site specific delivery it is possible to circumvent natural barriers such as the blood aqueous or blood retinal barriers, in some cases enabling therapy that otherwise would not be feasible. Sustained and controlled delivery further reduces patient burden by decreasing dose frequency and by improving compliance, which will reduce the overall burden on the health care system.

There are several disadvantages to controlled and sustained delivery as well. The formulator has to protect against the potential for dose dumping as a possible failure mode of the delivery system. These systems often require more complex manufacturing processes and yield higher cost of goods. Finally, biocompatibility of materials of construction needs to be assured.

There are a multitude of different types of drug delivery systems that exist preclinically and clinically. For the purpose of this chapter, we will break these systems down into erodible and non-erodible drug delivery systems. Erodible-type delivery systems are often dissolution controlled systems and include encapsulated reservoirs or matrixes. For matrix dissolution systems drug is uniformly dispersed throughout the system. Drug is then released through dissolution of the system or diffusion and as such release is first order. Sometimes a drug can be its own delivery system by virtue of its low intrinsic dissolution rate as is the case with triamcinolone acetonide.

Erodible systems can also be diffusion controlled matrixes. These matrix devices consist of drug dispersed homogeneously throughout a polymer matrix. Drug diffuses out of the system with a counter diffusion of water into the system. The process proceeds with a receding boundary front of diffusing drug within the implant. This type of system usually releases drug in a first order fashion and incudes matrix implants made from poly lactic acid (PLA), poly lactide-co-glycolide (PLGA), and polycarpolactone (PCL). Some polymers such as polyanhydrides and poly(ortho)esters are surface eroding and can theoretically provide a zero order release from a matrix system.

Non-erodible systems have the advantage that they can offer zero-order release kinetics. These are reservoir-type implants. Release kinetics are governed by drug diffusion through rate-controlling membranes. Release from reservoir matrices can be through porous or nonporous membranes. For porous membranes, release is a function of compound/membrane diffusivity, surface area of the membrane, partitioning into the membrane and the concentration in the reservoir, or more accurately drug activity in the reservoir. Hence, as long as drug activity is constant and the mass transfer properties of the membrane do not change, through swelling or aging, etc., then release will be constant and zero order. For porous membranes, release becomes a function of pore surface area and membrane thickness. For constant membrane mass transfer properties, release should be constant with constant drug activity. However, changes in hydration, tortuosity, and porosity may affect release rate.

Non-erodible implants

Non-erodible implants for treating posterior segment disease were the first on the market. These systems provide near zero order release without significant burst. The down side is that they may require surgical removal after their drug payload is exhausted. This can be challenging if a foreign body reaction to the implant has occurred and may increase the risk of traction retinal detachment.

Retisert™ and Vitrasert™ (Bausch & Lomb, Rochester, NY) are FDA approved for the delivery of fluocinolone acetonide and ganciclovir, respectively. Retisert® is a non-erodible implant of a fluocinolone acetonide tablet contained within a drug-permeable polymer. Surgical implantation and removal is required.

Iluvien™ is a fluocinolone acetonide intravitreal insert. It is a smaller size than Retisert® and can be injected through 25-gauge needle. The system is designed to release drug over 18–30 months. The system is expected to stay in the eye permanently, eliminating complications associated with implant extrusion

Bioerodible systems

Biodegradable implants are the natural counterpoint to non-erodible systems. These systems erode or dissolve eliminating the need for removal. This obviates the risks associate with additional surgery, but it also allows for more flexibility in vitreal placement as the implant does not have to be retrieved. They are eliminated safely from the body and can be administered by injection rather than surgery. The polymer matrix comprising these systems degrades into nontoxic metabolites as drug is delivered. Drug release is generally first order. Examples include Ozurdex® approved for retina vein occlusion and noninfectious posterior uveitis and diabetic macular edema and Brominidine DDS, currently in the clinic for glaucomatous optic neuropathy (Brimonidine DDS for Glaucomatous Optic Neuropathy, investigational, ClinicalTrials.gov Identifier: NCT00693485). Ozurdex® is a sustained-release dexamethasone intravitreal implant. The implant contains 0.7 mg dexamethasone within a PLGA copolymer matrix. It is inserted into vitreous using 22-gauge single-use applicator in an in-office procedure and does not require sutures for wound closure. The implant has been shown to deliver dexamethasone to the retina at therapeutic drug concentrations for up to 6 months [45].

Newer approaches include the use of poorly soluble solvent vehicles. ICON Biosciences has developed its Verisome® technology as an intraocular delivery platform. The technology involves injecting a suspension of drug in a poorly soluble solvent. The drug releases as the solvent solubilizes giving a more linear release and little residual vehicle upon exhaustion of the delivery system.

Future Directions

Compliance and effective delivery of ophthalmic drugs remains an issue, especially in the aging population. There is a need to address the patient centric issues surrounding self-administration. Hopefully, this will continue to drive innovation to

find new and innovative ways to improve topical ocular delivery to the eye. Additionally, we expect novel anterior segment and posterior segment delivery systems, implants and devices to further ensure patient convenience, compliance, and treatment efficacy. Delivery to the posterior segment is most effectively achieved by direct intravitreal injection or implantation. Less invasive administration will be a significant goal for new small molecule, protein, and peptide delivery systems. Sustained delivery will also greatly reduce patient and provider burden.

As biologics become more important for treating ocular conditions there will be a heightened need to address issues specific to this class of drugs. Proteins offer unique challenges. Proteins are macromolecules and as such have low ocular bioavailability. They also pose stability challenges, requiring activity to be maintained throughout the manufacture process, on storage and throughout the drug release period. The formulator also needs to be conscious of aggregates that may form within the delivery systems. New drug delivery systems, polymers and devices are being developed that should vastly improve delivery of drugs to the anterior and posterior segments of the eye. These include systems as diverse and encapsulated cells and microelectromechanical systems. It is an exciting time to work in the area of ocular drug delivery.

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Developing Drug Administration Devices for Geriatric Use

Tom Sam

Abstract Older patients, frequently suffering from multiple chronic diseases, tend to have difficulty in using injectables, patches, eye droppers, nebulizers, inhalers and more complex devices, since such administration devices often require challenging preparatory, administration and disposal steps. Preventing user error is important, especially in the case of critical errors affecting the outcome of the treatment. Prescribers can employ the therapeutic trinity tool to discuss and select the optimal administration option for their older patients; depending upon the choice, prescribers may need to test the older patients for cognitive and physical ability to properly handle the device. Knowledge of the impact of physical and cognitive limitations of elderly patients for drug self-administration is a prerequisite for companies designing administration devices to be used by an aging population. Strict adherence to regulatory requirements for the development of drug/device combination products, such as applying design control and risk management under a suitable quality management system, is essential for obtaining a finished administration device with acceptable safety and the desired performance in older patients. This includes usability and human factors studies of both prototype and finalized device designs, performed in environments simulating those of home and domiciliary care. Directly involving older patients in all phases of development of administration devices is highly recommended. Usability testing of administration devices should be performed with all relevant subsets of the older adult population, paying attention to the specific human factors of each subset, including their physical, sensory, emotional and intellectual capabilities. Here, companies must take into account that the manufacturers include adequate numbers of older population, even within a single age category, is very heterogeneous, and it is therefore recommended that elderly persons with different degrees of frailty in validating the safety and performance of administration devices.

Keywords Geriatric device · Self-administration · Usability · Human factors · Home care

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S. Stegemann (ed.), *Developing Drug Products in an Aging Society*,
AAPS Advances in the Pharmaceutical Sciences Series 24,
DOI 10.1007/978-3-319-43099-7_21

Introduction

Older adults (>65 years) form the most heterogeneous population, with individuals ranging from energetic and healthy to frail and severely ill, often suffering from multiple chronic diseases. However, older individuals from the new generation in general do not want to be labelled as old or as elderly. They want or are expected to continue living as younger adults with everything under control, continuing to stay in their own homes. They understand their right for care, but also realize that they have to take responsibility for their own situation. Caregivers and health professionals therefore face challenges in adapting the way they design care. Consensus in the Netherlands is that the following five concepts are keys to success in this situation [1]. (1) Older adults need to retain control in their own hands, consciously think about their home and environment, and invest in resilience to set goals and stay connected with loved ones. (2) Health care should promote a conscious life style and early detection of vulnerability, thereby potentially delaying and sometimes even preventing the negative effects of aging. (3) The personal needs of older adults must be central. Listening to these needs and acting accordingly is a prerequisite for good housing, welfare and quality of care, taking into account the older adult's financial constraints. (4) An optimal balance should be found between informal and formal care, between disciplines and lines, and between the home front and the institution providing care. (5) Promising innovations should be selected and implemented, and room should be made for new initiatives. Older adults should be involved both in the development and implementation phases of such innovations.

The changing health care environment for older adults also requires new modalities for medical care. Here we focus on the impact of the administration of medications, more specifically on the use of self-administration devices by the older patient. Unlike standard types of medicines such as tablets and capsules, the number of steps involved and the complexity of handling administration devices usually require much more input from the patient. When not carefully designed, taking the older user into consideration, the risk that drug administration might go wrong can be substantial. What are the specific requirements of self-administration devices for older adults? What are the options and what are the limitations? Here it is helpful to understand the contribution of the separate parts of a therapeutic delivery system and to obtain a holistic view of the relationship between the administration device and the other components of self-administration.

The Therapeutic Trinity Concept

Syringes, pens, inhalers, eye droppers, dosing cups and transdermal patches are all examples of administration devices frequently used by elderly patients. They can be an integral part of an entire system, such as an insulin cartridge placed inside an

insulin pen device packed in a tray inside a carton package. It is also possible that such parts are not integrated, but separately co-packed, e.g. in a single blister pack. In some cases the administration device is referred to only in the patient leaflet, and must be obtained separately from the pharmacist or in other ways. Finally, it is possible that administration devices are only generically indicated or not even specified, but that their use is a logical outcome of the pharmaceutical dosage form or dose, e.g. a spoon, a dosing cup, an oral syringe or a tablet splitter device. To further add to this complexity, in practical situations the regulatory classification of administration devices may vary. For example, the FDA considers a transdermal patch to be a combination product, since it comprises two regulated components—a drug and a medical device—that are physically combined and produced as a single entity. In the EU, however, a transdermal patch is considered a dosage form, in the same category as tablets and capsules. In this document, the focus is on the user interface of the administration function of the system—in short, on the administration device. The various situations above represent different regulatory classifications, and this may differ by country and by region. Depending upon the regulatory situation, the administration device is or is part of a medicinal product, a medical device, a drug/medical device combination product, an assistive product or a household tool. Regardless of the regulatory classification or the exact way the various constituent parts are brought together, it is important to recognize that it is the combined action of all parts that leads to the desired therapeutic outcome, and it is the administration device that is responsible for the main user/device interaction.

These devices are used either directly by the patients themselves for drug administration or by caregivers and health coworkers, depending upon the condition of the patient, the specific health care setting and the device complexity. In order to provide optimal therapeutic outcomes for patients, administration devices must be designed in such a way as to form an integral part of the so-called therapeutic trinity, along with the other two components, the pharmaceutical product and the packaging (Fig. 1) [2]. During development, the individual constituent parts themselves, as well as their interactions with one another, need to be optimized towards a combined product with optimal therapeutic outcomes for the elderly patient.

Developing administration devices that will perform optimally in the hands of older adults requires in-depth understanding of the aging population in general, and the individual patient in particular. As stated in the introduction, as a key to success, optimal development requires not only adequate consideration of the patient use requirements, but the direct involvement of the elderly in the development of the administration device as well.

The therapeutic trinity concept can be used both as a guiding principle during development and for option analysis during the medication prescription process. Physician and patient, together, can select the trinity of optimal usability for the patient, a combination that may not necessarily be the cheapest or best on the market, but the one that is most suitable for that specific patient. This could mean a different formulation or a different but therapeutically interchangeable active pharmaceutical ingredient, possibly allowing for a different administration device or

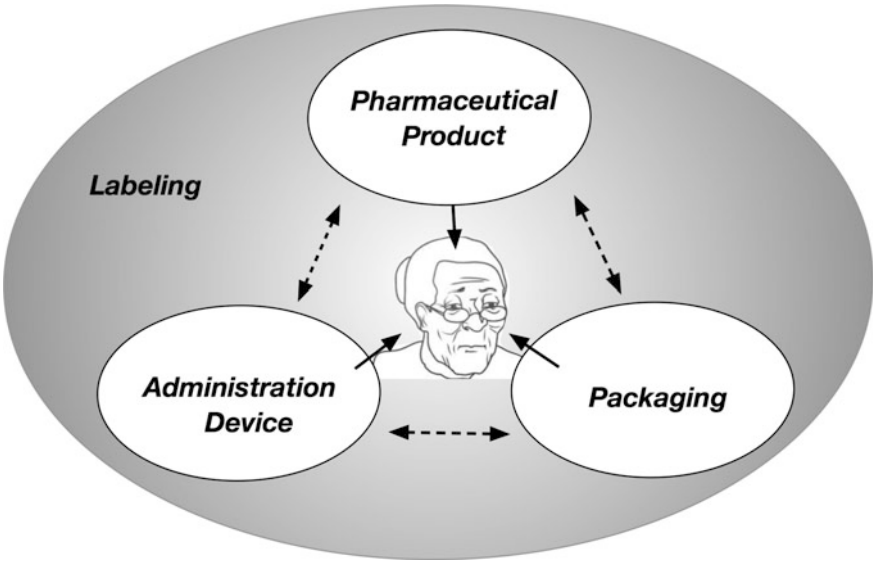


Fig. 1 Development of a "therapeutic trinity" with optimal therapeutic effect requires the mutual optimization of administration device, pharmaceutical product (active ingredient and formulation), and packaging towards the needs and capabilities of the (elderly) patient (scheme adapted from [1]). Labeling including device Instructions for Use is an integral part of the finished product

route. This exercise may lead to the choice of a different type of administration device or a device from a different manufacturer with a more suitable design. Or it may lead to a product with different packaging having more suitable characteristics. In this context, one should realize that the simplest approaches will generally be the most effective, and this could well be a simple tablet or oral solution. The above implies that physician and patient must be aware of the alternatives or be able to search for them in the appropriate databases.

Developing Drug Administration Devices, Emphasizing Usability and Human Factors Testing

The only way to arrive at a drug administration system suitable for a certain target population and disease is to incorporate not only the technical requirements but also the usability requirements into the development process right from the start. It is, in fact, a well-accepted regulatory requirement to demonstrate that usability principles and human factors have been respected in the development process. Instead of looking critically at the user as the cause of error, usability testing must be employed by the manufacturer to scrutinize device design for potential safety issues, focusing on how the product performs and how easy the device is to use

repeatedly over time. In the European Union the regulatory status of drug/administration device combinations is defined by the mode of action of the principal intended use. In practice, therefore, a drug/device combination is usually dealt with as a medicinal product, perhaps with a device constituent part that needs to adhere to the essential principles of the EU medical device regulations. In the USA, these products are considered drug/medical device combination products, with the drug needing to adhere to the pharmaceutical legislation and the administration system to the medical device legislation. In some cases the administration device is marketed separately from the drug product, and in this case the administration device is to be developed as a standalone medical device. This also holds true for dosing devices such as pipettes and measuring beakers intended to administer the medicine. In either case, the bottom line is that the administration device is developed applying the mandatory medical device standards, including usability testing. Important standards for developing medical devices are ISO 13485, Quality Management Systems [3], and ISO 14971, Risk Management [4]. Clinical evidence must be provided to support the use of a medical device in humans [5]. In the development process of drug/device combination products, the company should take care that both the drug product and the device are developed in such a way that the combined product has optimal quality, and hence is safe and effective for the patient/user. The developer must optimize the impact of the device on the medicinal product and vice versa, since it is the combination of the two that determines the overall benefit/risk ratio. Here we focus on use-related hazards rather than on device failure hazards, realizing that these may partially overlap. The use refers to the basic function of the device, such as dose metering, flow resistance and handling sequence. The interface refers to how the device communicates with the user, e.g. the dose counter, graphics to guide the device's use and the degree to which operations are intuitive.

EU Medical Device Directive 93/42/EEC emphasizes the need to consider ergonomic design and that the level of training and knowledge of the user should be taken into account. The aim is to design for patient safety by reducing the risk of use errors related to the ergonomic features of the device and the environment in which the device is intended to be used. The device design should consider the technical knowledge, experience, education and training, and where applicable the medical and physical conditions of intended users (design for lay, professional, disabled and/or other users). In the case of design for self-administration, the patient is the intended user; in the case of intended assistance by a health coworker, the device should be developed taking this into account.

Usability refers to the process of understanding how a product will be used to achieve a desired task. Usability is defined in the ISO/IEC 62366 standard [6] as the characteristic of the user interface that establishes effectiveness, efficiency, ease of user learning and user satisfaction. When translating this standard definition to the daily practice of developing administration devices for older adults, usability assessments seek to answer questions such as: How difficult is it for older adults with a specific disease condition to use this drug administration device in their home environment? How much time does it take for the older adult to complete a

task with the drug administration device? Does the administration device accommodate the abilities and needs of the older adult user? How much re-learning do older adults need when there are gaps in use? How often do older adults make errors during use? How serious are those errors? What can be done to reduce or eliminate user error? And is the drug administration device enjoyable or frustrating to use?

Evaluation of Human Factors (HF) is intrinsically embedded in a robust usability process and involves the study of how humans interact with the world around them. The aim is to improve safety and performance, and to evolve the device through improving the use experience. Human factors are defined in the ANSI/AAMI HE75 standard [7] as the application of knowledge about human capabilities (physical, sensory, emotional and intellectual) and limitations to the design and development of tools, devices, systems, environments and organizations. Human factors examines the physical, cognitive and social abilities of the various user and stakeholder groups, their demographics, lines of communication and hierarchy, workload, fatigue and situational awareness. An evaluation of the use environment scrutinizes complicating factors for device-user interactions such as physical dimensions, lighting, noise pollution, air temperature, material choices and electrical power availability. The functional series of tasks that revolve around preparing, operating and concluding the use of a device are also interrogated and deconstructed. Outcomes of the usability/HF studies of drug/device combinations may influence the patient's perception and attitudes towards the treatment, demands of the user and support to the patient to adhere to the dose regimen, and may even lead to reconsideration of the dose and the route of administration. Successful usability/HF studies potentially support claims that the administration system saves time and resources for the health care system, eases the administration or self-administration in cases of chronic diseases, solves storage and disposal issues, reduces errors, leads to better compliance and reduces risks for infections or injuries.

Medical device product realization encompasses several design steps (Fig. 2) in which human factors and usability engineering take place. An ISO standard [7] (which is voluntary, however, and therefore not a strict requirement), an FDA Guidance Document [8] and an IEC standard [9] detail the steps in analyzing, specifying, designing, verifying and validating usability related to the safety of the medical device. The international standard IEC 62366 for medical devices, Application of usability engineering to medical devices [9], is a standard which specifies usability requirements for the development of medical devices. It is harmonized by the European Union (EU) and the United States (USA), and therefore can be used as a benchmark to comply with regulatory requirements from both these markets.

The device design process can be subdivided into several steps. The first step is defining the intended use, the intended users and the intended environment of use. In addition, the intended medical application, patient population, part of body or tissue in contact or interaction with, the user profile, the conditions of use and the operating principle need to be specified. One approach for capturing and assessing the primary use factors is a combination of in-depth user inquiry and in-field or

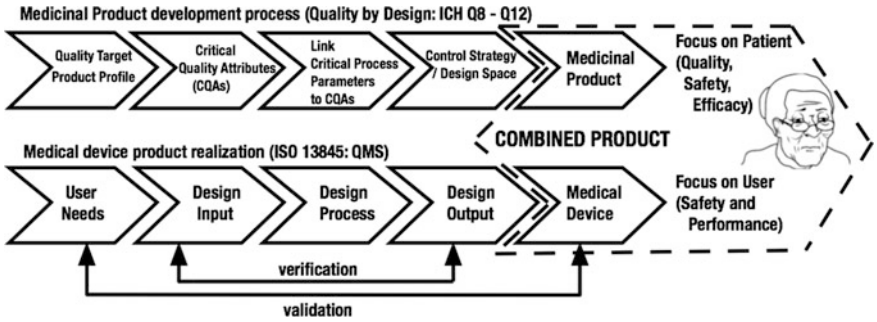


Fig. 2 Schematic representation of the development process of a drug/device combination product with two development lanes which need to be interconnected from the start through risk management and human factor/usability testing applying an appropriate quality management system (QMS) (Scheme adapted from [100]). ICH Q8–Q12 refers to the quality guidelines covering the quality by design concept for the development of medicinal products from the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH), describing the various steps to be taken including the definition of a Target Product Profile, and the evaluation of critical quality attributes (CQAs) and critical process parameters. ISO refers to the International Standards Organization

simulated contextual observation [10] Other types of research activities can also be deployed, ranging from focus groups to team interviews, surveys, competitive research and ergonomic assessments. Qualitative approaches can be used as well, such as interviews until theoretical saturation. Users of home use devices differ from health care professionals. Home use devices should be designed for ease of use and understanding, since home users typically cover a larger range of capabilities and disabilities with regard to physical factors (size, mobility, dexterity, coordination, flexibility, strength, stamina), sense/perception (vision, hearing, tactility), cognition (ability to process information, literacy level, cognitive impairment, experience and willingness to learn or adapt to the device) and emotional differences related to the use of the device (e.g. anxiety to operate). Consider that users, and especially older adults, may interact with the device in inappropriate ways. For home use devices intended for medical conditions that can cause functional impairments, it is important to design the devices to be usable by individuals with such impairments. Older adults quite often suffer from multiple chronic diseases, which could influence device use for treatment of any one of the diseases. In fact, among the growing US elderly population, 30 % have three or more co-morbidities [11]. The detailed steps of use should be deconstructed and documented in task workflow mapping exercises, which will later become a framework for risk analysis.

In designing a home use device, the company should account for the range of environments in which it might be used in the applicable environmental conditions, e.g. urban/suburban/rural, school/office/retail environments and train/plane/car [12], and how these locations would affect not only the device's ability to function but also the user's ability to use the device safely and effectively. Especially for the

more complex home use devices, the responsibilities of the care partner, the caregiver and the care recipient should be specified. Design of portable and body-worn home devices should anticipate that users will travel. During the development phase, pilot or formative usability/human factors studies are usually performed, including prototype tests and mock-up reviews, to allow for identification of unknown problems such as negative effects of the environment, exceeding the capability of the user, gaps with the expectations or intuition of the users, unexpected use by the users, or unveiling of expected inappropriate use for which adequate controls were not applied. Risk analysis should evaluate not only human factors errors and failures, but also their probability of occurrence and potential impact on clinical consequences, and their root causes. If usability testing is required, either the residual human factors risks must be deemed acceptable, or modifications should take place on interface design, user instruction and/or training to further mitigate the risks. After each modification, retesting should be done to assess the effectiveness of risk reduction and the absence of new risks introduced by the modification.

In this step, the use-related hazards are identified, and an estimation and prioritization of the use error risks is given. Preparation of industrial design concepts and computer modeling or rapid prototyping is essential at this stage, initially as straw-man stimulus, but then quickly evolving into more functional appearance models to uncover deeper usability insights and elicit user feedback. An estimate of probability of use error can be obtained by consideration of the most frequently used functions. Known/foreseeable hazards and hazardous situations can be identified by evaluating task requirements (e.g. cleaning needs, transportation requirements), analyzing the context of use (spatial, social, technology, hygienic, physical, activity), constructing a mental model for use and defining the user interface. In a typical usability test session, representative device users perform selected tasks under conditions of simulated (not actual) use in an appropriately realistic environment.

Step two involves the establishment of the usability specifications, followed by implementation of risk controls. Acceptance criteria are defined for the primary operating functions in terms of usability, user interface design and implementation. It is important to note that the Patient Information Leaflet/Instructions for Use (IFU) document is not considered to offer risk control for any device, because warning labels can be ignored by or confusing to the user. In cases in which the device needs to give a signal to the user, it is recommended that such a signal is given in at least two of three modes: visual, auditory and tactile. If needed, some types of risks can be mitigated by holding appropriate training sessions covering, in addition to standard handling, the emergency procedures for care recipient, caregiver and care partner in case of serious adverse events.

In step three, usability verification and validation must take place. The final usability testing/human factors studies should be performed with the finalized device design and labeling (IFU, brochures) and should be repeated if design or labeling changes are required. The usability/human factors validation study is used to gather evidence that the administration device is safe and performs adequately as

intended. The final study tests the fully functional model of the device in its finished packaging with all support documentation in the simulated use environment, replicating workflow distractions and delays between training and actual use. The study focuses on the tasks and tests for user comprehension, ergonomic ease, dependence on Instructions for Use, task completion, error frequency and close calls, successful timed tasks evaluation as well as subjective performance rankings. The design validation must ensure that devices conform to the predefined user needs and intended uses. At least 15 participants from each distinct user group need to be recruited to provide a sufficiently reliable sample. User input is gathered from close-ended interview questions and the data are tabulated for comparison against benchmark metrics from comparable devices, if available. Particular emphasis at this stage is on potential error frequency and root cause analysis. It is important to establish whether new risks have emerged in these validation studies, and if so, whether the overall residual risk should be further mitigated or can be considered acceptable.

In the post-marketing surveillance stage, it is important not only to monitor the known/foreseeable risks, but especially to be aware of unanticipated risks. It is important to realize that in the final design of the device, prioritization and balancing of user needs and feature tradeoff often have taken place. How CGMP compliance of the manufacturing of a combination product is assured, including control of changes, is covered in the FDA guidance on CGMP requirements [13].

User Characteristics of the Older Adult Population

The United Nations divides the elderly population into age groups of elder persons (60–64 years), old persons (65–90 years) and very old persons (>90 years). Approximately half of the adults over 55 years suffer from some kind of functional limitations or impairments (vision, hearing, motor and/or cognitive). How can the characteristics of the aging patient influence the development and use of drug administration devices?

1. Older adults may suffer from perceptual changes, especially loss of sight, hearing and touch. Loss of sight may influence the readability of patient leaflets with instructions for use of the administration devices, and of text on the administration devices themselves, especially under the generally dim conditions of a patient's home setting. Loss of hearing may hamper the signaling of audible feedback signals, such as the clicking of pen injectors. Loss of sensation and fine motor control may lead to difficulties in manipulating buttons, knobs and levers.
2. Older adults may suffer from decline of psychomotor functionality, affecting grip strength, dexterity, coordination, manipulation and mobility of hands and arms, which may affect their capability of appropriately handling administration devices.

3. Older adults may suffer from a reduction in cognitive functionality, which may lead to difficulties when the user/device interface is overly complex, when feedback is not presented clearly or intuitively, when there is no adequate instruction for use, when manipulating controls gives unexpected results, or when they are asked to remember difficult or complex operational routines.

In addition, psychosocial factors may play a role when individuals do not feel comfortable using administration devices. This may be due to the lack of previous experience with similar devices, the perceived complexity of the device, the lack of opportunity to use the device experimentally or lack of exposure to new devices in social context, the opinion that they can administer the medicine without the device, or a mismatch between the device and the lifestyle of the older person. A complicating factor is that older adults even in the same chronological age range are a very heterogeneous group with largely differing capabilities. The capability to handle an administration device may vary substantially across elderly patients of the same chronological age group [14]. This is due to the variation in the degree of frailty among the elderly, on one hand caused by the variability in the diminishing physiological and mental capabilities, and on the other hand by the substantial proportion of elderly individuals suffering from one or more chronic diseases. The frailty index represents the proportion of deficits that older adults accumulate over time, and can be evaluated from a structured clinical examination including vision loss, hearing loss, impaired mobility, vascular problems, gait abnormality, impaired vibration sense, difficulty in toileting, difficulty in cooking, difficulty in bathing, difficulty in going out, difficulty in grooming, skin problems, resting tremor, changes in sleep, difficulty in dressing, urinary complaints, gastro-intestinal problems, diabetes, hypertension and limb tone abnormality [15]. Rather than comparing individuals of similar chronological age, therefore, it is better to take frailty into account and consider patients of the same biological age. The difference between chronological and biological age can be estimated from an individual's frailty index. Since the frailty index is a sensitive predictor of survival, personal biological age strongly correlates with mortality, even more than chronological age. Biological age can also be estimated directly from biomarkers (recordable molecular or cellular events) indicative for an individual's development.

The user/device interface encompasses all components of the administration device, including the labeling with which the user interacts. Device labeling includes instructions on the use of the device itself, plus package inserts and package labels. Successful drug self-administration will take place only when the perceptual, psychomotor and cognitive capabilities of the older patient are still at a level that exceeds the demands of the device, in order to successfully administer the drug. Also, adequate health literacy is required. Sight, hearing and touch are the three senses that are responsible for the majority of the perceptual interactions with an administration device (Fig. 3).

Administration devices to be used by elderly patients should be developed with the understanding that aging has a substantial effect on visual performance (Fig. 4). Age-related eye diseases include cataracts, age-related macular degeneration,

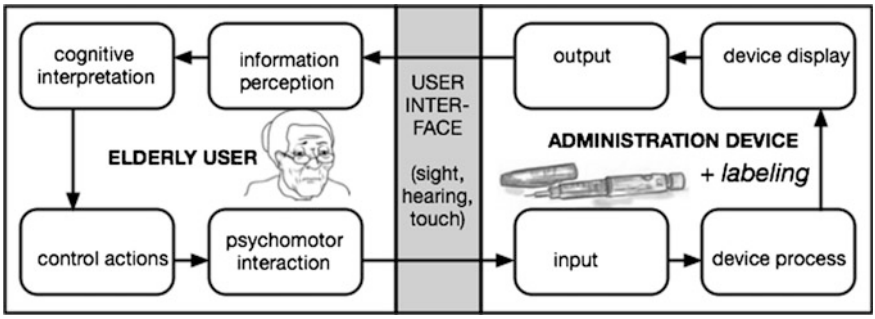


Fig. 3 Schematic presentation of the interface between a(n elderly) user and a drug administration device, the actions performed by the user and the device, and the interactions between them (Scheme adapted from [101])

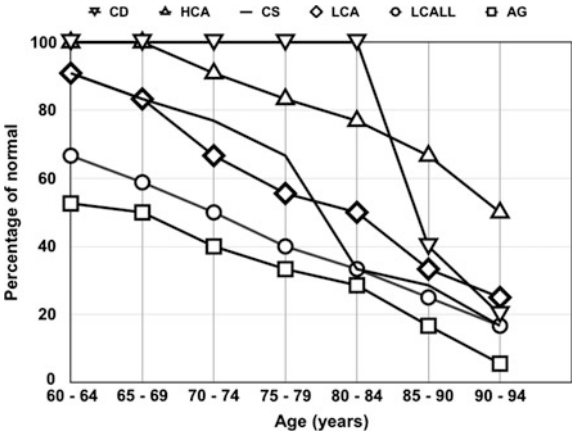


Fig. 4 Development of administration devices to be used by older adults should consider the effects of aging on the various aspects of vision performance e.g. low-contrast acuity (LCA), high-contrast acuity (HCA), low-contrast acuity in low luminance (LCALL), acuity in glare (AG), color discrimination (CD) and contrast sensitivity (CS). Data taken from Brabyn et al. [102]

glaucoma and diabetic retinopathy. High-contrast acuity, the capacity of the eye to see fine detail under conditions of high contrast, declines with age. However, low-contrast acuity, manifest under low luminance conditions, which is important when viewing grayscale images, declines even faster. The relevance of luminance for using administration devices by the elderly at home becomes clear when one realizes that home lighting can be as much as 4 times dimmer than hospital and office lighting. Whereas color discrimination shows a sharp deterioration only after the age of 80, acuity glare, the ability to focus vision when in the environment competing light sources are present, at high age is virtually reduced to zero. The ability to visually distinguish an object that contrasts poorly with its visual surroundings shows a rapid age-dependent decline similar to that of low-contrast acuity. Designers of senior rooms are discouraged from adding a brighter bulb in the center of the room, since it increases glare and casts shadows on work surfaces; it is recommended instead to install bulbs casting light directly on the work surfaces

to create safe, effective lighting. In general, elderly people require three times the amount of light to see as well as younger people and they are more sensitive to glare and light changes. Older people have a decreased ability to see in dim light and to see contrast and have decreased depth perceptions and visual acuity.

Administration devices to be used by the elderly should be developed with the understanding that age-related decline of auditory function can be substantial (Fig. 5). It may be difficult for the elderly person to hear beeps and alarms above 2 kHz, to hear low-amplitude beeps or alarms, and to hear verbal feedback that is not clear and reasonably paced. Moreover, it may be difficult for the older adult to localize sounds and to discriminate acoustic signals that are short in duration [16].

Administration devices often require hand use to manipulate small interface components, e.g. to dial, push buttons, slide switches or turn knobs. Fine motor control of the upper limbs such as grip, dexterity, coordination, manipulation and mobility are therefore critically important for proper use of an administration device. A reliable and valid objective parameter of the functional integrity of the hand is grip strength [17]. There are two types of functional handgrip: power grip and pinch grip. Power grip is employed when the hand is grasped around an object. Pinch grip is when the fingers are on one side of the object and the thumb is on the other [18]. The change in strength of these grips with age is well documented [19]. Depending upon the administration device, it may be useful to test the elderly user for power and/or pinch grip as a measure for the functional capability of the hands to fulfill the requirements for handling the administration device. Also the tactile threshold point above which an external stimulus such as vibration feedback evokes a response in the patient, especially at the fingertip, can be critical to the performance of an administration device [20]. The thresholds of touch sensation increase with age, including those for light touch, vibration sense and spatial acuity. Older subjects, for instance, need twice the distance to discriminate two points. Loss of sensation and fine motor control can therefore lead to serious difficulties in proper use of administration devices.

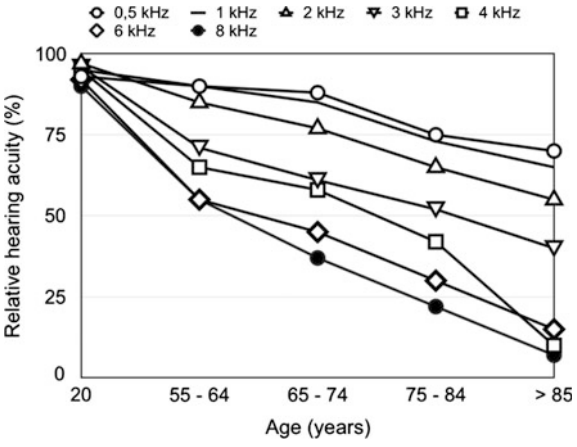


Fig. 5 Development of administration devices to be used by older adults should consider the effects of aging on hearing acuity (here defined as 100 % minus relative increase in pure-tone thresholds hearing level). The rate of decline depends upon the frequency range. Data taken from Kiely et al. [103]

Understanding the functioning and use of administration devices requires cognitive capabilities and a minimum of health literacy. Patients need to understand the instructions as given during training and in the Instructions for Use, and need to be capable of translating the knowledge acquired into appropriate actions. Decline of cognition occurs with age [21]. Except for vocabulary performance, performance declines in all cognitive domains across all age groups [9] (see Fig. 6). However, an individual's past experience, living environment, social situation and level of education may also influence cognition decline [22].

When selecting elderly patients for self-medication, prescribing physicians, especially when they need to use more complex administration devices or regimens, should recognize the fact that many older people who are developing dementia are not diagnosed as such in the early stages of disease or are never diagnosed with dementia at all. One US study showed that physicians were unaware of cognitive impairment in more than 40 % of their cognitively impaired patients [23]. The National Institute on Aging recommends that patients be screened for cognitive impairment if the patient is over 80 years, when the patient himself, family members or others express concerns about changes in memory or in thinking, or if problems/changes in the patient's memory or thinking are observed. Other risk factors that could indicate the need for cognitive impairment screening include low education, history of type 2 diabetes, stroke, depression and difficulty in managing money or medication [24]. It is suggested that physicians apply similar criteria when screening for prescribed medicines to be self-administered.

In order to decide whether an elderly patient is capable of self-administering medicines, it is important to know not only the chronological age of the patient, but also to have information on her or his personal health condition. Impairments in physical, cognitive and/or social capability may have turned the relatively healthy and fit elderly person into a frail person, not capable of autonomous use of administration devices. To guide such decisions, objective and standardized methods are recommended to provide quantitative estimates on the degree of frailty.

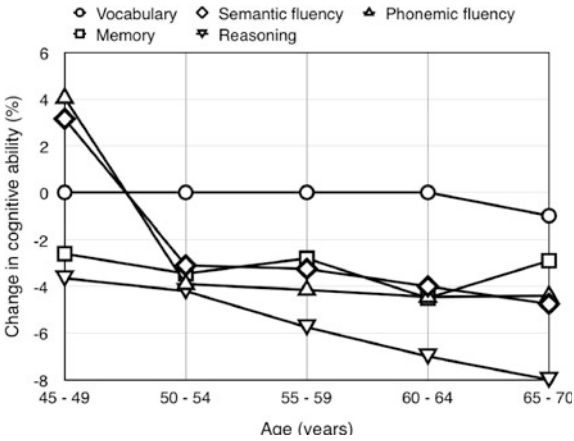
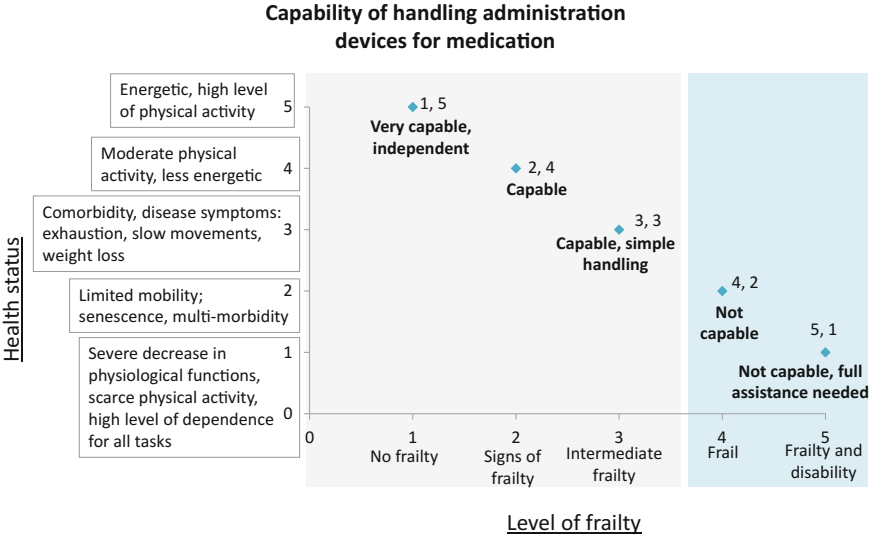


Fig. 6 Development of administration devices to be used by older adults should consider the effects of aging on the various aspects of cognitive ability. Data taken from Singh-Mantous et al. [21]

Although frailty is a complex clinical syndrome and includes features such as weakness, slowed motor function, weight loss, muscle wasting (sarcopenia), exercise intolerance, frequent falls, immobility, incontinence and frequent exacerbations of chronic diseases, relatively simple tests such as gait speed and handgrip strength can be used as surrogate parameters to estimate a person's degree of frailty. The frailty of the population increases non-linearly with chronological age, being on average approximately 10 % at the age of 60 and 30 % at the age of 95 [25]. It has been recommended, therefore, to screen all persons of 70 years and older for frailty [26]. A global clinical assessment of frailty based on physical function and level of independence with activities of daily living has been proposed based on distinguishing three classes of frailty (see Table 1 and Fig. 7) [27]: (1) Fit and well, (2) Mildly/moderately frail, (3) Severely frail. Such a classification may be used to estimate whether the patient is capable of more complex handling as is needed for employing self-administration devices.

Prescribers should realize that for a large segment of the older population, chronological age is not a relevant marker for aging, because the elderly population is very heterogeneous. The aging process occurs in different individuals at different speeds and impacts (Fig. 7). Within every age group a significant percentage of

Table 1 Categories of fitness and frailty in elderly people and potential impact on self-administration capability of medication



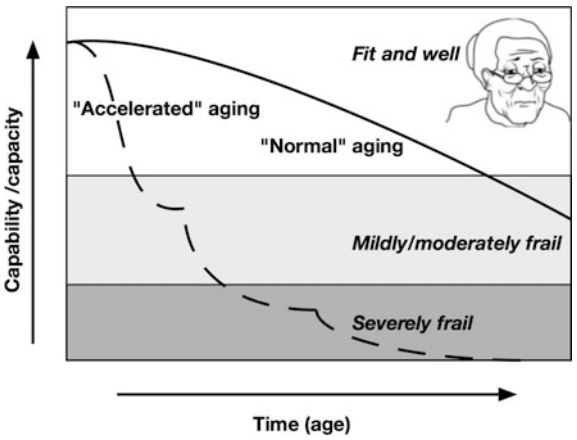


Fig. 7 Individuals display different physical, cognitive and social capability trajectories over their life course. Those individuals aging faster cross the thresholds of frailty and disability (severe frailty) years before death (based on a study from Rockwood et al. [27] to reflect that accelerated aging often occurs as consequence of a series of incidents and/or chronic diseases acquired)

older people can be considered healthy. In the USA, 48 % of those aged 51–54 and 28 % of those aged >85 have excellent or very good self-reported health status; similarly, 89 % of those aged 51–54 and 56 % of those aged >85 report no health-based limitations in work or housework [28]. Judging capability to take medicines and handle administration devices can therefore never be based on chronological age alone. Consequently, the concept of age-appropriateness for dosage forms or administration devices is non-practical, in contrast to what has been suggested [29].

Instead of using a general frailty criterion to estimate a person's capability of handling complex devices for self-administration and need for support, a self-medication risk assessment tool could be developed similar to the one piloted by Lubinga et al. [30], considering 13 items related to medicine taking, covering comprehension, motivation/insight, reading labels, dexterity and coordination.

Home Health Care Environment

The use of medications and their administration devices by the elderly patient is increasingly taking place at home, due to two parallel health care macro trends. First, there is the increasing intent among both healthy and frail elderly individuals to stay at home as long as possible; and second, more recovery time is being deferred to the home, as patients are discharged sooner from the hospital, and nursing homes delay and limit access to only the severely frail. Moreover, health care cost is an important driver of self-administration [31]. Patients are expected to undertake their own care using products with minimal, if any, professional training. Since the increase in longevity is accompanied by increases in chronic conditions, these now require management in the home and attention from community health services. This has led companies to develop innovative technologies suitable for the

home situation, including devices for drug self-administration, assistive devices, and even robotic and domotic systems. Design for safe use of medical devices and new technology should consider the many human and other factors (Fig. 8) that potentially contribute to the safety and quality of the treatment in the home health care situation [32]. This includes assessment of the capability of lay caregivers and the suitability of the home environment for device operation. An optimal physical environment that promotes accurate medication use includes five key areas: (1) illumination, (2) minimizing interruptions and distractions, (3) reducing sound and noise, (4) considering physical design and organization, and (5) designating medication safety zones. These ideal environmental conditions are recommended by Grissinger [33] to minimize distractions for an elderly patient.

Even if administration devices have been developed for self-administration and patients may have been trained for their use, designers and developers should consider that in daily practice untrained caregivers may perform the actual medicine administration, as was found for self-administration in an institutional setting [34].

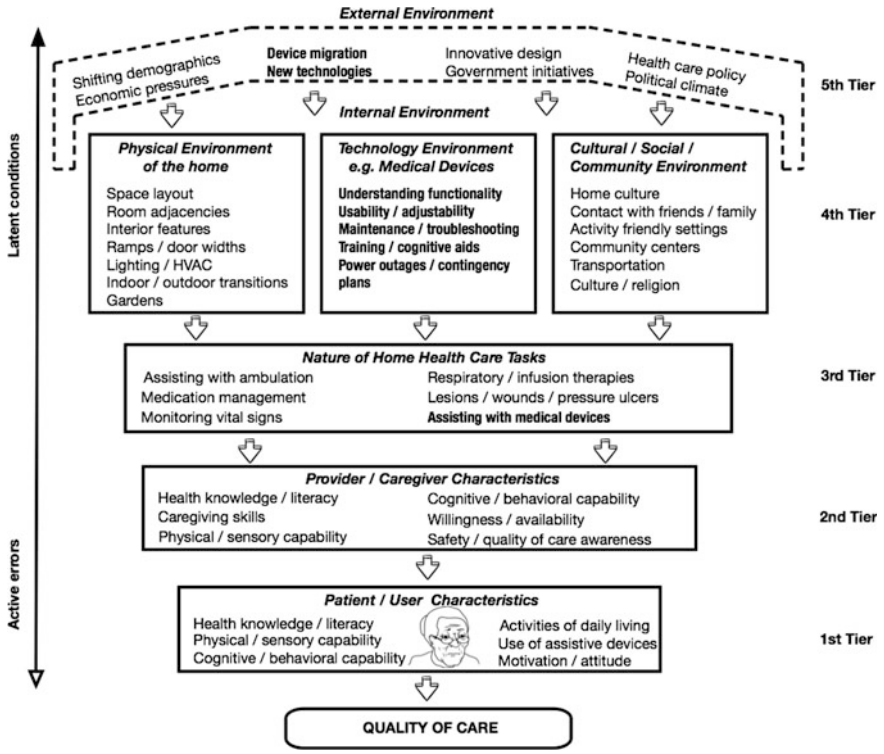


Fig. 8 Apart from patient characteristics, four additional tiers of human and other factors can be distinguished ultimately influencing the safety and quality of the treatment of elderly patients employing medical devices and other new technologies in a home health care setting (an original scheme based on discussion from Farroni et al. [31])

Administration Devices Used by and for the Elderly Patient

The most prevalent diseases affecting the elderly patient are coronary heart disease, stroke, cancer, pneumonia and the flu. Many of the elderly patients suffer from two or more of the conditions shown in Table 2. This makes the geriatric patient a complex patient. It also implies that designers and developers of self-administration

Table 2 Administration devices used in the medical treatment of the most prevalent conditions affecting geriatric patients

Condition	Examples of drug administration devices (self-administered and/or assisted and/or by health coworker)
Diseases affecting heart conditions (hypertension, vascular disease, congestive heart failure, high blood pressure and coronary artery disease)	Nitroglycerin transdermal patches are used to prevent episodes of angina in people who have coronary artery disease
Dementia, including Alzheimer's disease	Different medication compliance aids are available. Simple pill boxes have separate compartments for days of the week and times of day. They can help people remember to take their medication on the right day and at the right time, especially in the early stages of dementia Automatic dispensers for pills to be taken regularly are also available. These are pre-filled by the local pharmacist and then locked. When the medication needs to be taken, the dispenser sets off an alarm and the right compartment opens, allowing the person to access his or her medication. The alarm may continue until the pills are removed from the dispenser. There are also devices that can send an alert to a friend or relative to notify them if the medication has not been taken Transdermal rivastigmine treatment has the advantage of improving adherence in comparison to multiple oral daily treatments [104] or as an alternative in case of swallowing problems
Depression	Commercially available antidepressant and antipsychotic medications that use an administration device are loxapine for inhalation [105] and selegiline for transdermal administration [106]. ADASUVE is an inhalation powder supplied in a single-use, disposable inhaler containing 10 mg of loxapine base. Because of the risk of bronchospasm, ADASUVE is currently in the US available only through a restricted program under a Risk Evaluation and Mitigation Strategy. ADASUVE is not approved for the treatment of elderly patients with dementia-related psychosis, because of an increased risk of death. Studies performed to date have not demonstrated geriatric-specific problems that would limit the usefulness of selegiline skin patch in the elderly
Incontinence (urine and stool)	Oxytrol patches delivering oxybutynin to treat overactive bladder are applied twice weekly and are available as over-the-counter product

(continued)

Table 2 (continued)

Condition	Examples of drug administration devices (self-administered and/or assisted and/or by health coworker)
Arthritis	Half of all people >65 years has some form of arthritis. Pharmacological treatment with corticosteroids may include intra-articular and soft tissue injections with triamcinolone acetonide suspension and methylprednisolone sodium succinate for intramuscular or intravenous injection. Self-administration of injectable biological treatments has been made more convenient by development of user-friendly devices ranging from ergonomic pre-filled syringes to auto-injectors and pens
Osteoporosis	Treatment may include a once yearly intravenous dose of zoledronic acid, a 6-monthly 1 mL/60 mg/1 mL subcutaneous injection of denosumap, or a 20 μg subcutaneous injection daily of teriparatide, a synthetic form of human parathyroid hormone, in the thigh or abdomen using a multi-dose prefilled pen
Diabetes	More than 25 % of the US population aged ≥65 years has diabetes. Patients suffering diabetes are approx. twice as likely to suffer from Alzheimer's-type and multi-infarct dementia [107] Insulin therapy makes use of vials and injection needles, pre-filled syringes, pens or auto-injectors. For those markets where it is available, inhaled insulin may be useful for elderly patients as an alternative to injected insulin with greater acceptance of inhaled-insulin therapy for patients with Type 2 diabetes who refuse or are unable to self-inject insulin
Breathing problems	Medical conditions that can cause breathing problems are chronic obstructive pulmonary disease, which includes pulmonary emphysema, chronic bronchitis, and asthma; pneumonia; heart failure; neurological disorders such as stroke; and cancer. Basically two types of inhalers can be distinguished, the pressurized metered dose inhaler (MDI) and the dry powder inhaler (DPI). Drugs used for treatment of COPD and asthma which employ inhaler and/or nebuliser devices for pulmonary drug delivery include aclidinium, beclometasone, budesonide, ciclesonide, fluticasone, formotorol, glycopyrronium, indacaterol, ipatropium, mometasone, olodaterol, salbutamol, salmetorol, sodium cromoglicate, terbutaline, tiotropium, theophylline, and umeclidinium
Frequent falls, which can lead to fractures	Falls are the leading cause of injury-related deaths. About 30 % of adults over the age of 75 and 50 % over the age of 80 has at least 1 fall each year. About 1 in 20 of these falls leads to either treatment for a fracture or a hospital stay. Homes should therefore be monitored for falls hazards (cords, rugs, poor lighting, etc.) and older adults educated about what they can do to reduce their risk of falling. It may be useful to identify those medicines that may cause dizziness and drowsiness. As an example, fentanyl patches may cause some people to become drowsy, dizzy, or lightheaded, especially in their first days of treatment
Parkinson's disease	Rotigotine transdermal patches are used for the treatment of Parkinson's disease

(continued)

Table 2 (continued)

Condition	Examples of drug administration devices (self-administered and/or assisted and/or by health coworker)
Cancer	Fentanyl patches are used for pain management
Eye problems (cataracts, glaucoma, macular degeneration)	The statistics of successfully delivering eye drops to the eye is bad. Several types of eye drop dispensing aids are available to assist in directing the drops to the eye and/or ease the squeezing of the bottle. Eye droppers for multiple use are generally more easy to squeeze than those intended for single use, but may have sharp edges

devices for these diseases and conditions cannot neglect that a large proportion of the patients will be geriatric patients suffering from one or more of these impairments. The current administration devices used by elderly patients, however, do not deserve to be named geriatric devices yet, since they were not developed especially for this patient population, but developed for diseases occurring in the entire adult population.

Only limited and incomplete information can be found in the public domain on the usability and human factor testing of specific administration devices. Literature referring to the user group of older adults is especially scarce. Apart from a few good examples, it appears that there is significant room for improvement. Appropriate incorporation of usability studies and human factors testing in the design and development process is needed to further improve these self-administration systems to allow for safe and effective use by the older adults.

Use of Spoons, Oral Syringes and Dosing Cups by Older Adults

For older adults, the oral route is in general the easiest route for administering medication and therefore the most often used. However, oral dosing may suffer from user risks associated with the use of devices, e.g. in the case of splitting devices for tablets or use of administration devices to measure and administer liquid medication. For the latter purpose, oral syringes, measuring spoons and dosing cups can be used. Studies have found that a considerable proportion of patients and caregivers make errors when dosing liquid medication with measuring devices [35]. This can only be expected to increase with age, since elderly patients often have tremors and generally experience severe difficulties in accurately measuring liquid products. In case of the use of dosing cups, the medication bottle and the dosing cup have to be held at eye level, and the prescribed dose has to be poured into the cup. For older patients it may be more difficult to read the dosing cup graduation and to measure the liquid medication at the base of the meniscus. Especially

challenging is inappropriate graduation or use of dosing cups measuring liquids in anything but milliliters. The FDA has provided some guidance in this area [36].

Also, self-loading and administration of medication with oral syringes is rather difficult to do accurately, especially for those suffering from poor coordination or hand weakness. For older patients it is difficult to turn the bottle upside-down to fill the syringe and, at the same time, to control the dose volume going in.

Use of Syringes and Profiled Syringes by Older Adults

The classic way for a patient to administer an injectable drug is to draw a volume of drug solution from a vial or ampoule into a syringe, with previous addition of a diluent solution if needed, followed by subsequent injection. This procedure may require up to ten discrete activities. The user/device interface encompasses the following elements, which need appropriate design and human factors consideration: thumb pad, flange, plunger rod, barrel needle shield, needle, drug visibility, label visibility, safety mechanism, end of dose feedback, packaging and IFU.

Discomfort with administration technologies has been associated with low therapy adherence. For decades needle-related pain had been associated with injections. However, advances in injection technology have led to needles with improved needle tip designs reducing injection pain and anxiety [37]. For example, patients with type 2 diabetes no longer rank pain in the top 5 of objections as a barrier to injection [38]. Surprisingly, health care professionals persistently had significantly deviating perceptions of patient pain, thereby negatively influencing effective injection therapy [39], demonstrating the significance of the second tier in home health care (Fig. 8).

Especially for those patients who have vision problems, it may be a challenge to draw up a correct drug volume, e.g. of insulin. If vision impairment is mild, a magnifying device can be used which enlarges the size of the markings on a syringe and holds the bottle and syringe in place while drawing the required volume (see Fig. 9). Vials and syringes requires substantial handling by the patient and may exceed the capability of the elderly patient. A pre-filled syringe with its preset volume or an autoinjector pen where the dose is dialed into the pen is probably easier to use.

Only in rare cases have administration devices been developed especially with the geriatric patient in mind. More often, devices have been developed specifically for diseases which have a large incidence in the elderly population. An interesting example is Cimzia, showing many features of an ideal geriatric device.

Case Study: Cimzia

Cimzia is an example of a pharmaceutical product with a device designed to take the physical limitations of the rheumatoid arthritis (RA) patient into account.

Fig. 9 BD Magni-Guide™ device supports visually impaired patients by magnifying the scale on the syringe with a factor of 1.7 (Photo reproduced with permission from Becton-Dickinson)

Cimzia (certolizumab pegol) is a biologic therapy for RA treatment requiring a once- or twice-monthly subdermal injection in the patient's upper leg or stomach area. The mean age of RA patients is in 55–59 years, implying that a substantial proportion of the patient population is older than 65 years. Many people suffering from RA have numb joints, and traditional syringes are therefore usually too small, fiddly and sometimes too painful to use. Moreover, RA patients may only have 25–30 % of the strength of a healthy person. Whereas the injection using lyophilized powder for reconstitution could be prepared and administered only by a health care provider, the new prefilled syringe was specially designed to allow for self-injection, albeit after proper training by a doctor or nurse and with the necessary medical monitoring [40].

Throughout the design and development phases, the Cimzia design team worked closely with six severe RA patients, thereby ensuring that the device would work well for patients with a wide range of dexterity levels. Rather than focusing on a kind of artificial average patient, in these usability studies the focus was on true individual patients, which is considered better practice. Throughout development many different prototypes were tested (Fig. 10). The syringe was designed with a loop on the needle shield, allowing patients to remove the syringe cap without the need for great force. By reducing the needle shield removal force, uncontrolled movement of the patient's hand snapping back towards the needle does not take place, and accidental needle sticks can thereby be avoided (Fig. 11). Parts of the syringe are coated with thermoplastic rubber, which makes the syringe soft and easy to grip. Despite joints that are sensitive to pressure and weakness in their hands, the

Fig. 10 Older patient suffering from arthritis pulling the needle shield from the Cimzia pre-filled syringe (Photo reproduced with permission from Smart Design) [40]

Fig. 11 Prototypes of the Cimzia prefilled syringe used to optimize the user/device interface and make the syringe suitable for a wide range of dexterity levels covering even the most severe arthritis patients (Photos reproduced with permission from UCB S.A. and Smart Design) [40]

RA patients were now able to push down the oversized plunger rod with 48 % more force, enabling more comfortable injection.

Like the syringe, the Cimzia packaging was designed and developed with intensive cooperation from RA patients paying close attention to ergonomic and biomechanical aspects. The packaging was designed to be functional, user-friendly and helpful. The easy-to-open, three-step kit was written in plain language, making it easy to read and understand. The tray accommodates a wide range of patients' dexterity limitations when removing the syringe. As part of the packaging components, a "step-by-step" guide provides the key information from the full Patient Information Leaflet.

Use of Autoinjector Systems by Older Adults

Autoinjectors have been shown to provide a number of benefits, including a reduced risk of injection site reactions, reduced discomfort and greater ease of use compared with manual (syringe plus needle) injections [41]. Patient satisfaction and self-injection rates increase when switching from a prefilled syringe to a prefilled pen, as was demonstrated for elderly patients (mean age 71 ± 15 [SD] years) with chronic kidney disease. At baseline, 48 % of patients self-administered darbepoetin alfa with the prefilled syringe, whereas 74 % did so when they could make use of the SureClick® pen [42].

In a study with 65 RA patients with mild to severe hand disability, the Becton-Dickinson Physioject autoinjector was tested for usability by performing six simulated subcutaneous self-injections [43] (Fig. 12). Fourteen patients were in the age range of 66–80 years. Three steps are required for successful injection: (1) correct activation of the system (use force to press the button), (2) correct pressing of the system to the injection site (use force to press the autoinjector), and (3) removal of the system after the end of the injection (visually detect end of injection). With regard to device performance, all of the automated features and other functions of the device (button activation, full volume delivered and needle cover automatically activated) worked correctly. The needle cover automatically activated on every occasion and no accidental activations were observed. The study showed that patient age, hand disability and extent of previous experience with self-injection had no impact on the ability to successfully comply with the Instructions for Use and to perform self-injection. Perceived ease of use and simplicity of the three-step process resulted in high acceptance scores. Although the

Fig. 12 Simulated subcutaneous injections were performed in a foam pad, mimicking skin behavior [43]. The release button can be activated only if the system is pressed well to the injection site (Photo reproduced with permission from Becton-Dickinson)

difference between 84 and 71 % for young adults (<65 years) and old adults (>65 years) to accept all three main device functions was not significant, a significant difference for age was found in the willingness to accept further treatment by self-injection with the tested autoinjector. The outcome of the study may have been influenced positively, however, by the testing environment, since this simulated a physician's office or a clinic with sufficient lighting rather than the home situation. Unfortunately, no data were provided on the cognitive capability of the patients enrolled. This is important, since it is known that intellectual ability plays a crucial role in self-administration. Comprehensive-geriatric-assessment, especially the Barthel index, was found to be useful to assess the ability of self-injection in insulin therapy by elderly (>70 years) diabetic patients. There was a significant difference between self-administration and non-self-administration ($p = 0.000019$) [44].

A formative study with 36 patients on the usability of a disposable pen platform device for self-injection showed the following distribution of potentially relevant user errors and deviations from the IFU over the subsequent user steps: (1) attach needle (4 %), (2) prime (24 %), (3) select dose (4 %), (4) inject (12 %), (5) hold (21 %), (6) dispose of needle (35 %) [45]. Six user subgroups could be distinguished including subgroups with visual impairments (diabetics with retinopathy), tactile impairments (diabetics with neuropathy) or motor impairments (arthritis patients), health care professionals, caregivers and adolescents. Each of these groups presented different challenges for the user–interface design. Although the subgroups with impairments had larger average numbers of errors per injection (two or even three in some cases), it was believed that the difference in experience rather than the level of impairment explained the observed differences in error rate. It can be argued that for older adults similar findings would hold as for the subgroups with impairments. Although this specific study is not very conclusive, it provides an example of what a study could look like when it would evaluate the usability of an administrative device in different subgroups of older patients.

Use of Transdermal Devices by Older Adults

Advantages of transdermal patch systems are that they are simple to use and can usually be applied independently of meals. Noncompliance to treatment is a recognized issue for elderly patients suffering from long-term neurologic conditions. These patients are often taking multiple medications, so any reduction in the frequency of dosing may increase compliance and may also reduce the burden on their caregivers [46]. In a survey of caregivers, ease of use of transdermal patches for older patients was a common reason for preferring a patch to oral medication [47], although patients themselves may find it more difficult to remember to replace their multiple-day patch compared with the daily routine of oral ingestion. Disadvantages can be skin reactions on the application site and lack of adhesion, as was reported for older patients who substituted the Exelon® (rivastigmine) transdermal patch with the Permente® patch [48, 49].

Transdermal patch delivery systems available for the treatment of neurologic conditions in adult populations include the rivastigmine patch for the treatment of mild to moderate Alzheimer's disease and Parkinson's disease dementia, the rotigotine patch for the treatment of Parkinson's disease and restless legs syndrome, the selegiline transdermal system for the treatment of major depressive disorder, and the lidocaine patch and capsaicin patch for the relief of pain from postherpetic neuralgia. In clinical practice, no significant differences in absorption of drugs from transdermal delivery systems have been demonstrated between young and old individuals [50].

One particular advantage in the use of patches is their physical presence on the skin. If visually detectable, this provides reassurance to the patient and caregiver that the medication has been administered [51]. Visibility of patches is now considered a critical aspect of regulatory assessment in the EU, not only to detect removal of older patches to circumvent overdosing, but also to detect unintended and risky transfer of the patch to other persons, especially children. In its Drug Safety Communication [52] the US Food and Drug Administration required color changes to the text on fentanyl pain patches so they could be seen more easily in an effort to prevent accidental exposure.

Rotigotine transdermal patches have been reported to not always stick well and tape is used to overcome this; also, the silicone adhesive has been given rise to dermal problems. Application-site reactions were generally mild to moderate in severity; where reported, up to 3 % of patients had severe skin reactions [53]. To prevent patches falling off and sticking to someone in close contact, patients should check periodically by sight or touch to make sure that the patch is still sticking to the skin properly. Patients should tape down the edges of a patch that become loose or cover the patch with a sticky adhesive film.

In patients with dementia or cognitive impairment, a beneficial approach to monitoring of patch placement and dosing could be marking the date of application on a piece of medical tape applied in close proximity to the patch to serve as a reminder of date of patch placement [54]. This method of risk mitigation may reduce adverse drug reactions, including overdoses. While some advocate the practice of writing directly on the backing of the patch, it is unknown whether ink could cross this barrier and interact with active drug. Furthermore, a sharp pen may puncture the backing liner of the patch, leading to leakage and contamination of the environment [55].

Microneedle patches are seen as a promising development overcoming current delivery problems, e.g. of macromolecular medicines and vaccines. An initial study using placebo patches indicates that microneedle patches are usable and may lead to improved intention to use the medication [56]. Usability of microneedle patches for self-vaccination against influenza for naïve adult patients was assessed by skin staining, whereas acceptability was measured with an adaptive-choice analysis. When a self-administered microneedle patch was offered, intent to vaccinate increased from 44 to 65 %. The majority (64 %) of those intending vaccination would prefer to self-vaccinate. Seventy participants inserted patches with thumb pressure alone and the remainder used snap-based devices that closed shut at a

certain force. The best usability was seen with the snap device, with users inserting a median value of 93–96 % of microneedles over three repetitions. There were no serious adverse events associated with the use of microneedle patches.

Use of Inhalation Devices by Older Adults

Over 10 % of the US population aged 75 years has chronic obstructive pulmonary disease (COPD) and the primary treatment is with inhaled medication administered with handheld devices or nebulizers. Meta-analyses of studies with randomized controlled clinical trials comparing the clinical efficacy of medications delivered by pressurized metered dose inhalers (pMDIs), dry powder inhalers (DPIs), or nebulizers failed to show that the method of administration impacted clinical efficacy outcomes [57], probably because the methods were not sensitive enough. A more sensitive measure for comparing drug delivery efficiency of the various devices is the quantity and location of inhaled drug deposited within the lungs. Studies have shown that deposition is mainly governed by the patient's inhalation flow, the aerosol velocity and the particle size of the inhaled drug [58]. The inhalation and breath-hold time spans should be long enough to allow for distribution to the peripheral airways and for adequate sedimentation. The choice of an inhalation device for an individual COPD patient should therefore be based mainly upon these three factors.

Cognitive ability, manual dexterity and strength are needed to handle inhaler devices [59]. In practice, an elderly COPD patient with a limited inspiratory flow rate, who may not be well trained or monitored and who has co-morbidities such as Parkinson's and dementia, will be expected to be more susceptible to use errors for a particular product when compared to a younger asthmatic patient [60]. Unfortunately, most of the studies with MDIs and DPIs exclude cognitively impaired or neurologically altered patients, or patients otherwise doubtful to properly use these devices, e.g. due to limited manual dexterity or hand strength. Cognitive function appeared to be an important determinant of the ability to acquire and retain techniques necessary for competent use of inhaler devices. Several small trials suggested that patients with limited cognitive impairment, as indicated by their abbreviated mental test scores, may be unable to learn techniques for use of both MDIs and DPIs, whereas those having significant cognitive dysfunction could not properly use an MDI [61–63]. When self-administration of inhaled medications is being considered, tests of cognitive abilities may therefore be warranted for patients in the advanced stages of COPD and for those of more advanced age.

Age-related osteoarthritis and neurologic conditions such as Parkinson's disease and stroke influence the capability to handle inhalation devices [64]. In fact, in a comparative study up to one-third of older patients lacked the hand strength to generate the minimum force required to activate a pMDI device [65], and many elderly patients with mild-to-moderate impairment of manual dexterity have difficulty with the hand–breath coordination required to use a pMDI device. In order to

overcome this problem, pharmacists can provide large-volume spacers to be used with the pMDI device [66]. In this case a large proportion of the dose may be lost in the spacer, but this is compensated for by the fact that the patient can inhale as part of normal breathing. For DPIs, hand–breath coordination is not a problem for aerosol generation since they rely on breath activation. However, some level of manual dexterity is still required for dosage preparation with single-dose DPI devices for loading, puncturing and disposing of the capsule containing each individual dose.

Venture et al. [67] evaluated 93 patients with a mean age of 82 ± 4 (SD) years with various respiratory disorders using several classes of inhalers, including large-volume spacer devices and both manually and breath-actuated pressurized metered-dose inhalers, dry powder inhalers and capsule-based devices. Basic Geriatric Assessment indicated that five patients had moderate or severe cognitive impairments, two patients had dependence in function and 13 in instrumental activities of daily living, 20 patients had symptoms of mild depression and five had stable depression, whereas 37 patients were found to be at psychological risk. Adherence to treatment in this heterogeneous group was as low as 44 % (n = 41), and no significant difference was found in terms of age or type of respiratory disorder. A patient's inhalation technique was considered acceptable with a score >75 %, but only 40 % of the patients had an acceptable score, indicating a large gap between ideal and actual technical performance in practice. In this study, inhalation technique scores could not be correlated with age, institutionalization, caregiver assistance, inhaled drug, basic geriatric assessment scores or treatment adherence. Treatments of elderly COPD patient should therefore be based on the patient's individual capabilities and preference [68], and assessment of the older person's ability to correctly use his pressurized MDI or DPI should be integrated into the follow-up visit to the physician. Patients who remain unable to effectively use handheld inhalers despite instruction (e.g. unable to coordinate inhalation with actuation of a pressurized MDI or unable to generate sufficient peak inspiratory flow to use a DPI) could be considered for nebulizer use. Patients who could benefit from the use of nebulizers are all patients with cognitive impairment, inadequate manual dexterity, e.g. due to arthritis, Parkinson's disease, or stroke, or those who have manual weakness [69].

Nebulizers can be used for inhaled drug delivery both in hospital settings and at home. Although nebulizers are not recommended in western countries as first-line treatment for acute situations [70], they are still popular in countries such as China, where they represent as much as one-third of the market share for orally inhaled products.

Once loaded, a nebulizer continuously aerosolizes a liquid formulation which the patient inhales by breathing through a face mask or mouthpiece. Because of the mode of action of a nebulizer, the amount of drug received by the patients is dictated by their breathing profile. Ultrasonic nebulizers need an electricity supply, which can be a limitation in certain instances, while jet based nebulizers rely on the availability of a compressed air source. Both technologies result in nebulizers that can be quite bulky, and that consequently lack the portability and convenience

associated with conventional inhalers. Moreover, jet nebulizers can be quite noisy due to the need for an associated compressor. These problems can be overcome by the use of battery-operated nebulizers with mesh technology, which are both portable and silent. Elderly patients employing nebulizers in their homes experience a wide range of practical issues, leading to a 50 % prevalence of problems with nebulizer use for patients with COPD [71]. Problems are encountered at all stages. Prior to nebulization, problems were found related to setting up the equipment, lack of instructions, manual dexterity and time required. During medication administration, problems were found related to the inhalation technique and the duration of nebulization, and in understanding how to achieve optimal efficacy. Post-administration, problems were found that related to inadequate cleaning of nebulizer components, access to accessories and the use of damaged parts or self-repairs. Issues which may compromise clinical outcomes include loosely fitting nebulizer caps, missing vaporizer heads and failure to use the mouthpiece correctly. An ill-fitting mask may result in decreased drug deposition in the lungs, and also to deposition on the patient's face or in the eyes, potentially causing adverse effects such as glaucoma. Problems with manual dexterity, having poor grip, difficulty opening vials and poor eyesight were contributory factors to problems for many patients. The quality of self-administration by elderly patients using nebulizers should therefore be closely monitored by health care providers.

Injectable insulin may pose problems, especially for older adults who have vision problems, trembling hands, or who suffer from cognitive diminishment. Elderly persons may have difficulties measuring an appropriate dose of insulin and finding a place to self-inject on a frail body [72]. For older adults to remember to take the insulin may be difficult already, but it may be even more difficult to match what they have eaten with how much to inject. And if the senior diabetic patient has to take both a nighttime and a mealtime insulin dose, the inadvertent injection of the wrong type of insulin is one of the most common reasons for elderly patients to end up with hypoglycemia in hospital emergency rooms. In 2015, Afrezza inhalable insulin was introduced by Sanofi in the US market, which may serve as an alternative insulin delivery modality for elderly patients to help achieve blood sugar control. Afrezza is an ultra-rapid-acting, inhaled insulin used to control high blood sugar in adults with type 1 and type 2 diabetes (Fig. 13). The drug is available to patients as a cartridge in 4-unit and 8-unit strengths. It is administered 15 min before mealtime. The insulin as delivered through Afrezza has an onset of two to three minutes and a duration of action of approximately 1 h. The product may ease managing diabetes by overcoming the difficulty of counting carbohydrates and by making it easier for the elderly persons to use their insulin, which potentially could result in greater compliance and in improved quality of life [72]. Since starting elderly patients on injected insulin may pose a barrier to treatment, inhaled insulin may potentially lead to beneficial effects of early insulin initiation in older adults with type 2 diabetes mellitus, without increasing the risk of hypoglycemia or greater total direct health care costs [73]. Afrezza is not meant as a substitute for long-acting insulin; in patients with type 1 diabetes, Afrezza must be used in combination with long-acting insulin and may help reduce the number of daily

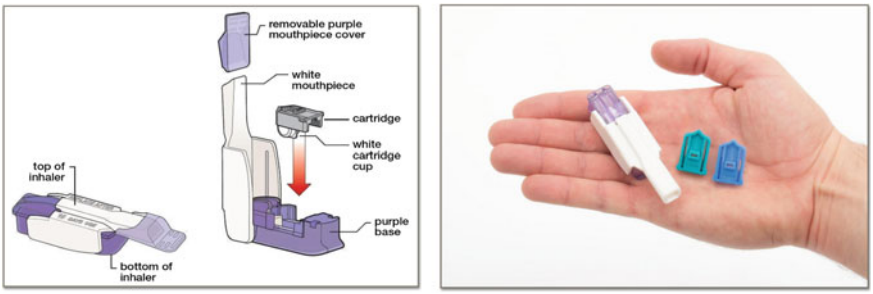


Fig. 13 Afrezza inhaler device containing a dry formulation of human insulin in two cartridges with strengths of 4 and 8 units (Photo reproduced with permission from Mannkind)

injections. Whether the benefits can be reached in older patients, as discussed above, is debatable. In January 2016, Sanofi pulled out of its worldwide marketing agreement with MannKind, the manufacturer of Afrezza, due to poor US sales. Apparently the advantages of inhalable insulin over injectable insulins were not sufficient to outweigh the higher cost, a situation similar to Exubera inhalable insulin developed by Nektar and distributed by Pfizer a decade earlier.

Use of Enteral Infusion by Older Adults

In Parkinson's patients the emptying of the stomach is delayed and unpredictable, affecting the timing of when orally administered medicines are absorbed by the small intestine. An alternative delivery mode was therefore developed for patients with advanced idiopathic Parkinson's disease with severe motor fluctuations who do not respond to oral treatment, but still respond to carbidopa-levodopa. The alternative is to circumvent the first part of the oral route by employing Duopa (Fig. 14), a portable infusion pump with an enteral suspension of the standard Parkinson's drugs carbidopa and levodopa. The system has been available in Europe for 15 years, but has only been available since 2015 in the USA. The pump system bypasses the stomach by delivering these two medicines straight into the patient's duodenum (the first section of the small intestine) using a surgically placed permanent tube [74]. This approach allows treatment of the "off" episodes in Parkinson's patients, characterized by slowness, stiffness and difficulty of moving. The enteral delivery takes place over 16 consecutive hours using an infusion pump and a transcutaneous tube with jejunal extension. At the end of the daily infusion, patients disconnect the pump from the tube, flush with room temperature potable water with a syringe, and take their nighttime dose of oral immediate-release carbidopa-levodopa tablets. The patient has to keep the area clean where the tube enters the body, the pump has to be flushed every day and the medication has to be refrigerated. Most of the side effects are related to the delivery tube or the

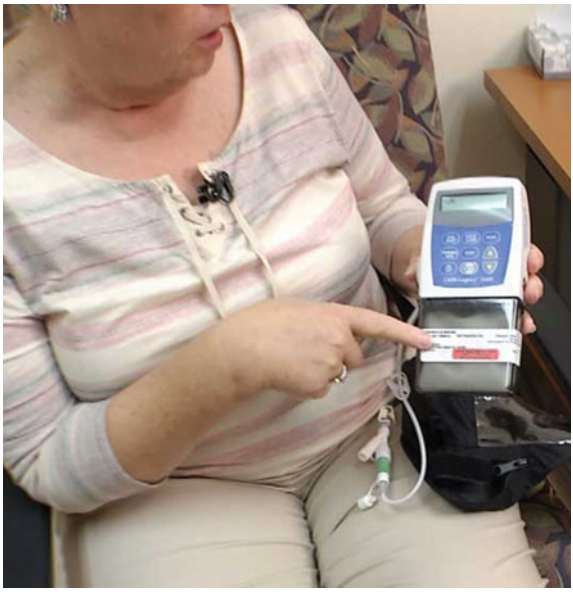


Fig. 14 Parkinson patient interfacing with the Duopa portable infusion pump. The grey reservoir at the bottom of the pump is the cassette loaded with carbidopa-levodopa. These drugs are pumped through the cassette tubing, passing two connectors, through the stomach tube and passing the stoma site into the small intestine. (Photo reproduced with permission from AbbVie)

abdominal wall surgical site, including movement, knotting or clogging of the tube, and infections at the surgical site. For use of the pump, reference is made in the patient leaflet to the instructions for use that come with the portable infusion pump. Although the system has been developed for patients with Parkinson, which is especially a disease of the elderly, from the above it is already clear that not all older advanced Parkinson's disease patients will be physically or mentally capable of using this particular medicinal product, even after extensive training.

Use of Eye Drop Dispensing Aids by Older Adults

Taking eye drops can be a challenge for many patients, especially for older adults. The design of the packaging plays a critical role [75]. In her thesis, Wagner showed the impact of educational and physical barriers of elderly patients on their adherence to using ocular pharmaceuticals and placed this into the theoretical framework of the Health Belief Model [76].

A study on self-administration of eye drops in 409 visually impaired glaucoma patients and retina patients (visual acuity of 20/60 or worse in 1 eye, significant field loss, or both) demonstrated that ophthalmic therapy implies a big delivery problem [77]. Patients wasted drops, contaminated bottles, and had inaccurate perception of their abilities. Approximately one third could not get a drop onto the eye and only 30–40 % succeeded in placing a drop onto the eye without touching

the tissue around the eye. Of patients claiming not to miss the eye, nearly one third actually missed.

The ability and skills of older patients to properly instill an eye drop onto the ocular surface was studied for a group of 25 patients diagnosed with dry eye or glaucoma. Only 52 % of the older patients managed with a single eye drop, 16 % needed two drops and 32 % needed three or more eye drops [78]. The first eye drops were deposited by 32 % into the conjunctival sac, 32 % on the outer corner of the eye, 8 % in the inner angle, 8 % in the nose, 12 % on the cheek and 8 % in other areas. Patients 80 years and older demonstrated massive problems in opening single-use containers and in self-administering eye-drops [79]. Factors contributing to the low success of self-application were the lack of previous experience with the specific kind of eye drop container and the patient's limited visual acuity.

An issue with the switching from branded to generic ophthalmic preparations can be attributed to differences in bottle shape and stiffness, since change of packaging can make applying drops more difficult for an older patient [80]. Xalatan®, for instance, comes in a flat bottle, whereas many generics of the drug come in round bottles that are more difficult to squeeze. There can also be substantial dose variability between branded and generic formulations, simply because the tip might have a bigger or smaller hole. This demonstrates that neither the generic company nor the health authorities paid sufficient attention to the usability aspects of the administration system.

Increasingly, single-dose containers are being used, since they have the clear advantage that they can be formulated without preservative. Single-dose containers differ from the conventional eye drop bottles in size and shape, and in softness of the plastic material. It was reported that glaucoma and dry eye patients aged 80 years and older experienced more difficulty in opening and applying drops from single-dose containers compared to conventional eye drop bottles [80]. Difficulties in the correct instillation of eye drops correlated significantly with decreased visual acuity. In a more recent study [81] with healthy older adults of mean age of 73, the study participants managed unit-dose pipettes at least as well as the conventional eye drop bottles. Explanations offered for the divergent outcomes among studies include differences in previous handling experience and differences in single-dose dispensers, but also differences in age [79]. At least one important factor not to be overlooked is the difference in physical barriers between the two studies, and the difference in biological age.

The above clearly demonstrates the need for assistance, either in the form of persons, e.g. caregivers, or of suitable assistive administration devices in the form of eye drop dispensing aids. Such aids should overcome as much as possible the problems encountered by older adults, such as lack of physical support for the eye dropper bottle, difficulty in aligning the dropper bottle with the eye to allow the drop to fall into the eye, trembling, limited vision, touching the eye with the bottle, difficulty in squeezing the bottle, especially when arm and wrist are at a sharp angle, dexterity challenges, and difficulty in tilting the head backwards horizontally. The dispensing aid should preferably help patients avoid the nervousness encountered when using dropper bottles for the first time, and should also keep the dropper tip

from touching the eye to prevent irritation or, even worse, the spread of infection. An eye drop dispensing aid (Fig. 15) should help patients to self-medicate and become independent in managing their own condition, particularly when it is long term, such as in the case of open-angle glaucoma. The dispensing aid must match the patient's needs and must also fit the eye drop bottle. Although overcoming the force to deliver a single drop by squeezing the eye drop bottle is seen as one of the major functions of the dispensing aid, force measurements have indicated that three of four dispensing aids tested actually increased the force requirements [82]. The Opticare Arthro model, on the other hand, with its extended arms, actually lowers the squeezing force and assists patients who suffer from severe arthritis or have great difficulty lifting their hand to their eye to instill their drops. However, there appear to be other, more important factors in play than mere force. The Eyot eye dropper aid, for instance, creates a sharp contrast between its red colored surface and the white dropper tip for greater accuracy, which is especially important for patients with poor vision. The aid firmly supports the bottle to prevent trembling, which lowers the chance of drops missing their target. When patients are prescribed several different eye drop products, they may need an individual aid from a different manufacturer for each bottle. Eye drop aids are available by prescription, but some pharmaceutical companies provide them free of charge for their products. In this case, the eye drop aid often fits only with the company's bottles. Despite the many assistive eye drop devices on the market, thus far none has overcome all common obstacles to patient compliance—lack of compatibility with commercially available eye drop bottles, difficulty in squeezing the bottle to deliver the drop, inaccuracy in dose administration and complexity of design.

The SimplyTouch Eye Drop Applicator is a new type of device and may be helpful for those who can hold a tiny spoon-like device approximately one and a

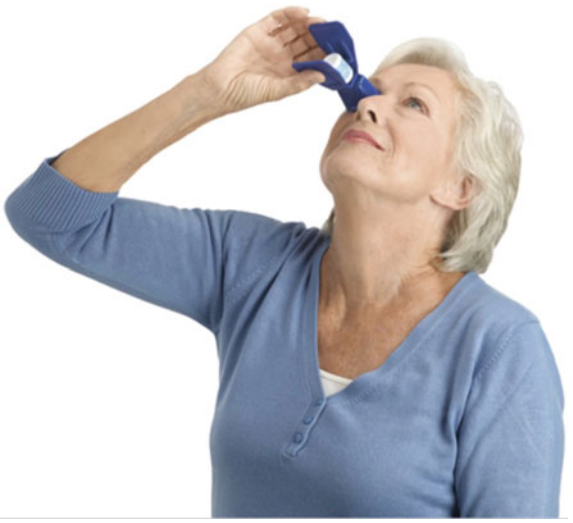


Fig. 15 Combination of dropper and squeezer allows the patient to self-administer eye drops (Photo reproduced with permission from Owen Mumford Ltd.)

half inches long, with the slightly concave cup's diameter being about 1/4 inch [64]. This tiny applicator is made of grippy, rubbery, slightly flexible elastomeric material. One side is stamped Rx for prescription eye drops; the flip-side shallow cup is marked for nonprescription (OTC) drops. Application requires squeezing a drop from the dropper onto the cup of the applicator, pulling down the lower eyelid and touching the applicator to it. The user may administer the drop without having to tilt the head, while maintaining an eyeglass-assisted view into a mirror. Application of the drop occurs from the peripheral line of vision. When contact is made to the eye, surface tension is relieved and the drop safely transfers into the eye. The applicator should to be washed for sanitation in soapy water after each use.

Use of the Device IFU by Older Adults

Labeling, including the device Instructions for Use (IFU) and quick reference cards, is an integral part of a drug/device therapeutic product (see Fig. 1), and as such, should be subjected to usability and human factors testing. Best practice is to test the IFU explicitly in a separate formative study early on and use the feedback from this study to modify the IFU prior to subsequent formative studies or the summative usability study. The IFU can never compensate for poor use of the device, and risk mitigation should be done as much as possible through further optimization of the device/user interface. The more self-explanatory and simple-to-use the administration device is, the better. The elderly population is at high risk of being unable to understand their prescription instructions. Here one must realize that a large portion of the older adult population—over one-third of the US population—consists of individuals who are functionally illiterate or low-literate, for whom the instructions, which are typically written at the sixth-grade level, are still too difficult. A significant number of individuals may not have a good understanding of the way a drug has to be administered and so may not take their drugs correctly. Health authorities are, therefore, rightfully interested in the performance and use of administration devices in the absence of instructions to evaluate their dependency on such documentation.

It appears that many patients struggle to use and interpret medical-related instructions. Plain language materials have been shown to improve patient understanding and adherence. Simple language is recommended [83], for example "take" instead of "to be taken," and it is best to be specific where possible, for example "in the morning" rather than "daily." Smith et al. [84] tested user comprehension and ability to administer a biologic agent with an auto-injector pen through a 15-step self-administration procedure. Participants given "plain language" instructions had a significantly better understanding of how to prepare for and self-administer medication with a pen than those given standard instructions, and were consistently more accurate in demonstrating how to self-inject. This shows that IFU instructional language can significantly contribute to risk mitigation regarding drug self-injection. Pictograms are a key component in designing medication information

to improve comprehension, recall and adherence. Patient counseling on the intended meaning and use of pictograms greatly enhances their effectiveness [85].

In the context of older adults, one has to consider their physical and cognitive limitations in reading and interpreting the Instructions for Use. Use a print size that the older adult is able to see (preferably 14-point font size, or 18 points or larger for glaucoma patients) and use high-contrast dark print with bold font to emphasize important text. Use serif typeface for print materials, such as Times New Roman, since these typefaces have tails on the ends of their letters that create an illusionary line, which can help guide the eye across the print. And in case colors are needed, use of yellows and reds is better than darker colors such as blue and green, which are more difficult for older people to distinguish. Do not use color on color highlights on pages or a "traffic light" system for the user to indicate what to do or not to do, since most color blind users cannot be relied upon to know the difference between red, green and orange. Furthermore, glossy paper should be avoided since it creates a shine that can make text difficult to read. Also when a paper is too thin, the reader may be able to see through it to the text on the other side of the page, which will make it hard to read for the older adult. The old booklet on writing user instruction manuals for medical devices for home use may still provide some good advice [86].

Use of Assistive and Auxiliary Devices by Older Adults

The subpopulation of older adults with intellectual and developmental disabilities (I/DD) presents unique challenges related to appropriate medical treatment [87]. These adults are more likely to develop chronic health conditions at younger ages than other adults because of biological factors related to syndromes and associated developmental disabilities, limited access to adequate health care, lack of financial support, and lifestyle and environmental issues. Compared with the general population, they experience higher rates of obesity and sedentary behaviors, and have poorer nutritional habits.

Additionally, adults with I/DD can have a shorter life span compared with other older adults, which is thought to be caused by an accelerated aging process, apparent in their increased rates of cataracts, hearing loss, osteopenia and hypothyroidism, and a genetically elevated risk of developing Alzheimer's disease. As individuals with I/DD are now living longer, geriatric providers and care team members need to consider how to address the health care needs and common clinical issues in this subpopulation. Assistive devices may be of help. It is a common misconception, however, that all persons with developmental disabilities have severe physical, cognitive and behavioral impairments. Many individuals have very mild disabilities, and some who have severe physical deficits are cognitively intact [88].

ISO 9999 provides an international classification of assistive products covering all products that can be used by persons with disabilities [89]. The goal of ISO 9999

is to promote communication internationally about the use of assistive products by people with disabilities, including elderly people. A product is defined as "assistive" if it contributes to the functioning of a person with a disability. It may also improve the health of the user, in which case it may be classified as a medical device as well as an assistive product. As discussed above, dedicated legislation for medical devices, with which compliance is mandatorily, exists at the international and regional level. For assistive products not intended to improve the health of the user, no specific legislation exists, and therefore these products are freely available on the consumer market. When a product is classified as both a medical device and an assistive product, the legislation regulating medical devices fully applies. Subclasses of assistive products for administering medicines include injection syringes, injection needles, injection guns, infusion pumps, accessories, products for inserting suppositories, and products for measuring, dispensing or modifying medications to ensure their proper use (see Table 3).

Table 3 ISO 9999 classification of assistive products for administering medicines

Subclass	Title	Description
04 19 04	Assistive products for measuring, dispensing or modifying medication to ensure proper use	Devices to help a person measure the correct dosage of medicine, taken orally or injected; to dispense the correct dosage of a medicine; to modify a tablet, capsule or pill to obtain a lower dose of the active ingredient; or to modify the form of a medication to facilitate its proper administration or consumption. Included are, e.g., pill crushers and assistive products for dosing used in conjunction with injection syringes
04 19 06	Injection guns	Devices with a trigger for introducing liquid medicines directly into the body through the skin
04 19 09	Injection syringes, single use	Devices with a plunger for introducing liquid medicines directly into the body through a needle inserted in the skin. Each syringe is intended to be used once only
04 19 12	Injection syringes, multi-use	Devices with a plunger for introducing liquid medicines directly into the body through a needle inserted in the skin. Each syringe can be sterilized and reused
04 19 15	Injection needles, single use	Needles intended to be used once only
04 19 18	Injection needles, multi-use or permanent use	Needles that can be sterilized and reused and/or needles that can stay in the body for a long period of time

(continued)

Table 3 (continued)

Subclass	Title	Description
04 19 24	Infusion pumps	Devices attached to the body for the automatic administration of medicine. Included are, e.g., insulin pumps
04 19 27	Unpowered infusion pumps	Intravenous drip systems for the administration of medicine
04 19 30	Assistive products for inserting suppositories	Inserter for suppositories
04 19 33	Accessories for assistive products for administering medicines	Included are, e.g., products for positioning and fixation of needles

An example of an assistive product of relevance to elderly patients is the e-pill Vibrating Count-Down Timer and Alarm, which is a vibrating medication reminder designed for persons who are deaf or hard of hearing. Strong vibrations lasting 60 s remind the user to take medication on time. Another example is the First Crush Electric Pill Crusher that crushes and grinds tablets into fine powder, reducing the physical strength needed to crush pills thereby reducing repetitive motion injuries by caregivers and patients. (A critical issue here which many elderly patients do not realize is that some drug products cannot be crushed without affecting the product's bioavailability and thereby its safety and efficacy.)

The Inject-Ease Syringe Injection Aid (Fig. 16) has been designed for one-handed use and to allow access to hard-to-reach injection sites. After placing the loaded syringe into the injection aid, placing the tip against the skin and pressing the button, the needle automatically passes through the skin. The user controls the rate at which the medicine is injected.

The Sure-Grip Suppository Inserter (Fig. 17) is designed for use by people with physical disabilities. The device consists of a plastic probe with an adjustable polyethylene collar attached to a stainless steel frame and a large loop handle. The inserter has a hollow area to include the suppository and is mounted against a weak spring. The probe and collar can be adjusted for angle and for depth of penetration, and both are attached to the plastic handle that loops over the hand. Such a hand loop requires minimal strength and dexterity. That the use of such devices is not

Fig. 16 The inject-ease syringe injection aid, an assistive product for administering medicines via the parenteral route (Photo reproduced with permission from AmbiMed Inc.)

Fig. 17 The Sure Grip Suppository Inserter, an assistive product for administering medicines via the rectal route

without risk is evidenced by reports of rectal perforations in the case of enema self-administration [90].

Self-care auxiliary aids include multi-compartment devices (punch packs, boxes and trays), medicine bottle openers, pill extractors, eye drop dispensers, tube squeezers, cream applicators, talking labels, pill splitters and crushers, oral syringes, measuring spoons and dose cups, inhaler aids (grips, spacers) and medication alarms.

An auxiliary device commonly used across all patient ages and abilities is the tablet splitter. Despite their wide use, however, the majority of splitters available in pharmacies and Internet shops are of poor quality. In an experiment comparing three commercially available types of devices for splitting simple round tablets, none of the splitters met the regulatory requirements for split tablets [91, 92]. Small, round or unusually shaped tablets usually lead to the largest deviations from equally split halves. To overcome this problem, the Tabtime All Shapes pill cutter comes with 12 different inserts to enable precise cutting of tablets of almost any shape. Despite the fact that this cutter has been CE marked as a medical device, most of the customer reviews at Amazon.com were critical of its performance [93]. The Equadose splitter, with a body made of aluminum, has a design that utilizes two opposing blades that come in from the sides to effectively score the tablet prior to splitting. Although it can accommodate just about every tablet size and shape, there is no mechanism for centering the tablet for splitting, so obtaining equal halves relies on eyeballing the center. The fact that it is difficult to stably place the tablet in the middle likely makes this splitter less suitable for older adults or people with arthritis, as it is difficult to steady the pill. A more suitable option for older adults and the nearsighted may be the Ezy-Cut Pill Cutter with built-in magnifier, which has adjustable arms to center the tablet, and a safety shield. Harder tablets are more likely to fragment or powder, leading to drug loss. The accuracy of tablet splitting is influenced not only by tablet size, shape, hardness, splitting method and apparatus, but also by human ability. Whereas studies with healthy volunteers indicated that neither age nor tablet-splitting experience appeared to be predictive of variability [94], the ability to correctly use a splitting device is known to decline with patient characteristics such as impaired hand function, limited visibility and mental retardation [90].

Future Trends for the Older Adult

Older adults shop at home, order food from home, follow educational courses at home, and fuel their e-bikes and mobility scooters at home. Care is expected to follow this trend, enabled by innovations such as telemedicine, electronic cell-phone applications, wearables, domotics, robotics, lab-on-a-chip and the Internet of Medical-Things (IoMT). Home, rather than the hospital or the nursing home, is becoming the center of the older patient's world. Home care of the future may compensate not only in cases where the older adult has lost the ability to independently leave the house, but also for other diminished physical and mental capabilities. It will also allow for telecare and telemedicine, where the formal or informal caregiver is not in the same place as the person receiving care, but employs new communication tools such as webcams, electronic monitors, email and websites to interact with patients, transmit data and provide instruction [95]. The new emphasis on home care may not have only positive effects. The expected further intrusion of devices into the homes of elderly individuals, including those meant for drug administration, may have a psychosocial impact on the lives of older adults. It even may alter the extent to which elderly patients consider their house as their home, if the character of the house becomes more hospital-like [96]. This should be avoided.

An example of IoMT technology used to optimize self-administration is an app-enabled inhaler sensor that attaches to the top of the inhaler to collect data on the time and place asthma and COPD patients experience symptoms. The company Propeller has received FDA 510(k) class II medical device clearance to measure and improve medication adherence, predict exacerbations, and help reduce the frequency of symptoms and exacerbations in asthma and COPD [97]. The sensor wirelessly syncs with patients' smartphones, providing them with personalized feedback and education to better control their conditions. By using in-app notifications, text messaging and a follow-up from a clinical support team, the device has demonstrated improved medication adherence.

An example of a robotic device for drug delivery is the FDA-approved system for intravenous delivery of propofol [98], and although it is used to provide robotic anesthesia to sedate patients in hospital, it is only a matter of time before robotic systems will be able to assist in administering drugs to the patient at home. In the near future, personal robotic caregivers (nursebots) may be introduced to assist elderly people suffering from chronic disorders in their everyday lives. In the more distant future, autonomous mobile robots may live in the private smart home of chronically ill elderly persons. These smart homes will have sensors along the ceiling, doors, and under the mattress to help the robot system assess things such as the person's location inside the house, whether there is healthy movement and how much time is spent on sleep. The robot will remind the user to eat, drink water, take medicines and go to the bathroom. The robot is also likely to provide a platform for telemedicine; the patient's doctor could use the robot to connect remotely with the patient [99]. At the same time, the robot could collect information from wireless

glucometers, blood pressure cuffs and other medical devices in or on the body to seamlessly relay data to the patient's health care practitioner. In the future we may see that next to or instead of the human user/device interface, the device/device interface will become critical for safe and effective treatment of patients. The robotic device then provides comprehensive patient monitoring and adjusts drug delivery accordingly.

Concluding Remarks

Administration devices for self-medication used for diseases predominantly occurring in the older adult population should be designed and developed with full consideration of usability and human factors aspects of the broad range of elderly patient characteristics. Rather than by chronological age, the intended older adult user should be adequately specified in terms of physical and cognitive capabilities needed for successful use of the specific drug administration device. The environment in which the self-administration device is tested should usually not be a clinic or office setting, but should simulate the conditions where elderly patients normally live and administer their medication: their homes.

In order to ensure their intended use, patients and caregivers should be well informed about the portfolio of existing administration devices which require prior consent from the prescriber. In addition, information on cost and reimbursement may be essential.

Only after properly training and instruction should the elderly user be left to his own routine self-administration, probably with regular checks on compliance with the required procedure.

Acknowledgments The author thanks Dr. Ing. Anne de Boer (University of Groningen), Dr. Gert Bos (BSI), Prof. Dr. Annick Ludwig (University of Antwerp), Dr. Diana van Riet-Nales (Dutch Medicines Evaluation Board) and Mr. Patrick Vronen (Oculentis) for critical comments and suggestions.

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Manufacturing Platforms for Patient-Centric Drug Products

Mark W. Wilson

Abstract This text aims to provide a brief overview of tablet and capsule manufacturing approaches, to highlight some of the industrial engineering issues that exist in standard secondary manufacturing processes for oral solid dose products (which may often be overlooked by those who are unfamiliar with pharmaceutical production activities), and to provide a review of dose forms that are commonly employed for elderly patient groups. At present, a limited set of oral dose forms is used by the industry for this purpose, some of which formulation approaches offer potential benefits in terms of ease of swallowing by elderly patients, and these product types are considered briefly. The aim is to provide an overview and summary of existing formulation and manufacturing approaches that are used for the provision of dose forms for elderly patients, noting the associated practical issues and challenges.

Keywords Tablets · Capsules · Oral Dose Forms · Manufacturing processes · Unit operations · Production challenges · Economics · Industrial engineering · Chewable tablets · Effervescent tablets · Oral dispersible tablets · Granule products · Films · Soft gelatine capsules

Introduction

In the past decade, the pharmaceutical industry has begun to place great emphasis on understanding the specific needs of pediatric and geriatric patients. George W. Merck, in a speech at the Medical College of Virginia, in December 1950, provided an early quotation on "patient-centricity" that was later placed on the cover of a 1952 Time magazine. "We try never to forget that medicine is for the people. It is not for the profits. The profits follow, and if we have remembered that, they have never failed to appear. The better we have remembered it, the larger they have

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S. Stegemann (ed.), *Developing Drug Products in an Aging Society*,
AAPS Advances in the Pharmaceutical Sciences Series 24,
DOI 10.1007/978-3-319-43099-7_22

been." (Please see [1, 2], for discussions on this famous quotation.). It is be welcomed that, over 60 years after Merck's statement, the concept of placing the patient at the center of product development activities is becoming increasingly fashionable in the pharmaceutical industry.

Pediatric and elderly patient groups have different and varied needs, and the increasing level of concern for these specific requirements in the industry, by the pharmaceutical development community, and by other stakeholders, is both necessary and welcome (as discussed by Mentzer [3] and Van Riet-Nales et al. [4]). In considering the most appropriate dose form for a specific active and in evaluating how the industry could better meet the needs of these patient groups, it is important to recognize the strong links between formulation choices and manufacturing processes. In particular, the significance of secondary manufacturing, and its constraints, from an industrial engineering perspective, is important to bear in mind. Products must be manufactured in an economically effective fashion, and the nature of oral dose forms imposes many restrictions on the manufacturing processes.

Pharmaceutical manufacturing is divided into two major stages. First, there is the production of the active pharmaceutical ingredient ("API") or "drug substance," which is usually referred to as "primary manufacturing"; second, there is the conversion of the drug substance into products suitable for administration ("drug products"), which is usually referred to as secondary manufacturing. This chapter focuses upon the challenges within secondary processing for what are usually termed "oral solid dose products": these, as their name suggests, are pharmaceuticals which are administered orally by swallowing, such as tablets and capsules. While a variety of administration routes and dosage form types are routinely used in formulation development, oral solid dose products account for a large share of all medicines that are manufactured across the industry. There are benefits and challenges in the use of other approaches such as oral liquid or oral suspension products, transdermal products and creams and ointments, but these approaches constitute separate fields of formulation activity, and utilize substantially different manufacturing processes to those that are employed in the manufacturing of oral solid dose forms.

Manufacturing processes have changed radically over recent decades in a number of industries, with the advent of increasing automation, continuous manufacturing, the use of sophisticated prediction and tracking systems, the rigorous application of lean manufacturing principles, and the creation of more personalized products. These approaches are being applied to an increasing extent in pharmaceutical manufacturing, despite the natural conservatism of a highly regulated sector, and there is considerable potential for the industry to develop novel approaches, and to apply innovative technologies that have reached commercial scale, in order to provide medicines that better meet the needs of pediatric and elderly patients.

New formulation technologies aim to deal with these constraints of existing manufacturing processes in an innovative fashion, while providing dose forms that may offer patient benefits, and a discussion of two specific approaches is provided elsewhere in this text. One technology is a personalizable "polypill," which may facilitate a reduction in the "pill burden" for elderly patients and which may enable

a modest increase in rates of adherence to medication regimens. A different novel formulation and manufacturing process, the "liquid dispensing technology," enables the production of a wide range of dose strengths of highly active, low dose compounds in an efficient and cost-effective manufacturing process, and can be used with some of the standard dispersible dose forms that may be preferred to standard tablet formulations by elderly patients. It is hoped that the brief summary of existing approaches that is provided in this section and the accompanying discussion of two specific novel technologies, which have the potential to provide benefits for elderly patient groups, will be useful and complementary.

Solid Oral Dose Form Manufacturing

The modern pharmaceutical industry has a long history, with the origins of the predecessor companies of many multinational firms dating back around 150 years or more. In addition, the industry operates on a large and near-global scale (the UK-based Association of British Pharmaceutical Industry [5] estimated the industry size as being $900 billion in 2014), with large pharmaceutical companies operating in most countries of the world.

Production of tablets is required on a vast scale (with many billion tablets produced each year in the US alone), and the processes involved date back, in many cases, to the early 1900s. Given these facts, it is perhaps surprising that the production of tablets and capsules is highly inefficient from a manufacturing engineering viewpoint, that true production equipment utilization rates are very low and that interruptions to production flows are frequent. These inefficiencies arise from the nature of the production processes themselves, from the conflicts between different functional expectations of the formulation, and from the ways that the industry provides quality assurance. (Product quality is typically assured by the assessment of material using relatively slow offline analytical test methods, and in-process material is often held for lengthy periods while test results from the prior stage of manufacturing are awaited.)

Tablet Manufacturing

Several processes are involved in tablet manufacture (which is often referred to as "compression") and these are described briefly below (Fig. 1). The standard initial step is a milling or screening process. The size reduction that takes place in the initial milling or screening process is often minimal, and is often termed "de-lumping." Substantive milling is often conducted in a "drying and finishing area" or "finishing suite" at the end of the primary manufacturing stage; consequently, the milling at the start of secondary manufacture is primarily aimed at breaking up any agglomerates that have formed since the end of primary

manufacturing. Supply chains are often complex with materials being shipped from a primary site in one country to a secondary one in another, and agglomerates may form during transport and storage. The "de-lumped" material is then blended with harmacologically inactive materials (which are known as "excipients"), often using large bin or V-blenders.

In order to facilitate accurate metering of powder in the commercial tableting press (which is required to achieve a consistent dose and tablet weight), a consistent powder flow is required. In some cases, the drug substance properties allow a direct compression process to be utilized, and this process route minimizes the number of processing operations that are required. In many cases, the formulation requires treatment in order to improve the powder flow properties of the blend. Some materials may be size-enlarged ("granulated") using a dry process, such as

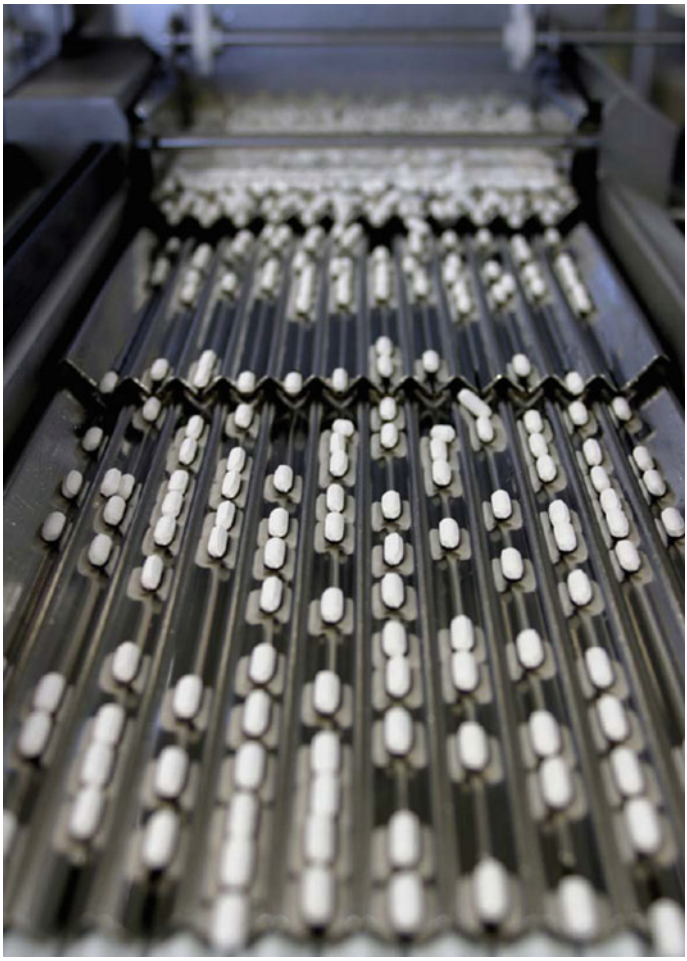

Fig. 1 Caplet-shaped tablets on a blister-packing line (Image courtesy of GlaxoSmithKline)

roller-compaction, in which "slugs" or "ribbons" (i.e., compacted blocks) are produced; these are then milled in a low-energy milling process, and additional excipients, such as lubricants, are added to enable tableting to take place satisfactorily. Many pharmaceuticals, and particularly those that are recently introduced products, require the use of a wet process, with the addition of water, in a high-shear granulator. The choice among the three key options of direct compression, dry granulation and wet granulation process routes depends on the physical properties of the active pharmaceutical and its behavior in a dry-compaction system. Due to processing costs, direct compression is preferred, when this is possible, to granulation, and dry granulation is often preferred to wet granulation. In those cases when it is applied, the wet granulation process and subsequent steps are used to adjust the compaction properties of the active drug powder to enable tablets to be formed. Another key consideration is the stability of the drug substance in the presence of water, which may preclude the use of a wet granulation process, and require the adoption of a dry process.

A widely applied process, wet granulation is a key unit operation in the pharmaceutical industry and is used to improve powder flow characteristics, in order to facilitate accurate metering in tableting processes, to aid in achieving acceptable levels of product uniformity and to enhance the compressibility of the drug substance. Ideally, the resultant granules should have a fairly uniform (and reproducible) distribution of drug particles within the bulk carrier (or excipient) solids. In a typical wet granulation process flow, the water is initially added to the powder blend, and the wetted materials are exposed to high-shear mixing in order to cause the formation of large agglomerates. The resultant material is then transferred to a dryer of some form, in order to allow the water to be removed, and additional excipients are added in a subsequent blending step. (As an example, a disintegrant, which is used to cause the tablet to swell in the patient's body and to assist in the break-up of the tablet, is usually added after granulation, as an "extra-granular excipient," as exposure to moisture affects the behavior of the material and the tablet disintegration properties.)

A series of applied forces, as noted below, serve to create bonds between particles in wet granulation processes. These bonds must be sufficiently strong for the size-enlarged agglomerated materials to survive further downstream processing, and the detailed mechanics of the wet granulation process are complex with bonds both being created and broken between particles [6, 7].

- Adhesion and cohesion forces in the immobile liquid films between particles
- Interfacial forces in mobile liquid films between the granules
- The formation of solid bridges after solvent evaporation
- Attractive forces between solid particles
  - Electrostatic forces
  - Van der Waal's forces
- Mechanical interlocking

Processes are typically operated by being left to run for a set period of time, by which time it is presumed that the batch will be fully processed but not "over-granulated"; however, sophisticated measurement systems such as torque-rheometry (which assesses granulation end-points based on power consumption) are becoming more common. The wet granulation process is "forgiving": batches of materials with different particle sizes, or with varying physical properties, can be accommodated in the process and the unit operation can be used to produce satisfactory blends for tableting. Consequently, the process is widely used and is the dominant approach employed for the production of newly introduced pharmaceuticals. Wet granulation process design is generally empirical in nature, necessitating a level of process and product characterisation in product development.

Fluid-Bed Drying

It is necessary to dry the wetted material that results from the granulation process, and this is usually accomplished in fluid-bed dryers, whereby a warmed, low humidity gas (which is usually air) is passed through the powder via a gill plate. A wide variety of dryer types exist and to avoid the time and effort of moving material these plant items are often co-located with the wet granulation equipment (in "granulation suites"). Processing times are typically less than an hour, and comparatively large batches of material can be processed: batch sizes are often between 150 and 300 kg, and capacities of 1200 kg are achievable according to manufacturers [8].

Fluid-bed drying (Fig. 2) is an integral part of the overall granulation process, and aids in the conversion of inter-particle liquid bonds to more durable solid bonds. The inter-particle bond strength is important to enable the material to withstand the drying process and to preserve the granule structure, and moisture level is a key determinant in the breakage characteristics of the output granules [9]. Process control for fluid-bed drying is important in order to ensure that the product is of an acceptable and uniform moisture content, as an inappropriate level of residual moisture can have a negative effect on compressibility of the tableting blend, and on dissolution and stability of the final product. The material from the drying process may undergo a size-classification ("de-lumping") process, in order to ensure that no large agglomerates are included in the feed blend for the subsequent compression process.

Compression Blends

A number of pharmaceutically inactive materials that affect the powder and tablet properties ("excipients") are added to the blend as "extra-granular materials," in order to provide suitable flow and tableting characteristics and in vivo performance characteristics. In order to bulk out the tablet, diluents or "fillers" are added to the

Fig. 2 A fluid-bed dryer being inspected during operation (Image courtesy of GlaxoSmithKline)

blend. Materials that are commonly used include lactose (crystalline and amorphous material), microcrystalline cellulose and dicalcium phosphate. Crystallized lactose is produced via crystallization and milling processes; amorphous material is produced through spray-drying. The latter material has excellent compression properties; however, it is hygroscopic and may crystallize in certain circumstances. Celluloses also have excellent compression properties and are chemically largely inert, but are also hygroscopic. The propensity of these materials to absorb water may impact product stability and shelf life or may require specific product packaging approaches (such as the use of desiccants in bottles of tablets). Dicalcium phosphate is insoluble in water, and non-hygroscopic, but is easily wetted and forms slightly alkaline solutions when in contact with water, and so may be incompatible with some drugs. In addition, it is a "brittle fracturing" material and abrasive and as a result high levels of tablet punch wear are typically encountered when this material is used, even when high levels of lubricants and glidants are incorporated into the blend; these abrasive properties may lead to imperfections in tablet breaklines or in "debossed" lettering.

Naturally, the behavior of the tablet in vivo is of the utmost importance. It is critical that the tablet rapidly disintegrates in the patient's body, so that the drug may be released. Disintegrants are added to ensure that the tablet breaks down rapidly into smaller particles within the patient's body, in order for dissolution to occur. Many disintegrants work through facilitating water uptake and the consequent rupture of the tablet, through swelling. Starches (for example, potato, corn and maize starch) are often added, at a level of approximately 10 %, as swelling disintegrants; some novel "high-swelling disintegrants" (or "super-disintegrants") have been developed, which are usually modified starches or celluloses, and these are usually added at a level of approximately 5 % (e.g., sodium starch glycolate, cross-carmellose sodium).

Lubricants and glidants are often added in the post-granulation blending step. Lubricants are materials that minimize sticking between the compression blend and the tablet die and punch walls; materials such as magnesium stearate are typically added in small amounts (of less than 1 % in the case of magnesium stearate, or 2 % when dicalcium phosphate is used as a diluent) in a very fast blending step. Glidants are materials that aid in the flow of particles within the blend over one another, in order to allow smooth flow into the tablet die and effective operation of the tableting process. Materials such as various forms of silica and talc are added in modest amounts (1–2 %) along with lubricants. Other excipients may be added to tablet formulations, such as flavorings, or dry powder colourings. Lubricants and glidants are also commonly used in direct compression processes.

Tabletting

In modern presses for tableting (or, as the process is often known, "compression"), the blended powder is fed from a hopper into a die. The flow of this material is critical: in order to ensure consistency of output tablet weight, the die must be filled properly on each occasion and this requires that the feed powder is free-flowing. A lower punch may either be held static or pressed into the die from below; an upper punch is pushed into the die with substantial force. The compression forces form a compact due to both adsorption forces between the solid surfaces and solid bridges. This latter form of bond occurs when solids are mixed at their interfaces (assuming that the molecules in the solid can move, at least for a very brief period during compression, for example due to the melting of the solid, or due to a transition of the material from a glassy to a rubber-like state) [10, 11]. The importance of the granulation process is highlighted by the fact that granule properties (bulk density, porosity and strength), affect powder rearrangement and deformation and fragmentation of the granule. These characteristics impact the ability to obtain a compact of sufficient mechanical strength to withstand commercial manufacturing, packaging and distribution, and of suitable porosity to facilitate tablet disintegration and dissolution.

Tablet presses run at speeds of up to 500,000 tablets per hour (although throughputs of around 100,000–350,000 tablets per hour are more common). Rotary presses comprise up to 60 or more stations, mounted on a rotating turret. On these machines, a "feed frame" feeds powder into the die from the die table, where it arrives by gravity from the powder hopper. Tablet weight must be maintained constant through a production run, and tablet hardness is a critical performance characteristic that must be carefully controlled. The variable that is adjusted to ensure that mass (and consequently, dose) and hardness (and, therefore, acceptable disintegration properties) are within bounds is the tablet thickness. In practice, control of the tablet thickness to achieve a given target mass requires that the tablet density is varied. Modern machines have a pre-compression stage in addition to the main compression step. "The role of pre-compression is to reduce the porosity in two stages as the entrapped air in high speed tableting is a known cause of defects such as cracks and laminations" [12]. Pre-compression force may be used to control the press, and may be adjusted to respond to variations in the incoming powder feed [13, 14].

Some modern press designs feature specialized containment capabilities to enable processing of some highly active materials; these machines operate at moderate throughputs (as containment requirements affect the maximum production rates that can be achieved), and feature internal washing nozzles and fittings ("clean-in-place" systems).

Coating

Once formed, the tablets are usually coated in a "film-coating" process with a layer of hydroxypropyl methyl cellulose or a similar cellulosic material, which contains water-insoluble pigments (such as "aluminium lakes", iron oxides or titanium oxides) and other additives (such as plasticisers, which aid in film formation), in order to provide a visually attractive finish to the tablet, to provide some protection to the tablet itself and to enable identification of the tablet by any medical staff at the point of use [15].

The coating process takes place in a large perforated steel drum (Fig. 3): coating materials are spayed as a suspension onto the bed of tablets, which rotates slowly. Hot air is passed through the unit, causing evaporation of moisture. The droplets of film-coating material that are deposited on the tablet surface slowly coalesce into a contiguous film coat on the product, and both spraying and drying take place throughout most of the operating cycle of the coating process. Modern machines typically process 200–300 kg of tablets in production situations, but batch sizes may be as large as 500 kg.

While most film coats are used for cosmetic purposes, an "enteric coat" (of a different coating material) may be used to minimize tablet dissolution in the stomach, in order to allow for release further down the gastrointestinal tract. Enteric-coating processes may take several hours, and the resulting films are, typically, thicker than immediate release (i.e., cosmetic) coats.

Fig. 3 A film-coating pan containing a bed of tablets (Image courtesy of GlaxoSmithKline)

Capsule Manufacturing

Capsules are a widely used dose form. Their use may be due to a preference for this presentation for marketing purposes, or for various formulation reasons: capsules may taste-mask bitter drugs, and various specialized delayed release systems provide a means of delivery of drugs to the patient's intestine through enteric-coating or similar approaches. The cylindrical shape with rounded ends may facilitate improved swallowability, compared to a round tablet, although a capsule tends to be larger than a tablet for a given dose strength, due to the lower density of the powder material that it contains compared to a compressed tablet. The gelatin from which most capsules are made is a natural material that does not occur as such in nature, and which is manufactured by the hydrolysis of animal bones and skins, usually from cattle bones, which are dissolved in water with heating, in the case of pharmaceutical grade material. Due to religious sensitivities regarding the use of bovine or pig derived products, some fish-based alternatives exist, and the use of hydroxypropyl methylcellulose ("HPMC" or "hypromellose") derived capsules has grown in recent years [16–18].

The capsules are manufactured in high-volume processes by a handful of major manufacturers: shaped pins are inserted into vessels containing hot gelatin, a film then forms around each pin and the material is allowed to cool and solidify, with most of the water being evaporated in a lengthy process while the material is still on the pin. Pins are made in two diameters, with a slightly larger pin being used for the "cap" than for the "body." Once the cap and body capsule elements have dried, these parts are cut to length, removed from the pin and assembled into an empty capsule, in a process called "rectification" [19]. Concerns over bovine spongiform encephalopathy ("BSE") and other transmissible spongiform encephalopathy

("TSE") diseases have necessitated certification that the input materials are TSE and BSE-free. The capsule-making process has been subject to many decades of process improvement, raising yields and reducing costs. Modern capsules have a set of indentations on the inside of the capsule parts; when the capsule is filled and closed, the interference fit is strong enough to hold the capsule together during onward processing and packaging, and these capsules are said to be "self-locking."

Capsules for human medical use come in a set of standard sizes, designated by the numbers 0–4, with the body volumes that are noted below [20]. The vast majority of capsules are filled with powders, although a variety of other materials can also be filled to achieve specialist formulation requirements.

Capsule size	Body volume (ml)
0	0.69
1	0.5
2	0.37
3	0.28
4	0.2

In many cases, the active pharmaceutical ingredient powder does not flow freely enough for it to be used in a capsule-filling process without the addition of some form of flow aid. As in tablet formulation, other excipients (diluents, glidants, lubricants and disintegrants) may be included to aid the manufacturing process and to affect the performance of the final dose form. Frequently, the high bulk density of the powder requires that formulation additives are minimized, in order to enable the drug dose to be filled into a capsule of moderate size.

Jones [20] classified production powder-filling systems into dependent systems that use the capsule body directly to ensure that the correct amount of powder is filled, i.e., "dosating disk systems," and independent systems in which the powder is measured independently of the body or in a special measuring device, i.e., "dosators." Most modern plants operate independent systems as these provide higher throughputs. The most common approach, which employs a dosator system, is available in both intermittent motion and continuous motion machine types; the former type can produce 5000–60,000 units per hour, while the latter can produce 30,000–150,000 filled capsules per hour. The use of dosator-based systems requires the formation of a compressible plug that can be transferred to the capsule body, and so necessitates that the formulation can be compressed; consequently, these formulations can be described as being "tablet-like" [21]. Modern production machines are fully automated. Historically, machines have typically had capacities in the range of 60,000–100,000 units per hour, substantially below the throughputs of modern tablet presses (which typically produce 100,000–350,000 tablets per hour). Some modern capsule-filling machines, such as the G250 machine manufactured by Italian company MG2, have throughputs of 200,000–250,000 units per hour [22], substantially eliminating this differential.

Packaging

Tablets are commonly filled into bottles or blister packs. In bottle-filling operations, a variety of tablet-counting approaches are used including photoelectric sensing and the use of preformed disks or slats with a fixed-number of cavities. Naturally, the weight of each individual tablet or capsule is low in comparison with the weight of the container, so check-weighing is not wholly accurate as a method of confirming that the correct number of tablets or capsules has been provided, and most modern lines are fitted with infrared sensors or camera technologies as tablet-counting systems.

Blister packs (Fig. 4) are produced using a form-fill-seal process. Polyvinyl chloride ("PVC") or a similar thermoplastic material is supplied on a reel and blister cavities are formed through the use of heated die plates or drums. Aluminum "lidding foil" with laminated plastic or an adhesive is used as an upper layer: both layers are fed together, the tablets or capsules are fed into the wells, and the Blister packs are widely used and have many advantages as a form of presentation—the dose taken can be checked, the dose form is sealed away from the environment until shortly before ingestion, and patient leaflets can be readily supplied. However,

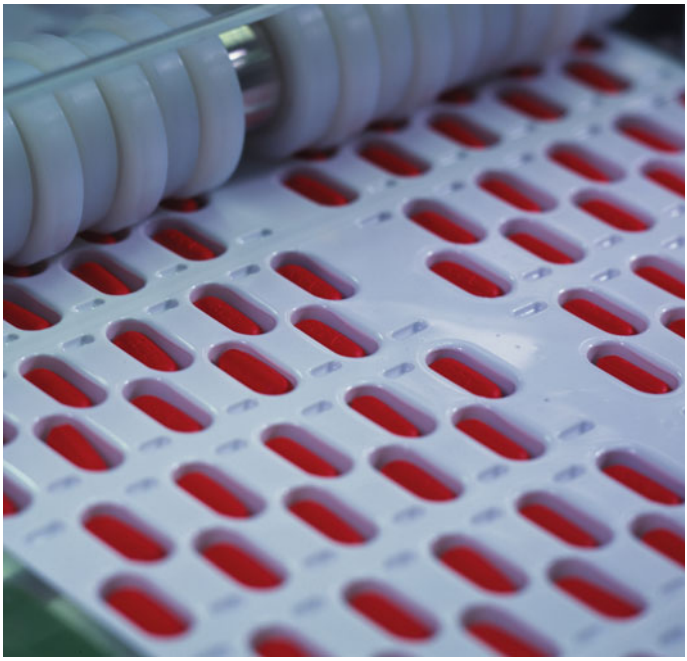

Fig. 4 Caplet-shaped tablets on a blister-packing line (Image courtesy of GlaxoSmithKline)

blister packs are more expensive to produce than bottle-packs of tablets and blister packs occupy more physical space. Upper and lower layers are heated and then pressure-sealed using heated rollers or platens. As the protective capacity of the polymeric material increases so too does the cost, with PVC packs costing less than polyvinyl dichloride ("PVDC") ones, which, in turn cost less than Aclar blister packs. (Aclar, which is poly-chloro-trifluoro-ethylene, or "PCTFE", is a specialist and highly protective material marketed by Honeywell; [23].) This range of materials provides differing levels of protection from moisture ingress and the different polymer films are characterized by their water vapor transmission rates. Aluminum-based packs, which are cold-formed (rather than thermoformed, as described above), can be used to minimize water ingress and to provide superior protection to PVC and PVDC, but at a significant additional cost. Machines typically operate at up to 400 blister packs per minute; for a 12-tablet blister, this production speed packs 4800 tablets per minute, or 288,000 tablets per hour. Packaging is typically conducted on automated lines that provide cartoning, leaflet insertion and labeling capabilities. It is notable that packaging costs are large relative to other production costs, that these costs increase significantly when greater product protection is required, and that for high-volume tablet products packaging costs may equal all other secondary manufacturing costs combined.

Industrial Engineering of Solid Oral Dose Form Production

The History of Tablet Production Processes

Many of the processes that are used in tablet production were established several decades ago. For example, tablet compression has a history that dates to the mid-nineteenth century, when the first patents were filed. The historical practice had been to produce small compacts of dried material through formation of the dough-like material into small shapes while wet, and then to dry these small compacts. Technically, the materials produced in these cookery-like processes are termed "pills", whereas in the manufacture of "tablets," in contrast, the material is dried before it is formed into small shapes [24].

Until the development of specialist containment presses in the last 10–20 years, it was sometimes said, with some justification that the most recent developments in press technology "came from the 1920s": the fundamental design principles of a key workhorse technology of the modern pharmaceutical industry were developed (and patented) in the 1920s and 1930s. By way of some brief examples, it can be noted that Arthur Colton patented the rotary tablet press, which is still the standard industry press design, in the 1920s, self-locking capsules (Fig. 6) were patented in 1894, and early capsule-filling machines (Fig. 5) date from 1918 [25]. One hundred years after the advent of tableting as a standard means of production, interest in "instrumented presses," which were equipped with sensors to enable measurement

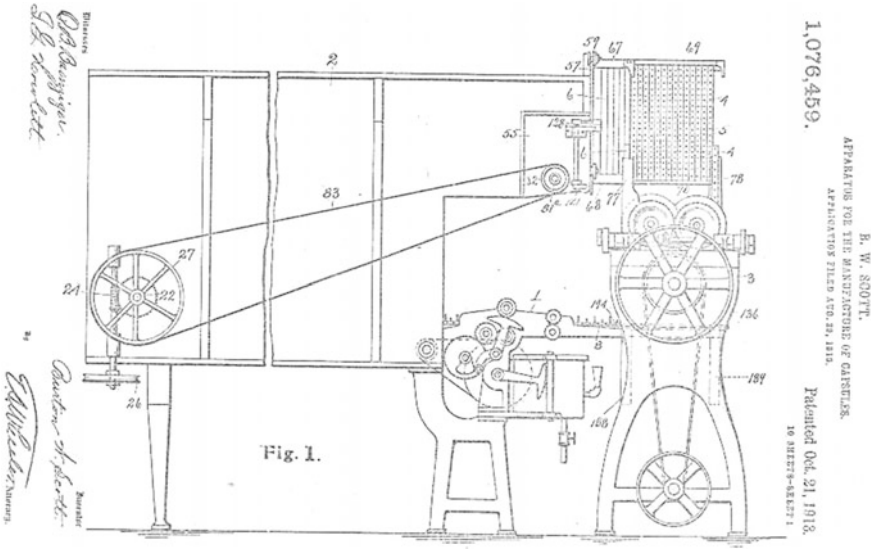

Fig. 5 Drawing from a patent on an early capsule-filling machine, 1918

and understanding of the production process, emerged in the 1950s and 1960s; this trend has influenced modern machine designs, and has been enhanced by industry and regulator interest in-process monitoring and "quality by design." The last major change to the set of unit operations that are used in tablet production was the introduction of film-coating into many factories in the 1980s; this new process took a decade or so to supplant sugar-coating processes, in which operators manually ladled the coating solution onto a spinning open drum.

Manufacturing Engineering Considerations

Relatively few academic studies have commented on pharmaceutical production costs and manufacturing engineering issues, and academic attention has, to some extent, been concentrated on other production management topics. (Among the published studies on production costs, Schaber et al. [26], discuss the economics of batch and continuous secondary production, Basu et al. [27] discuss manufacturing costs across a range of pharmaceutical companies; Suresh and Basu [28] discuss the importance of manufacturing costs to company profitability; and Pinheiro et al. [29], discuss the production costs specifically for antiretroviral drugs.) Other production topics are discussed in greater depth in the academic literature; for example, supply chain planning and analysis, specifically in a pharmaceutical industry context, has been considered in a number of recent studies (for example those by Masoumi et al. [30], Papageorgiou [31], Rossetti et al. [32], Sousa et al. [33],

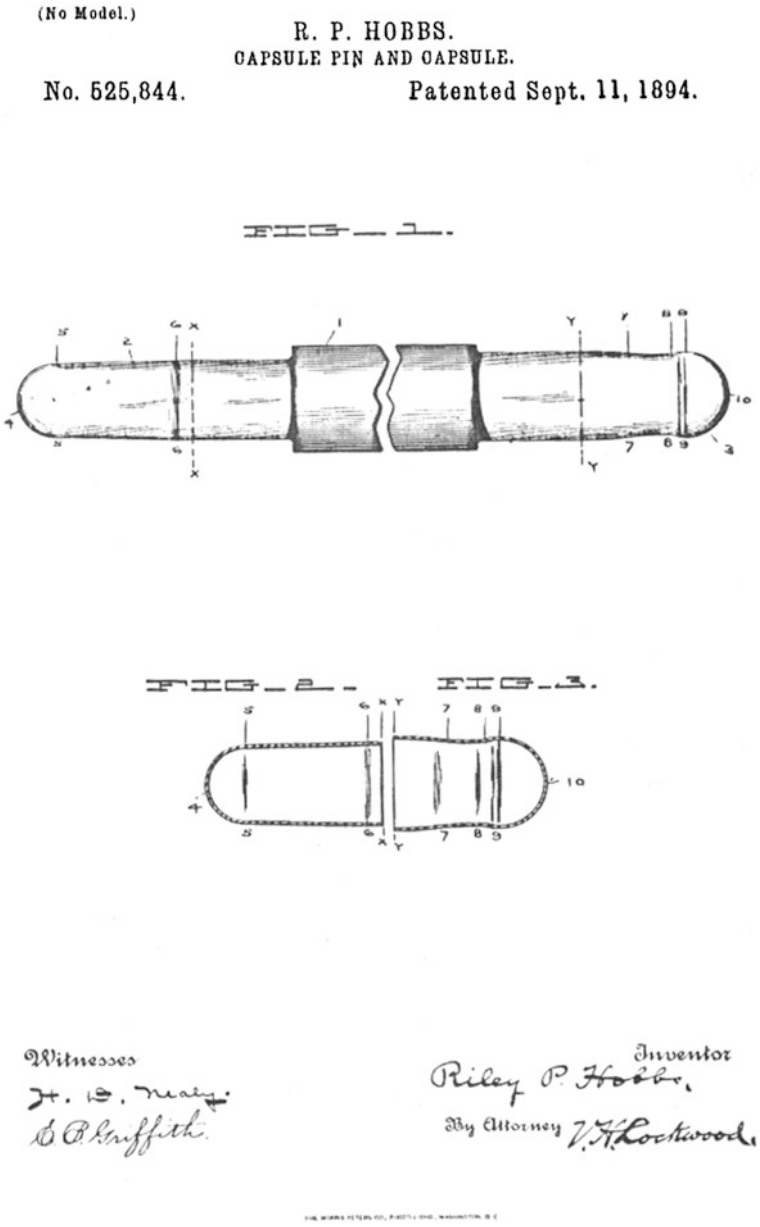

Fig. 6 Drawing from a patent on a self-locking capsule, 1894

Susarla and Karimi [34]). Despite this relative lack of academic attention, industrial engineering aspects of pharmaceutical production are of great importance, from a practical perspective, and the manufacturing system significantly constrains the range of dose variants that can be produced.

There are many challenges in modern tablet production and, naturally, an understanding of the issues rests on knowledge of the manufacturing processes involved. In particular, it is important to highlight that the process flow (Fig. 7) is highly inefficient from a manufacturing engineering perspective: milling and blending are fast batch processes and are followed by granulation, which is a semi-fast batch process; however, drying is a relatively slow batch process, blending is a very quick batch process, and tableting is a fast continuous process. (Conceptually, compression may be regarded as producing many batches of an individual tablet, but the process is run on a continuous basis in a production environment.) The process flow is completed by film-coating, which is a slow batch process, which may take from 1 to 2 h for the application of a standard cosmetic coat to as long as 10–12 h if an enteric coat is required (in order to protect the tablet from the acidic pH environment in the patient's stomach, for delayed release products). These durations are for the processing time only, and do not include the time that is necessary for set-up, clean-down and quality assurance activities. Given this set of unit operations, there is frequent interchange between fast and slow batch processes, and limited use of continuous throughput unit operations. As a result of these flow mismatches, various batches must be produced though the use of different sub-lots, the size of which varies from unit operation to unit operation. As an example, a large pre-granulation blender (e.g., V-blender) may be used to prepare a large batch of blended material, but this batch may need to be split into several sub-lots for granulation.

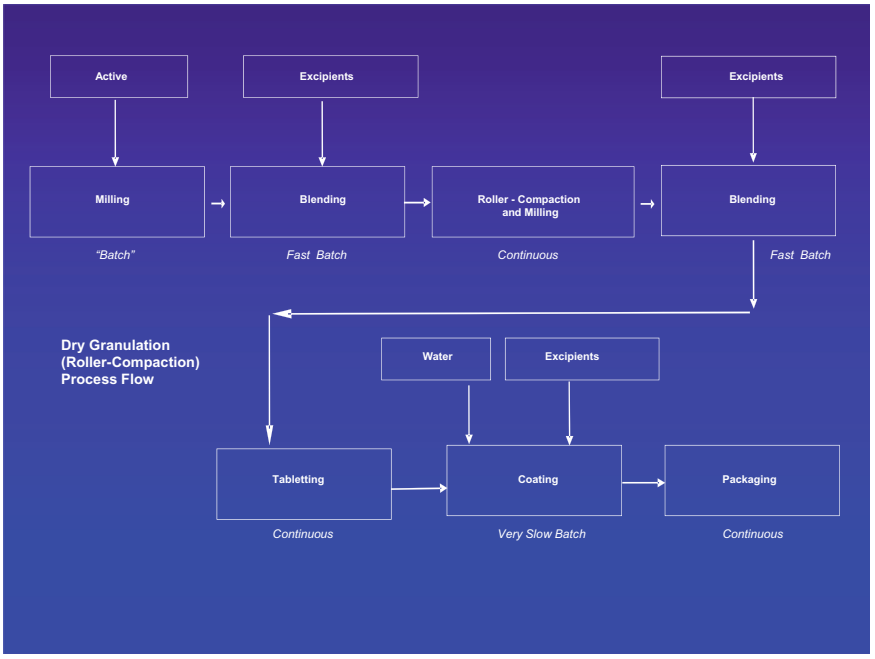

Fig. 7 Process flow diagram for the production of tablets by dry Granulation (Image courtesy of GlaxoSmithKline)

The use of batch processes necessitates preprocessing and postproduction operations to clean the equipment and to prepare the machine for the next batch; however, different machines are prepared in different ways and require different levels of effort for adequate cleanliness to be achieved. (Batch-to-batch production of the same product does not usually require full cleaning, unlike the switch from one product to another.) In addition, several process critical aspects of the machine typically must be checked and verified before the batch production commences, and the batch process may not be finalized (and the equipment "released" for fresh production) until offline testing of the material produced has taken place. As a consequence of cleaning operations, these preoperational checks and necessary but time-consuming quality tests, set-up and post-manufacturing operations frequently take as long as, or longer than, the direct production process itself. For example, a tablet production run that might take 6 h, excluding set-up, cleaning and quality testing periods, might require that the machine be utilized in total for 14–18 h.

Plant Operation Challenges

Cleaning and Scheduling

It is worth expanding briefly on these issues. If a product has a relatively low production volume and a limited shelf life, the need to assure an adequate shelf life in a complex global supply chain may require that the product is manufactured on a monthly basis. Partially as a consequence, manufacturing equipment is typically operated for multiple products during the course of a month's use, and multiple cleans between campaigns for different products must be conducted. Naturally, cross-contamination of a batch of one product by another must be avoided, and so the cleaning processes are carefully controlled; automatic cleaning by "clean-in-place" systems (that are integral to the machines) is often supplemented by manual cleaning, which requires time and effort. Following these activities, lengthy laboratory testing is often necessary in order to confirm the cleanliness of the equipment. Naturally, these factors add delays to the production schedule.

Set-up and Machine Configuration

Although one piece of equipment may be used for the processing of multiple drug substances in a given month, the machinery is likely to require to be configured or set-up differently for each of the products. For example, different punches must be fitted to a tablet press for the production of different products, in order to manufacture tablets of the specific sizes and shapes that are required, and with any necessary break lines or debossing (lettering) effects. Given these production intricacies and constraints, plant schedules inevitably contain substantial periods when equipment is not in use, even though it may be ready for production. Due to

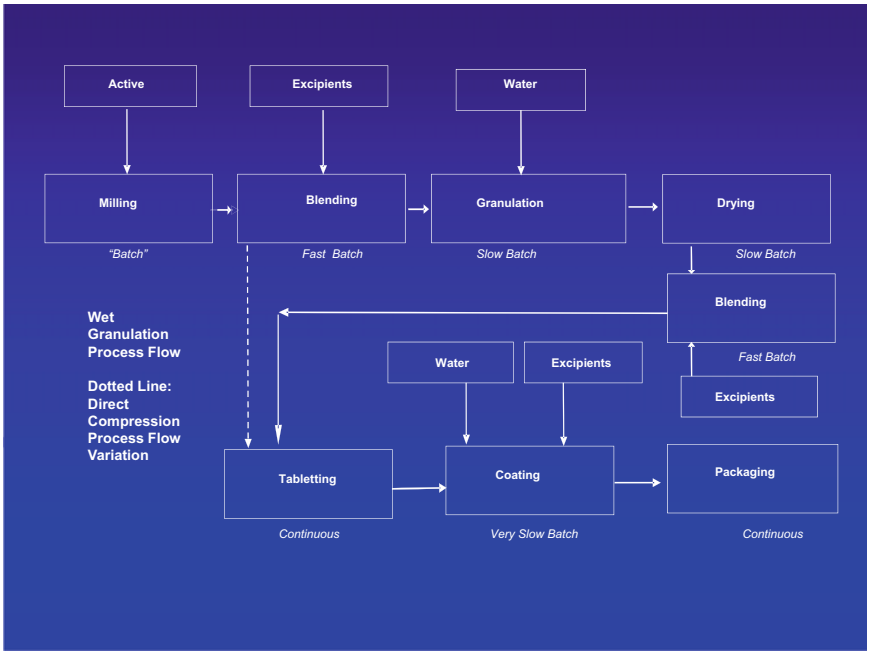

Fig. 8 Process flow diagram for the production of tablets by direct compression or high-shear wet granulation (Image courtesy of GlaxoSmithKline)

the varying throughputs of different processing steps (Fig. 8), which are affected by the specific equipment that is installed in a given factory, there are usually substantial inconsistencies in the product flow through the unit operations, and, consequently, many equipment items have considerable periods of non-use. As one example of this type of complexity, a common industry practice is to limit dilution of an initial compression powder blend to a factor of around four, so that a standard blend might be used to produce tablets with dose strengths of between 10 and 40 mg, or between 100 and 400 mg, for example, but production of tablets with dose strengths outside the set range would require production of a separate powder blend, and additional manufacturing activity.

Pack Complexity

There is substantial complexity in the number of pack variations that are produced. The requirement for different dose strengths, formulations and packaging variations may give rise to the situation that a single source of drug substance must be converted into 10–40 drug products and as many as 100–400 packaging variations (or stock-keeping units, or "SKUs"). This proliferation of packaging variants late in the manufacturing process arises due to local language, product leaflet and product registration requirements.

"Reserved Capacity" for Sales Increases

An additional complication is the potential reservation of manufacturing capacity in order to cope with demand increases: some innovator companies may choose to reserve plant capacity in order to allow for greater than anticipated sales of recently launched products, even though this course of action imposes significant costs. These companies face significant sales forecasting uncertainty, and the product registration files for each product (as approved by the regulatory authorities) state the specific sites of manufacture that may be employed. It is difficult, in most cases, to expand plant capacity, non-trivial to gain approval for supply from a new site, and complex to initiate supply from an additional site, even when one has been included in the regulatory filing; consequently, reserving plant capacity may be a pragmatic option to deal with demand fluctuations.

The Impact of Operational Challenges

As a consequence of these inefficiencies, true plant utilization in secondary manufacturing is of the order of 5–15 %. In these circumstances, costing and overhead allocation can be challenging: a large proportion of the budget of a secondary manufacturing site is consumed by indirect production costs such as testing facilities, quality assurance laboratories, engineering support and infrastructure. The direct costs of production are the labor for the production "run time," which is usually a modest fraction of the total time that the production machines are occupied, and material and energy costs, which are usually a very small percentage of the total cost of production (1–5 %). Yields in secondary processes are typically very high, being 98–99 % for each processing stage, so yield losses do not contribute greatly to production costs. Indirect costs usually dominate the direct costs, of which only labor, typically, is significant.

Many pharmaceutical companies operate a network of sites that comprises 6–10 primary production sites (i.e., large chemical plants) and 50–80 secondary sites. There are major legal and regulatory reasons for conducting some secondary activities in many countries, yet this approach implies that most of a company's manufacturing capital is dispersed across many secondary sites, and that primary production is "capital efficient" in comparison, even though the capital cost of each of the primary sites may be very high.

Complexity and the costs that this creates are critical issues in the operation of secondary sites. Many factories produce a range of hundreds of final pack variants: much of the complexity arises in packaging, with different packs or leaflets being required for specific markets, and co-marketing creates additional demand for pack variants. If a product is manufactured at one site for sale and distribution by two different companies in different territories, for example, as the result of a compound licensing or co-marketing arrangement, different tablet images, typically, will be required. Naturally, this is the case for all dose strengths, and so production of five

dose strengths would require production of ten tablet variants, with a similar increase in the number of final pack variations that must be produced. A production arrangement of this type typically requires the manufacture of many small batches, of modest size. Each batch, at every stage of processing that is required, necessitates the same level of plant set-up, cleaning and quality assurance offline testing; consequently, the necessity to produce many small volume batches creates lower utilization rates and increases substantially the ratio of time that equipment is not operational, yet is required for the batch and is not available for other production activities, compared to the time that the plant is used in direct production activities.

In extreme cases, the annual supply of a very low volume product may be fulfilled by a small manufacturing campaign of a handful of batches, or by the production of a single batch of granulated material for onward processing. In these cases, set-up and other non-direct production expenses are very high indeed relative to the direct processing costs. (The lowest batch size the author has been made aware of—in a case that was, admittedly, highly extreme—was one carton of blisters; Seaward [14].)

The Economics of Production of a Wide Range of Tablet Variants

Even in the absence of co-marketing arrangements, substantial complexity also occurs in tablet production. Many products are produced in 4–6 dose strengths, as this provides a range of doses for different states of disease progression, or age or weight of patient, yet does not impose unfeasible burdens on tablet production economics. Some products require a complex set of dose strengths for patient-to-patient titration, as is the case with many psychiatric drugs. Dose alternatives in these instances are typically provided by using combinations of a number of basic tablet strengths, e.g., a 50 mg dose might be provided by prescription of two 20 mg tablets and one 10 mg tablet. Given the long set-up and post-processing times that are required in production, and the need to allocate site fixed costs that are very large relative to the direct costs of production, complexity in production has a major effect on economic viability of a product. Economically challenging production schedules are those that feature a large number of small batches of different dose strengths and images (i.e., the appearance, such as the combination of color and the embossed logo); in this case, direct costs are moderate and substantial overhead production costs are typically allocated to low volumes, due to the occupation of machinery for the extended set-up and post-processing activities. In general, pharmaceutical companies have concluded that five or six dose strengths provide an adequate set of options to provide dosing flexibility to physicians and to meet patients' needs; however, when this is not the case, economics typically dictate that no more than five or six dose strengths can be provided, as to offer more dose variants would add considerable complexity to the production schedule and

raise costs for all dose variants beyond an acceptable level. In this circumstance, offering more variants would reduce volumes for other dose strengths, negatively affecting the production economics.

Generic producers operate sites that manufacture large numbers of tablets of each dose of an active. The cost base of a generic manufacturer is usually below that of an innovator company as, typically, generic companies do not invest to a large degree in research and development and so do not bear notable technical costs of new product introduction, such as the need to retain an extensive skill base in order to deal with any complexities that arise early in the product lifecycle. In addition, generic companies typically aim to operate using high-volume production runs in order to minimize operational costs. Consequently, the addition of extra complexity to the production schedule would significantly affect production economics. Given the low cost base of these organizations, the incremental effect of additional complexity could raise costs of production—due to a reduction in batch sizes and a decreased utilization of plant—by a greater percentage than in the case of an innovator company.

The Importance of Industrial Engineering Considerations

While the industry copes with these challenges to supply the global marketplace, it is important to acknowledge the constraints that these processes apply to the production of a wider range of products and to bear these limitations in mind when considering how elderly individuals might be provided with more patient-friendly dose forms. The difficulties that are inherent in mixing batch and continuous processes, and unit operations with different throughputs, create significant manufacturing complexity. The issues of extensive set-up, clean-down and quality activities, the need to move materials around a factory, and the dominant use of offline rather than at-line or online analytical technologies (in contrast to the practice in many industries) create inefficiencies that lower total plant utilization and increase manufacturing costs.

These characteristics of secondary production have led to significant interest in the industry in the potential of continuous secondary production, and it is to be hoped that the industry will be willing to adopt continuous manufacturing in the coming years. This approach offers the potential for lower in-process times, a reduction in the volume of material that is produced at risk (i.e., prior to quality checking) through the use of at-line or online quality measurements, and a lower cost of goods. As additional and highly significant benefits, this manufacturing platform potentially reduces plant space requirements (or "footprint"), lowers capital investment costs, reduces drug product requirements for development and shortens product and process development times. In contrast to the existing set of batch and continuous processes, significantly higher plant utilizations can be achieved. (For discussions of these topics see Schaber et al. [26], Mascia et al. [35]). Major academic institutions, such as MIT and industrial-academic consortia such as

the Engineering Research Center for Structured Organic Particulate Systems at Rutgers University ("ERC-CSOPS") have adopted extensive research programs in this area, with significant commercial funding and industrial involvement. Although continuous processes have been investigated commercially for many years, adoption rates have been low to date (for reasons that were discussed by Keith Plumb in a 2005 [36] paper entitled "Continuous Processing in the Pharmaceutical Industry: Changing the Mind Set"); nonetheless, some recent studies and developments suggest that this situation may change in the next 5–10 years (for example, see papers by Lee et al. [37], Poechlauer et al. [38], Singh et al. [39, 40]).

The challenges that are inherent in the traditional, batch-dominated manufacturing processes that are employed to produce immediate release tablets and capsules provide a perspective with which to consider specialist dose forms for elderly patients. Many tablet, granule and film presentations that are designed with elderly patients in mind, often with the aim of facilitating ease of swallowing by the patient, must be manufactured using specialist processes (for example, the casting techniques that are used to manufacture oral films), with the consequence that the secondary manufacturing cost for each dose form is substantially greater than for standard immediate release tablets or capsules. The set of dose forms that can be applied for specific use with elderly patients is discussed below, and this set of options (with associated constraints) constitutes a major part of the landscape of dosage form design for the elderly.

Approaches such as personalisation of medicine have been discussed widely in recent years, and yet traditional approaches can only produce economically a small set of variants, and the quality of a tablet that is released is assessed at a batch level, with no true verification of dose content at the individual product (i.e., tablet) level. Novel manufacturing technologies that address traditional manufacturing challenges in creative and unusual ways may offer the possibility to provide new presentations to patients that are more "patient-centric" and that provide inherent quality benefits, and two such approaches are discussed elsewhere in this volume. The brief overview of established formulation and manufacturing approaches that follows below provides a summary of existing practices, and a context for the consideration of novel approaches.

Special Dose Forms

In recent years, there has been an increase in the level of industry and regulator industry interest in how dose forms that are suited to the specific needs of different groups of pediatric and geriatric patients can be provided. (Among other authors, Salunke et al. [41], Sam et al. [42] and Standing and Tuleu [43] have provided studies considering pediatric dose forms, and Orlu-Gul et al. [44] and Stegemann et al. [45–47] have outlined some considerations in relation medicines for the elderly.)

A number of less standard oral dose forms are frequently applied to provide products for elderly patients. Each of these approaches presents different manufacturing challenges, and the cost of manufacturing each dose form typically exceeds the cost of standard tablet or capsule manufacturing, sometimes by a notable multiple. Many of these dose forms are predicated on avoiding or minimizing the swallowing difficulties that some elderly patients experience.

A number of authors have reviewed the characteristics that are desirable for medicines for the elderly, often in a broader consideration of the most appropriate characteristics for both pediatric and geriatric medicines. Perrie et al. [48] noted that "liquid and fast-melt dosage forms may address the need of patients who have difficulties in swallowing medication," but note that broader physiological aging effects need to be taken into account: "changes in the drug dissolution and absorption in older patients may require the formulation of oral delivery systems that offer enhanced retention at absorption sites in improve drug delivery." Stegemann et al. [49] commented that "the age-related physiological changes that affect the pharmacokinetic profile can occur during drug absorption, metabolism, distribution and elimination" and noted that "special attention should be drawn to the old and frail patients" as "this patient group develops a malnutrition stage and loses weight considerably," so that "continuing with the standard dose…patients are seriously overdosed." It is important that drug delivery for geriatric purposes is conducted with awareness of the physiological changes of aging and the ways in which these processes may affect drug absorption and metabolism.

Liu et al. [50] noted that dysphagia, or difficulty in swallowing, affects both pediatric and geriatric populations. Swallowing involves bolus transport and airway protection, with oral, pharyngeal and oesophageal components of "deglutition": "the natural process of aging is associated with a decline in swallowing affecting all three phases of deglutition…poor dentition and reduction in masticatory strength in older age are the main causes of increases in oral-phase duration and the amount of oral residue during swallowing" and "age-related neuromuscular decline contributes to a delay in triggering pharyngeal swallowing reflex and deceases in bolus movement." These authors add that it has been estimated that "70–90 % of the older population experience some degree of dysphagia." Stegemann et al. [46] reviewed dysphagia in elderly populations and commented that "about one-third of patients in long-term care facilities experience serious difficulties with swallowing solid oral dosage forms." Many of the presentations that have been developed with elderly patients in mind have the intention of allowing easier swallowing for those patients that experience such difficulties.

Chewable Tablets

The main approach to dispersible tablet formulation is to adapt standard tablet formulations to create tablets that are usually described as either "chewable" or "orally dispersible" (with the latter type being called "oral dispersible"

presentations in the terminology of some authors), depending on the degree of dispersion in the patient's mouth that is achieved. Chewable tablets are manufactured using standard tablet processes. The formulation is designed to disintegrate in the patient's mouth under the pressure of a mechanical chewing action; the particles pass into the stomach, allowing absorption of the drug in the stomach or intestine. The formulation of a chewable tablet is different to a standard one in that a disintegrant is not added as an excipient and the formulation typically utilizes substantial quantities of mannitol or sorbitol as filling agents. Stoltenberg and Breitkreutz [51] noted that "insufficient binding properties and compatibility" of mannitol require that other excipients are used to adjust the properties of the resultant blend, and that "various co-processed ready-to-use excipients are available for direct compression and …are readily available." Elder noted that a mixture of standard diluents and microcrystalline cellulose is often used to provide a blend with good compression and flow properties. While some patients may feel that chewing is preferable to swallowing, not all patients will be comfortable with the action of chewing a tablet, and chewable tablets may have limitations in some very young and elderly patients due to lack of dental development or loss of teeth [52]. In addition, and in order to ensure maximal acceptability, taste and mouth feel considerations are important in trying to develop a formulation that will be broadly acceptable.

These formulations are manufactured using fairly standard tabletting processes, such as high-shear wet granulation or direct compression with specialized excipients, and consequently has a moderate cost of goods. Production throughputs are typically lower for these formulations than for standard immediate release tablets products, and granulation approaches other than high-shear wet granulation are often employed. The cost of goods for these products is considered to be moderate when compared to other more unusual dose forms such as flash-dispersion tablets and films.

Effervescent Tablets

Effervescent tablets are dropped into a glass of water before the material is ingested, and utilize a reaction between a weak acid (for example, citric or tartaric) and a carbonate or bicarbonate, in water, to release carbon dioxide. This release promotes disintegration and dissolution. One notable feature of effervescent tablets is that the ingestion of the liquid may alter the pH in the patient's stomach, causing more rapid stomach emptying. Consequently, the drug may be absorbed in the intestine, and overall drug absorption may be comparatively rapid. Carbonate loadings in effervescent tablets may be quite high (up to one gram), and the tablets tend to be large. The product is manufacture using direct compression tableting processes, or using compression following granulation processes in which the materials are fused together. Due to the obvious conflict that arises in using a wet system in order to prepare materials that are designed to effervesce on the addition of water, high-shear

wet granulation approaches are not normally used to prepare tablet compression blends in the manufacture of these dose forms. It is notable that effervescent tablets are typically manufactured in specialized facilities where the humidity in the air is kept very low (below 20 % relative humidity) in order to prevent activation of the effervescent agents during processing. The required environmental controls add significantly to the cost and complexity of the manufacture of effervescent tablets. In addition, presentations of these dose forms typically employ sachets and "stick packs" that tend to be relatively expensive.

Oral Dispersible Tablets

Tablets that disperse in the patient's mouth may provide an attractive alternative to standard tablet formulations and may eliminate swallowing issues and difficulties for patients. A number of formulation variations exist, of four main types: dispersible tablet formulations that are adaptations of standard approaches, with extensive use of mannitol and similar excipients to enable rapid dispersion in the mouth; floss processing approaches; the Zydis flash-dispersion approach, which is proprietary to Catalent; and novel 3-D printing (or "additive manufacturing") approaches, as pioneered by Aprecia.

Sandri et al. [53] defined "oral fast-dissolving systems" as "solid drug delivery formulations that dissolve or disintegrate within a few seconds to a few minutes of introduction into the mouth in the presence of saliva, resulting in a solution or a suspension without the need for water". In practice, the terminology applied to "chewable", "orally-disintegrating" and "orally-dispersible" dose forms varies greatly among authors.

Standard chewable tablet formulation approaches such as melt granulation (or even, on occasion, direct compression) can be used to manufacture dispersible tablets. Such formulations typically use strong tablet disintegrants (so-called "super-disintegrants") and sugar-based excipients (such as mannitol, sorbitol or fructose). These sugars have high aqueous solubilities that provide rapid dissolution, which helps to create a pleasing mouth feel for the patient. (Mannitol has a negative heat of solution, and this characteristic imparts a "cooling" sensation in the patient's mouth; [21].) Taste masking is often required in the development of dispersible formulations of all types. In the case of orally dispersible tablets, coated particles may be used to mask the bitter taste of the active; however, great care has to be taken to achieve an acceptable "mouth feel," to avoid a sensation of grittiness, and to provide suitable organoleptic properties.

In floss processing, as pioneered by Fuisz Technologies, the drug is loaded into a polymer matrix and strands are prepared by a "spinning" process. These strands are then chopped and the fragments are incorporated into oral dispersible tablet formulations. The tablet disperses rapidly allowing release of the floss fragments; the drug is then released rapidly from the strands, due to the characteristics of the

polymer matrix and the high surface area of the materials. Processing must be conducted in specialized facilities and manufacturing costs are comparatively high.

The most well-known lyophilisation approach is the Zydis technology, which was initially developed by RP Scherer (which was a predecessor company of Catalent). Drugs are dispersed into a carrier matrix and filled into wells in a blister pack (Fig. 9); the material is then frozen in situ, lyophilised and a sealing layer applied. Sandri et al. [53] note that doses of up to 400 mg can be delivered using this approach, but that doses may be limited to 60 mg for water soluble drugs due to lyophilisation constraints, and that typical disintegration times in the patient's mouth increase at higher dose loadings. The technique creates a dose form with the characteristics of an open matrix, similar to those of solid foam. This structure allows the patient's saliva to enter the dose form and to permeate the tablet, allowing disintegration and dissolution to occur. Materials used in formulating the matrix structure include mannitol, natural polysaccharides, gelatine, polyvinylpyrrolidone, and polyvinyl alcohol. Costs for dose forms manufactured using this approach are typically high compared to those for other tablet production approaches, and broadly comparable with costs for manufacturing film-based dose forms.

Other freeze-dried dose forms have been developed, such as the "Quiksolv" and "Lyoc" approaches, and Sandri et al. [53] reviewed this type of dose form and described these approaches. The first of these technologies produces tablets which are less friable and sensitive to mechanical damage on handling than Zydis products. The dose forms are prepared by dispersing gas bubbles into a solution or suspension to form foam. All of the materials are initially frozen; the solid system is then placed in contact with a second solvent at a temperature that is between the solidification (freezing) points of the two solvents, so that the first solvent is removed, and the carrier solvent is then evaporated to leave a porous matrix. The

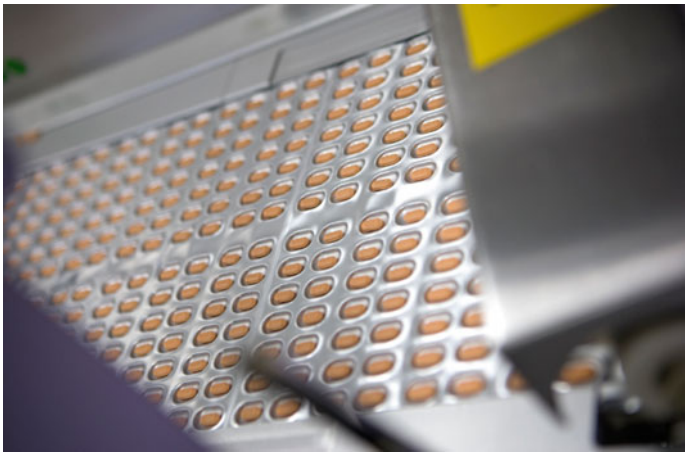

Fig. 9 Tablets on a blister-packing line (Image courtesy of GlaxoSmithKline)

Lyoc process places small particles ("nanoparticles") of drug in a matrix to produce a rapidly disintegrating dose form. In general, care needs to be taken in the handling and packaging of freeze-dried dose forms, due to their friable nature and the need for the use of moisture-resistant packaging. Taste masking of these dose forms can also be problematic.

A number of authors have discussed the potential for 3-D printing or additive manufacturing approaches to be used for the production of pharmaceutical dosage forms (Jonathan and Karim [54], provide a current review of this area). In this field, a number of major university research groups have emerged, such as those at the School of Pharmacy, University College London, which has investigated fused-filament deposition approaches [55–58], and the University of Nottingham, which has considered extrusion printing approaches [59, 60].

A US-based start-up company, Aprecia, has applied a 3-D printing technology that originated at the Massachusetts Institute of Technology to develop, to test and to register a formulation of levetiracetam [61]. This tablet formulation approach is unusual in that it can deliver a large dose (up to 1 gram) in an "oral dispersible" formulation and achieve a speed of disintegration in the mouth comparable to that obtained by a flash-dispersion dose form, with an excellent "mouth feel." Some oral dispersible tablets do not disperse rapidly, and others, even if disintegration is rapid, leave the patient with a gritty feeling in the mouth; consequently, it is unusual to be able to deliver a rapidly disintegrating dose form at a high dose level that avoids these effects. Manufacturing costs and throughputs have not been disclosed by Aprecia. Prior to the approval of this product, the prevailing industry view had been that the specialized equipment that is required for this approach was not able to produce dose forms at economically acceptable levels, and that the cost per tablet would be extremely high, significantly in excess of film dose form manufacturing costs. Enabling adequate throughput for a commercial product is a challenge in the development of such 3-D printing approaches; the industry typically manufactures hundreds of millions of tablets for a particular product per annum, and adapting a technology that can manufacture each dose form individually to compete with established high-volume manufacturing processes is a challenge.

Granule Products

In practice, many patients may take oral dispersible tablets and put these in a glass with water, stirring the tablet to aid disintegration, and then drinking the resulting liquid which contains small solid particles. Given the fact that such patient behavior is prevalent, an alternative formulation approach is to develop granular products that are designed to be used in such a fashion. These sachet-based products (or "stick packs") have application in pediatric and geriatric settings. In some markets, the use of "stick-pack" (or "dry suspension") products, which may be tipped by the patient directly into his/her mouth, is well-established, and it is important to note that some very young or elderly patients may have difficulties in taking chewable

tablets, due to lack of dental development or loss of teeth. (As an example of this formulation approach, Disch et al. [62] noted an experimental process for preparing acetaminophen granules, stating that at the end of the process "oral dispersible granules are produced that can be filled in stick-packs and which form a palatable, user-friendly dosage form that may be taken without water.")

The form of the packed product may be a rectangular sachet or a small tube that is filled with a granulated form of the active. Theoretically, the process for manufacturing the granular material could be identical to that used to produce granules for standard tablets. Instead of adding extragranular excipients and compressing a blend to form tablets, the granules may be filled directly into packs; as the flow properties of the blend need to be very good, extragranular excipients are usually added prior to filling. However, practical experience suggests that this type of formulation requires excellent flow properties, in order for the sachets and stick packs to be filled at normal production speeds, and that in general, standard granule blends do not have suitable flow properties for this application [21]. The concept of utilizing a common granular blend to manufacture both sachets of granular material and standard tablets is attractive (in order to allow the rapid development of sachets for pediatric and geriatric use, and to minimize development and testing activities); however, in practice, this type of platform approach is rarely possible.

The approach provides substantial flexibility with regard to dosing. The dose is varied by filling a different measured amount into the sachet, and although this has to be pre-set on the filling machine, it is possible to produce a number of dose strength variations comparatively readily. Machinery that is designed to fill sachets typically employs Archimedean screws (which are often called "augers") as the means of dispensing the powder. As is the case for powder dispensing processes, augers present a set of challenges to the formulator: very free-flowing powders tend to continue flowing when the auger has stopped, whereas very cohesive powders tend "to bridge" (block) and are not "pumped" by the auger [14]. Given these constraints, the compressibility and the flowability of the powder need to be tuned to the filling system.

Care needs to be taken with the pack design to ensure that it can be opened readily by an elderly patient, as the small size of many sachets and the manipulation that is required to open these may cause handling difficulties.

"Taste Masking" of Actives

For the dosage forms that involve disintegration of the tablet in the mouth and dispersion in liquid which is taken by mouth, an important consideration is the "taste masking" of the active drug to allow it to be sufficiently palatable for routine use by pediatric or elderly patients. It is often the case that drugs, especially those that are very soluble in water, have a bitter or foul taste; frequently, a particle coating or similar process must be applied in order to alter the patient's perception of the formulation's taste (i.e., "to mask" the taste, in standard industry

terminology). Taste masking, which is often performed at specialist companies, is an additional processing step that adds to the cost of goods and to the complexity of the formulation development process.

Mini-Tablets

A number of authors have proposed the use of mini-tablets for dosing of drugs to pediatric patients (for example, [63] and this approach may also have application in geriatric settings. Tablets of this type are produced at a size of 1–2 mm, and the required dose is provided by filling a number of these mini-tablets into a carrier such as a capsule. This process typically requires the production of multiple tablets, followed by capsule-filling, and, consequently, is expensive compared to the manufacture of a single large tablet. (Tissen et al. [64] described an experimental direct compression approach for the production of mini-tablets.) The weight of the dose that is filled can be challenging to control with such systems. The carrier (e.g., capsule) is typically filled via a fixed volume (i.e., volumetrically) and the difference between, for example, 19 and 20 mini-tablets may be less than the allowed weight tolerance [14]. Stoltenberg and Breitkreutz [51] described results from a study to formulate orally dispersible mini-tablets for pediatric use, in order to obtain ease of swallowing benefits, from the nature of the formulation, in addition to the potential dose-titration benefits that the small size of mini-tablets may potentially allow. One concept that has been proposed is to dispense mini-tablets from a device that is similar to those used for drink sweeteners, in order to provide accurate dose control [65].

Films

Film-based dose forms provide a means to avoid swallowing issues for elderly patients. The dose form dissolves in the patient's mouth, releasing the drug, which then travels down the throat into the stomach. Consequently, although this dose form is often described as being buccal, the route of administration is often regarded as being primarily through the gastro-intestinal tract; very few drugs can be absorbed buccally, and there is, typically, very little drug absorption in the throat or esophagus, and only limited absorption in the stomach [21]. (Adhesive buccal films are designed to remain in the mouth—through mucoadhesion—and to release appropriate drugs over a period of time, and, consequently to avoid first-pass metabolism in the liver to a significant degree; Lam et al. [66], Madhav et al. [67] have discussed "orotransmucosal" dose forms.) The film is a small, thin rectangular object, which may pose handling and manipulation difficulties for some patients. The film rapidly becomes wetted by the patient's saliva and dissolves rapidly,

enabling dosing of patients who are wary of tablets and capsules, or who have difficulties in swallowing.

While film-based dose forms provide patient convenience, from a swallowing perspective, there are major limitations to the dose that can be administered. The drug loading is limited to around 30 % in the film material (for further details see Hoffmann et al. [68]), and, unless a very large film is to be provided, this limits doses to around 20–25 mg. (On occasion, it may be possible to provide higher doses: Dixit and Puthli [69], noted the development of a process by Labtec GmBH, that could accommodate doses up to 30 mg, and Ernest [52] noted the use of a 50 mg film.) This constraint has affected the adoption of film-based dose forms, as has the relatively high cost of manufacturing; however, it is possible that industry conservatism may also have limited the use of these presentations, which could, perhaps, be more widely used than is the case at present. While the use of films for consumer healthcare products such as breath fresheners is well-established (for example, Pfizer launched a film-based Listerine product in the US in 2001), the use to date for approved pharmaceutical products has been limited. Hoffman et al. [68] noted that the first European prescription product, ondansetron, was introduced in 2010 by Hexal, a Novartis subsidiary company. Although this type of dose form may provide swallowing advantages for many patients, it is important to note that dehydration may affect the ability of some elderly patients to use film-based dose forms satisfactorily.

The manufacturing processes are specific to this dose form and require specialized and comparatively expensive capital equipment. (Borges et al. [70], provided a review of publications concerning these processes.) The drug is mixed in a solution of organic solvent and a film-forming polymer such as polyvinyl acetate (PVA) or a cellulosic derivative. The formulation may contain a number of plasticisers, colorants, flavorings and other excipients; these materials typically comprise around 40–50 % by weight of the final product, with the film materials representing 30–40 %. The mixture is spread onto a large bed—in the form of a tray—that is typically about 3 m wide and many meters long. The material sits on an inert backing film, which must later be separated from the product film. Control of the bed thickness is critical to achieving the desired product size and dose, and care must be taken, naturally, to ensure consistency of the material across the bed. The material is warmed and the solvent is evaporated to leave a film containing a moderate loading of the active drug; as the process requires the removal of a substantial solvent volume, care must be taken with subsequent handling of this material. The exact formulation and the speed of operation of the process needs to be tightly controlled, as a film that is consistent and smooth must be formed, while maximizing the throughput rate. In particular, as Hoffmann et al. noted, overly rapid drying can cause a film to form on the surface that temporarily suppresses evaporation, causing a ripple effect in the surface of the material. The film is then wound onto a large roller before being transferred to a smaller roller and then moved to a cutting line, where blades chop the film into the correct size of rectangles. These films are then packed into foil pouches and cardboard outer packs. Hoffman et al. noted that the film thickness is of 10–100 microns; the mechanical properties of the

film are of considerable importance, and a variety of nonstandard test methods must be employed to assess film characteristics.

In common with other orally dispersible dose forms, films are subject to challenges in providing appropriate taste masking, when an unpleasant-tasting or bitter active must be formulated. The use of different taste-masking approaches (typically through the addition of sweeteners or flavorings) affects maximum drug loadings and mechanical properties and may affect disintegration time.

Although the process uses only a few steps—solution make-up, casting and evaporation, cutting and packaging—the throughput rates are fairly low, and film-based dose forms typically cost approximately 5–10 times as much to manufacture as tablets or capsules.

Soft Gelatin Capsules

Soft gelatin capsules are manufactured through a wholly different process to that used to manufacture hard gelatin (i.e., standard) capsules. The dose forms have an unusual and unique appearance, being able to contain liquid in a clear outer shell, and this fact enables a variety of presentations to be developed for consumer healthcare products. The manufacturing approach can be used to contain highly active drug substances during processing, in some cases, as handling of powders is avoided, and the dose form offers an alternative to the manufacture of tablets in specialized containment facilities, through serial powder dilution, for oral solid dose manufacturing of such highly potent products.

Soft gelatin capsule manufacturing is a specialized process that is provided by a limited number of manufacturers on a contract basis. The process involves the incorporation of the liquid form of the active into a shell, in a complex set of steps (see Hutchison and Ferdinando [71] for further details). The gelatin is first dissolved in water and the plasticiser added; this is followed by addition of other excipients, such as plasticisers or colorants. The gelatin mass is then formed by a casting process into two gelatin ribbons; this material undergoes a change to become the soft gelatin material as it is fed to a die roller unit. Separately, the active filling material is prepared using standard mixing or homogenisation approaches. The two gelatin ribbons are fed between two die rollers, with the active liquid fill being added from above. The liquid forces the gelatin ribbons back against the gaps in the metal die rollers; as the roller turns the ribbons are brought together (as the indentation in the roller diminishes due to the die rotation) and the seal is formed. The capsules then exit the machine by gravity. The product is dried for a substantial time (for up to 2 weeks) in order to ensure appropriate physical handling properties.

Manufacturing costs for soft gel capsules are moderate, being above those of standard tablets but significantly less than those for more unusual dose forms such as films. Soft gel production systems operate at moderately high throughputs, but lengthy drying times mitigate against very low production costs.

Soft gels provide an alternative formulation approach. Any issues with swallowing that may exist with tablets or capsules are unlikely to be obviated by the use of soft gels, and there is, usually, an increase in the cost of goods. This formulation approach is typically applied to provide a unique product image, for example for consumer products, or to address food effects, or to deal with highly active materials without incurring the costs of operating extensive containment facilities for tablet production.

Novel Approaches

A number of academic studies have proposed novel dose forms for pediatric or geriatric use; however, many of these proposals are conceptual and would require many years of development and industrialisation activity to reach commercial production. Wening and Breitkreutz [72] proposed that films could be cut into different lengths in order to provide individualized patient-dosing, and noted earlier suggestions that the films could be wound onto spools with dispensing (cutting devices) attached. Preis et al. [73] proposed inkjet printing of the drug active onto a film-based substrate, in order to produce personalized dose forms. "Printing technologies will take fabrication of drug delivery systems to a new level if they are combined with existing platform technologies. This type of approach will potentially address the future tailor-made drug therapy and industrial needs to manufacture high-potent, highly sophisticated medicinal products."

In 2011, Capsugel, which is a major capsule supplier, announced the acquisition of a novel dose form technology, called FlexTab, from GlaxoSmithKline [74]. In this system the release profile of the drug in vivo is largely determined by the composition of the polymer-based shell of the dose form, with the active drug being formulated in a blend, primarily to achieve suitable flow properties, and filled into the capsule-like dose form shells. A set of 2–3 drugs can be placed into separate "payload" capsule compartments which are then joined, and each segment may be designed to have delayed or immediate release properties. This approach enables formulation of the active to be minimized by engineering of the dose form shell, minimizing some of the conflicts that are inherent in dose form development, and facilitates the provision of complex and unusual delivery profiles.

The challenges in developing such approaches are to deal with the industrial engineering aspects of production, as outlined at the beginning of this chapter in the context of tablet manufacturing, the dose limitations that printing, film-based and some other novel dose forms imply, and lengthy technology development cycles.

Conclusions

The advent, in recent decades, of novel technologies, such as the Zydis dispersible tablet approach and floss processing, is to be welcomed in that these approaches add new choices to the set of alternatives for formulating a pharmaceutical active that may be prescribed for elderly patients. Given that this set of choices is quite limited, despite the existence of the types of dose forms that are noted above, the emergence of a new technology is a positive development. Some manufacturing technologies, such as film-based dose form production and other specialist approaches, result in a high cost of processing relative to the costs for manufacture of a standard tablet or capsule, and this factor limits the commercial application of these technologies. In a recent review article, Slavkova and Breitkreutz [75] noted that the "geriatric population may profit from the convenient administration, lack of swallowing" and "ease of use" of orodispersible tablets and films, but that "only a few novel products have made it to the market as the development and production is usually more expensive than for conventional oral dosage forms like tablets or capsules." Naturally, there are many physical, chemical and biological constraints on product formulation; when these are combined with manufacturing and economic factors, the set of viable formulation and manufacturing approaches may become extremely limited.

As noted earlier in this chapter, there are a number of economic challenges in producing tablets or capsules, and in offering a wide set of dose options. The technologies that are widely applied are processes that were developed many decades ago, for the main part, and that have been refined over time. The set of processes that are required creates complexity in a production environment, and results in low true plant utilization rates. Moreover, it must be recognized that many firms have available plant capacity for tablet and capsule production, and so the adoption of non-standard production processes requires distinct choices and organizational co-ordination. A challenge that exists for the industry is to develop ways in which dose forms that are easy for elderly patients to use can be produced, and to accomplish this goal in a fashion that acknowledges the difficulties that are inherent in solid oral dose form production and the associated issues of production economics. In this context, it is to be hoped that the industry will continue to innovate and to develop novel processes that provide ease of use benefits, at acceptable manufacturing costs, in order to better serve the needs of elderly patients.

Acknowledgements The author gratefully thanks A Clarke, D Dinner, D Elder, T Ernest, D Seaward and S van den Ban for graciously and kindly providing comments on a draft version of this chapter.

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Novel Manufacturing Technologies for the Production of Patient-Centric Drug Products

Mark W. Wilson, Luigi Martini and Allan Clarke

Abstract The dose forms that the pharmaceutical industry provides to elderly patients are far from ideal in many regards, and recent trends in the industry have emphasized the potential benefits that may be obtained by emphasizing the patient's needs in the formulation and manufacturing design process (as noted by Van Riet-Nales et al. [1], Stegemann et al. [2]), i.e., "age-related formulations." Naturally, the physical and chemical properties of the active pharmaceutical ingredient (or "API") constrain the set of viable potential dose forms, and biological factors, which have a significant influence on oral drug absorption in a wide range of patient groups, are critical aspects of formulation and manufacturing process selection. The development of an oral drug product that can be manufactured using a robust process is a critical element both of providing a suitable medicine of appropriate quality to the patient and a commercial return to the pharmaceutical company. Within this highly constrained design problem, it may be possible for the industry to develop new approaches by thinking creatively about the entire set of highly connected formulation and manufacturing challenges, and to remodel factory operations or, potentially, whole supply chains. Regulators, and the pharmaceutical companies themselves, have historically taken a conservative approach to novel manufacturing technologies that may offer quality and cost advantages over the conventional supply chain paradigms. Innovations, in the examples discussed below, will not be adopted rapidly, as change on such a scale occurs slowly. However, it is interesting to consider the benefits that such drug product manufacturing innovations might provide to patients. In recent years, regulators and the industry have sought to develop such approaches that not only offer patient benefits but that do so at commercially acceptable costs, and which are designed using robust and established manufacturing engineering principles.

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S. Stegemann (ed.), *Developing Drug Products in an Aging Society*,
AAPS Advances in the Pharmaceutical Sciences Series 24,
DOI 10.1007/978-3-319-43099-7_23

Polypill · Adherence · Polypharmacy · Pill burden · Novel technologies · Manufacturing complexity · Highly potent · High-active · Liquid dispensing technology · Drug printing

Introduction

With regard to standard immediate-release tablet or capsule products, there are challenges in producing more than four to six dose strengths of a given pharmaceutical product, due to the nature of drug product manufacturing: the mix of batch and continuous processes that industry employs lead to low utilization levels of plant. Critically, the lengthy setup times, clean-down periods, and waiting times while quality test results are being generated, all add significant elements to production schedules, and lower utilization rates. (These effects are exacerbated for products with multiple dose strengths and low production volumes.) Clearly, these activities are essential, but these operations are not direct production activities, and so reduce overall plant utilization. Many of the processes that are used to manufacture tablets and capsules have been employed for decades, and while these unit operations have been refined, the process flow is far from ideal from an industrial engineering perspective.

In considering oral dosage forms that may be suitable for elderly patients, in addition to tablets and capsules, potential formulations include dispersible tablets, "flash-dispersion" approaches and film-based products; nonetheless, many of these formulations present dose or taste-masking challenges, or have high-manufacturing costs when compared to immediate-release tablets or capsules. Given these factors, tablets and capsules remain the dominant formulation types that are employed by the industry.

This chapter focuses upon two innovative formulation technologies, at different levels of commercial readiness. The text initially discusses the concept of "polypills," the potential use of such dose forms to reduce the "pill burden" of elderly patients, and an early stage technology that may allow for individualized polypills to be produced. A second technology is also discussed, which uses liquid dispensing in order to process high-potency pharmaceuticals; this approach, offers some unusual benefits when compared to alternative approaches, is fully developed and is suitable for the manufacture of some types of patient-friendly dose forms for low-dose compounds.

In connection with the latter technology, it is worth noting that the manufacture of high-potency drugs is significantly more complicated than the production of standard tablets or capsules (notwithstanding the complexity of standard manufacturing processes), due to the need to provide protection of the operator to accidental exposure to the active and due to the necessity to avoid emission of dust to the external environment. The control of the active pharmaceutical and of the dusts that are created during the manufacturing process is usually accomplished by fitting a number of containment and air-handling systems to standard tabletting or

encapsulation processes and to production plant. Typically, special enclosed and contained tablet presses and other equipment items are used in a facility that is fitted with extensive and highly expensive air-handling plant and material entry and exit systems, and in which material transfers are conducted using glove boxes and highly specialist valve designs.

In this context, it is encouraging that industry continues to seek to develop new manufacturing approaches that address the key constraints of pharmaceutics while acknowledging the industrial engineering challenges that must be dealt with, in order to provide widely adopted and commercially viable manufacturing platforms, for both standard and highly potent molecules. The description that follows outlines two such novel manufacturing approaches, which have notable potential for the provision of patient-centered dose forms.

"Polypills," Adherence, and New Technologies for Individualisation

"Pill Burden"

Many authors ([3–5], for example) have commented that many elderly patients face a substantial "pill burden"; as patients are frequently under treatment for a number of conditions, it is common for an individual to need to take many different medications in the course of a day. To add to the complexity, some products are required to be dosed once-daily ("od"), twice-daily ("bid") or three times daily ("tid"). In addition, some medications need to be taken with food, whereas others can be dosed with or without food. Given the industrial prevalence of oral tablets and capsules (in part due to the relatively low secondary manufacturing costs of these dose forms), a patient often needs to manage a dosing regimen of considerable complexity, involving many different tablets and capsules and, in some cases, some other types of medication. While this is not always the case, complex medication regimens are a very common situation that the independent elderly and the care-givers of more-dependent individuals must face. Although there may be dosing flexibility with regard to time of administration for some medications, the difficulties that patients face are considerable. It is common for individuals to be under treatment for 4–5 chronic conditions, and to need to take 8–15 tablets and capsules at 3–4 dosing occasions each day. Some tablets are not to be taken each day, but may be prescribed for weekly administration, or require dosing on every second day; in addition tablets that need to be broken in half are common. (Concerns have been voiced at the risk that the broken half of the tablet may not have the correct dose: Verrue et al. [6] state that "large dose deviations or weight losses can occur while splitting tablets" and that this "could have serious clinical consequences for medications with a narrow therapeutic-toxic range." Recent amendments to content uniformity testing guidelines and standards, such as section 2.9.47 of the European

Pharmacopeia, aim to deal with this issue, as noted in Pharmaceutical Technology [7]). The effect of these factors is that arranging a set of tablets and capsules for a week's medication for many elderly patients is a taxing business, and a task that is prone to inaccurate completion. Any mentally alert and able-bodied person who has filled out a weekly "pill dispenser" for an elderly relative will be able to attest to the complexity of the situation.

Naturally, as patients suffer additional health problems, or as disease states progress, the number of tablets and capsules that are required increases further. The rather abstract concept of a "pill burden" can be seen to be a real and significant factor that affects the success or failure of elderly patients to manage their medication. Clearly, in the case of patients who are struggling with many day-to-day activities, but managing to live independently, the confusion that complex dosing regimens create could be substantial, and could affect adherence significantly.

"Polypharmacy" in the Elderly

The prescribing of multiple drugs to elderly patients has been termed "polypharmacy," although many variations exist among authors as to the number of drugs that need to be prescribed in order to merit the use of this term. Potential negative consequences of polypharmacy are considered to be an increased risk of adverse drug effects, drug–drug interactions, drug–food interactions, and nutraceutical–drug interactions [4]. Jyrkka et al. [3] noted that previous studies record home-dwelling elderly patients receiving nine or more drugs at one time as being between 13 and 39 % of the relevant population. In a 2012 study, Kojima et al. [8] noted that the percentage of elderly patients (at age 65 years or older) on nine medications concomitantly is recorded in earlier work, by various authors, as being 40 % in the US, 15.5 % in Canada, and between 8.8 and 56.7 % in different European countries.

Sergi et al. [5] observed that "polypharmacy is a growing problem" as a consequence of "longer life expectancy and a consequent increasing prevalence of chronic diseases," and noted that polypharmacy "has important negative consequences, such as higher rise of adverse drug reactions and a decline in medication efficacy because of reduced compliance." These authors noted that "in the elderly, the need to take more than three medicines a day raises the likelihood of non-compliance in direct proportion to the number of different drugs that need to be taken … and with the number of daily doses." Sergi et al. noted a prior study by Malhotra et al. [9] and comment that: "Poor compliance has a negative effect on healthcare outcomes and cost, accounting for more than half of adverse drug reaction related emergency hospital admissions." Fulton and Allen [10], in a review article, also commented on the significant economic costs that appear to be caused by hospitalisations that arise from adverse drug reactions, as a consequence of polypharmacy in the elderly.

Pill Burden and Adherence

It seems clear that the lack of compliance with a treatment regime, or the degree of "adherence," is affected by many different factors. Psychological issues, such as the patient's degree of confidence in the doctor who prescribed the medication, the patient's state of health, the patient's feelings about himself/herself, the origin of the disease state (e.g. in the case of smoking-induced lung diseases), and practical factors such as the expense of treatment, may all affect compliance with a treatment regimen. Given this complex landscape, it would be inappropriate for any single change or development to expect to radically alter adherence rates. Equally, however, it is surely worthwhile for the industry to challenge itself to ask how medicines could be prepared in ways that are more suitable for elderly patients and to consider how adherence rates could be improved. The issue of pill burden (Fig. 1) is likely to affect adherence to some degree; the fewer medications that can be provided, and the easier these are to arrange in the correct dosing schedule, the more likely it is that elderly patients (or, to be frank, any patients) will comply with the expectations of the prescribing medics. The pharmaceutical industry goes to great lengths to assure the quality of its medicines, through the rigor of the clinical trials that it undertakes, through the conduct of extensive stability investigations, and through multifaceted quality release testing at the production site. In light of these necessary and laudable efforts, it is surely worth the industry's while to concern itself additionally with whether or not its medicines are taken, in the "real world," according to the correct administration schedule, and how adherence rates might be improved.

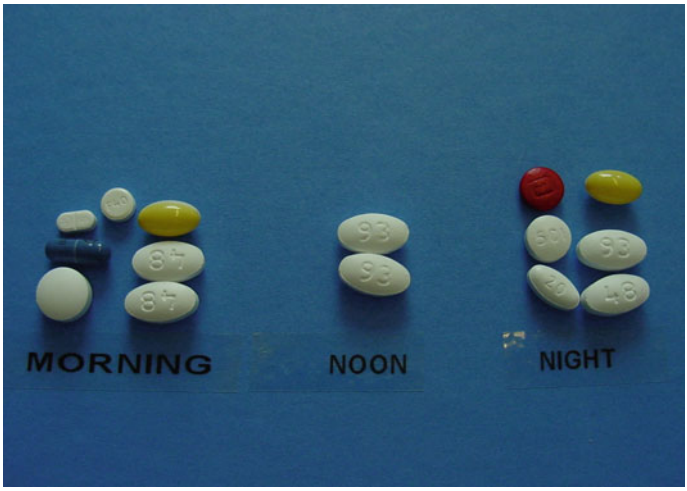

Fig. 1 Daily medication for one elderly patient known to the authors (2006) (Image courtesy of GlaxoSmithKline)

Adherence in Elderly Patients

Osterberg and Blaschke commenced a [11] review with a quote, attributed to Everett Koop (who is a former surgeon general of the US), that "Drugs don't work in patients that don't take them." These authors noted that, even in clinical trials for chronic conditions, adherence rates of 43–78 % are reported in the literature, and stated that: "Poor adherence to medication regimens is common, contributing to substantial worsening of disease, death, and increased health care costs." Jones et al. [12], noted the role of "heath literacy" on adherence rates, and also cited another Everett Koop, statement: "No medication works inside a bottle. Period." Ito, in a 2013 review article, [13] stated that adherence to treatment regimens is lower than physicians expect and that "the impact of poor adherence on treatment outcomes and healthcare costs is significant". This author added that: "Nonadherence has negative consequences. Failure to follow prescriptions causes preventable mortality, morbidity, and approximately 10 % of hospital admissions."

Wong et al. [14] analyzed adherence to hypertension medication in a group of 200,000 patients, comprising all relevant patients in the public healthcare sector in Hong Kong during the study timeframe, and with an average age of 58.7 years. The overall rate of optimal adherence among this large group of patients was 38.4 %. Junior et al. [15] reported adherence rates for patients in primary care settings in Blumenau in Brazil, and recorded a "prevalence of non-adherence" of 35.4 %, among a group of patients with an average age of 69.4 years. Smith et al. [16] noted that the way that adherence was measured appeared to affect the value significantly. In a UK sample of elderly patients with heart failure, adherence rates assessed by self-reporting and pill counting provided closely correlated results, but electronic monitoring systems sometimes provided significantly lower results. Stegemann et al. [17] reviewed a variety of approaches and systems to record adherence levels, and noted the complex challenges to obtaining accurate and meaningful measurements in this field.

A number of authors have noted that many factors affect adherence. Yap et al. [18] noted the impact of "patient, medication, health care providers, health care system and socioeconomic factors." Maloney and Kagan [19] noted that issues affecting adherence are varied, and may be linked to "age-related physical changes, comorbid conditions, polypharmacy, and drug interactions," and commented that economic factors, transport issues and levels of social support also affect adherence." Culos-Reed et al. [20] noted that "individual, interpersonal and environmental factors" affect adherence, and concluded that "perhaps of greatest importance is to focus on developing collaborative relationships between the practitioner and participant, as well as tailoring interventions to the individual" and the "social context". In a 2009 focus group study, Moen et al. [21] reported that the investigation results "suggest that elderly users of multiple medicines' concerns with their medicines reflect themselves, the doctors and system in general." The impact of psychological factors was highlighted by Balkrishnan [22], who cited a study by Sharkness and Snow [23]

that reported that "male veterans who knew that they would require lifelong treatment for hypertension were 1.3 times less likely to depart from the prescribed regimen that those who did not know this."

Provision of "Polypills"

Overall, studies suggest that adherence rates for many medications are low, and far from the high levels that are desired to achieve optimal patient healthcare. The effectiveness of a medicine depends on its use in domestic, hospital, and care home situations by real patients and healthcare professionals. These studies, which are merely examples from a substantive literature documenting moderate levels of adherence by many patients in varying situations, highlight the fact that adherence is a very significant issue in healthcare provision. Consequently, tools and techniques that can address root causes of lack of compliance with a treatment regimen may be effective in improving healthcare for individual patients and for broader populations.

There has been substantial discussion in the medical literature in recent years of a proposed fixed-dose combination "polypill" to prevent cardiovascular disease, following proposals made by Wald and Wald (see, for example, Wald and Wald [24]. Examples of this literature include a review of the potential of polypill approaches in primary and secondary cardiovascular prevention strategies [25], an evaluation on a clinical trial of such an approach [26], an estimation of potential healthcare benefits [27], and a review of the work to date in the field of secondary cardiovascular prevention [28]. Lafeber et al. [29] evaluated the potential benefits of such an approach to reduce vascular morbidity and mortality in patients with coronary artery disease, Vaduganathan et al. [30] considered the application of such approaches to heart failure, and Rosenthal and Gavras [31], proposed polypills as a first-line treatment for hypertension. Clinical trials that took place in India [32–34] and in New Zealand [35, 36] found that such approaches were partially effective. However, such approaches have been predicated on a single dose of each agent in a polypill and on prescribing the same polypill to all patients.

Some authors have suggested that "polypills" (tablets containing multiple actives) could reduce the pill burden for elderly patients who are receiving treatment for several chronic conditions by reducing the number of pills that must be taken. Salazar, Poon, and Nair recommended the use of combination tablets, on the basis that this would "aid in decreasing the number of tablets per regimen" and noted that a number of studies have recorded that "increased number of medications may decrease adherence" in the elderly, although the evidence "has not been consistent." While some studies provide evidence to support the proposition that fewer tablets will result in improved adherence, it is important to recognize that adherence is a multifaceted phenomena, and that pill burden is only one factor that may affect this.

Medical Practice

There are issues in providing only certain doses of key actives as combinations. Such a practice may give rise to complaints that this creates a barrier to changing a dose for a patient, as the nature of the dose form will change, should a dose and active combination be required that is not provided as a combination tablet. More broadly, this approach can be seen to be a way of restricting medical practice, in the sense that the use of combination dose forms of such types does not permit doctors an unrestricted choice. A quote from a Wall Street Journal article in [37] (29 January), which discussed combination tablets, illustrates this point: "...but doctors often avoid prescribing combination drugs because they come in a limited number of dosage choices, making it difficult to customize drug regimens or solve problems patients experience on a single pill." Clearly, these issues arise in connection with a cardiovascular polypill. Bittencourt et al. [38], in describing a trial to ascertain whether or not coronary artery calcium could be used to determine which patients could be treated using polypills, commented that: "It is noteworthy that the polypill is still under evaluation and also has some undefined limitations. First, because a single pill formulation is proposed, individuals with a contraindication to any of the components would not be eligible…Second, there is a significant rate of discontinuation due to side effects from polypills."

Although these objections may seem to be minor to some observers, these arguments are significant in that provision of combination dose forms in a restricted set of combinations of actives and doses moves the pharmaceutical manufacturer away from a position of neutrality with regard to selection of dose strength by the physician, and changes in the types of dose forms prescribed may affect patient perceptions and adherence.

Cannon, writing in a comment piece in The Lancet on the cardiovascular polypill [39], noted in 2009 that "this approach would obviously not be feasible with a pill with five or six components and each having two to four doses (which would lead to more than a hundred strengths of polypill)." This author asked whether or not "it might be feasible to consider having two to three broad strengths with some different doses of some components (e.g. the antihypertensives)" adding "there could be versions with only some components of the polypill, that would, for example, have fewer antihypertensive drugs." Cannon noted that administering a fixed-combination polypill, without combination or dose flexibility, could put some patients at risk, and questioned the appropriateness of this approach. Greater polypill variety "might help when treating a patient with only a single risk factors (e.g., a smoker without high blood pressure)" and asked: "Should such a patient be put on three antihypertensives, and thus have the risk of angio-oedema, glucose intolerance or bradycardia?"

Supply Chain Issues

Supply chain issues are of critical importance in considering possibilities for the provision of multiple actives in a single dose form. Many wholesalers and retail pharmacies perceive, rightly, that the provision of a combination tablet of two actives adds complexity to the supply chain, increasing the number of dose forms that must be supplied, and raising the number of products that must be stored at some point in the distribution system. This complexity can be perceived as unnecessary: both drugs can be supplied as separate tablets, so, from a pure supply chain perspective that ignores patient ease and similar benefits, combination tablets may create little value and add significant costs to supply activities. Some pharmacists may feel that it is unnecessary to have two forms of the same actives in the same doses available for administration, and that this duplication creates unnecessary costs and complexity. Naturally, from a perspective of striving to operate lean supply chains, this view has considerable merit. Consequently, many parties that operate key elements of the supply chain (wholesalers, distributors, pharmacy chains) may be resistant to pharmaceutical companies offering combination tablets, and may see such presentations as adding modest value and imposing substantial additional costs.

Manufacturing of Bilayer Tablets to Provide Combination Products

Combination tablets may be appropriate for use by elderly patients in order to minimize the number of tablets that the patient must take, and can be manufactured in the form of bilayer tablets through the use of bilayer presses. However, in addition to the manufacturing challenges that are noted elsewhere in this volume, there are a number of practical constraints to the use of this approach. In practice, bilayer presses tend to be moderately difficult to operate, with lower yields than other tabletting processes [40]. The operation tends to be fairly labile, with frequent halts in production, and very careful monitoring of tablet quality is required. These difficulties arise from the nature of bilayer tablets: compacts of both actives are formed and joined in a single process, with the powder blend of each active being fed from two sides of the tablet press. The different blends, which will, inevitably, have different physical properties, must join at the interface. There are inherent difficulties in operating a tabletting process, and the need for different materials to be formed into one compact creates an additional obstacle to successful processing. Although bilayer tablet formulation and production are viable, and are undertaken moderately frequently, the manufacturing process is less efficient than tabletting of a single active, and the additional formulation constraints that the process imposes are significant. Due to the intimate join, both actives must be compatible with one another, and suitability for formulation in this fashion must be explored in

development, as well as verified in standard stability tests. In addition, the formulation and process must be developed so as to minimise the potential for "delamination," i.e., splitting of the layers. (Wu and Seville, in [41], noted that the production of bilayer tablets "is challenging" as "the tablets are prone to fracture by delamination, normally along the interfaces between different layers, because of their inherent binding weakness.") Due to these constraints, the use of bilayer tablets, although moderately widespread, presents specific formulation and manufacturing challenges.

Manufacture of "Polypills"

The issues of production complexity and low machine utilization in tablet manufacturing affect the potential provision of combination tablets (Fig. 2). The provision of more than 4–6 dose strengths of a given active is not normally economically feasible: beyond this number, batch sizes are reduced, machine utilization falls, and the amount of overhead cost allocated to each tablet increases. Moving from the level of complexity of manufacturing five dose strengths to the level of complexity that would be required to manufacture eight is likely to render production uneconomic: the smaller the product volumes, the more fragmented would be the necessary production schedule, and the more expensive would be the final tablets.

These issues create considerable problems in considering the provision of multiple dose and active combinations as bilayer tablets. (Typically, while all possible active and dose combinations must be available, by regulation, only the most common variants are stocked in volume in the supply chain.) It is illuminating to consider the number of potential combinations or permutations that would be required to put no limit on physician's prescribing freedom and to offer all active

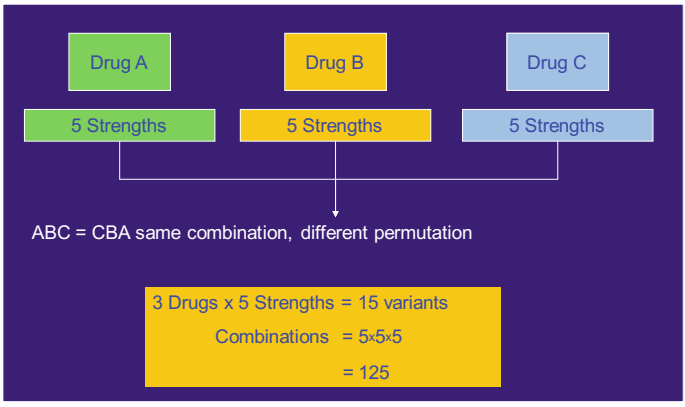

Fig. 2 Illustration of how treatment by multiple drugs with a range of dose strengths would give rise to large number of potential combination products (Image courtesy of GlaxoSmithKline)

and dose options as combination tablets. Consider three drugs (A, B, and C), each of which is manufactured in five dose strengths. A combination contains a set of three actives at specific dose strengths. (The order of selection, which matters for "permutations", is ignored.) These three drugs, each at five dose strengths, give rise to 125 combinations. Assuming only three-drug combinations, 125 different combination tablets would have to be manufactured to avoid any restriction on "medical practice."

Novel Approaches—The GSK "Polypill"

GlaxoSmithKline has recently developed a novel technological approach (Fig. 3) that acknowledges these challenges and offers a means by which, should the industry wish to adopt this approach, a variety of combinations could be provided to patients. The fundamental thesis behind this development is that reducing the "pill burden," by providing fewer tablets, is likely to improve adherence (at least to a modest degree), with consequent patient health care benefits, and that the provision of multiple combinations must be done in a fashion that avoids the restrictions on medical practice, the challenges to tablet manufacturing economics and the issues in supply chain management, of the kinds that are highlighted above (as noted by Wahlich et al. in [42] article.)

This technology relies on the manufacturing principle of "postponement of complexity," in order to allow the creation of individualized combination tablets to be a practical possibility. It is common in other industries for manufacturers to finish or to customize a product late in the production process. Car manufacturers, for example, may fit accessories or apply special paint finishes after most of the

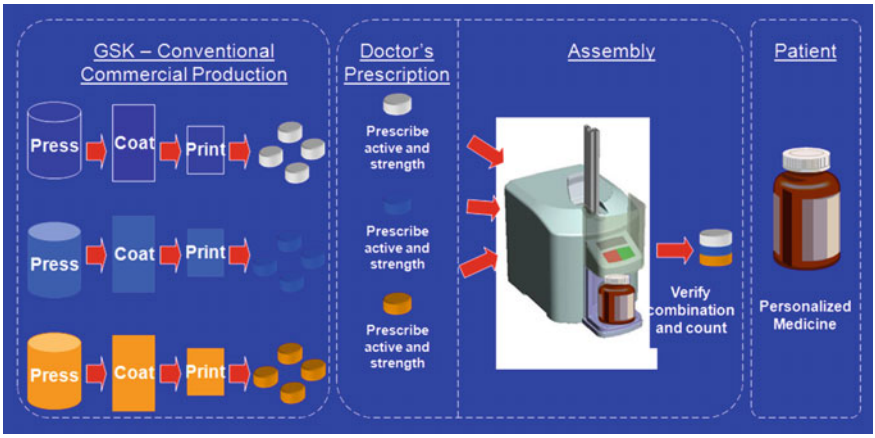

Fig. 3 Assembly could be performed at local distribution sites with the GSK polypill technology (Image courtesy of GlaxoSmithKline)

substantive manufacturing of the car has been completed; the car may be personalized to a specific customer, but this does not add complexity to the bulk of the manufacturing processes, only to those finishing tasks that occur late in the production flow. In a similar fashion, the GSK polypill technology combines materials late in the production process, enabling the creation of individualised dose forms on a patient-specific basis.

The technology is based on the assembly at a distribution site of series of tablet elements into a combination tablet. A machine selects the required tablets according to a patient-specific order in the control system, and adds a pharmaceutical-grade bonding material to join each pair of the tablet elements. In this fashion, a triple-layer combination tablet can be assembled for a specific patient. Moreover, each tablet can be different, so the complexities of a weekly dosing regimen can be dealt with. The tablets can be packaged into a blister pack that has clear labeling and that is patient-specific. This pack can then be distributed to the patient, either via mail, as is common for chronic medications in markets such as the US, or through a retail pharmacy operation.

A major potential benefit of this approach is that assembly could take place at a distribution site such as a pharmacy benefit manager location in the US, where mail-order prescription operations are conducted. Tablet elements could be manufactured in a standard secondary manufacturing facility and shipped in bulk to the distribution site. The machine at the distribution location could then be used to assemble the tablet elements into combination tablets that are ready for packaging and shipping.

Critically, the number of tablet elements that must be produced for each active would be no greater than the standard number of existing dose strengths, i.e., 4–6 variants per active. There would be, therefore, no increase in manufacturing complexity in standard secondary plants, no need to conduct labile bilayer tabletting operations, and no increase in standard secondary production costs. If the assembly process were integrated into a mail-order pharmacy operation, the increase in the total production cost for each prescription should be very modest; this assembly and final packaging operation would replace the typical final packaging that is conducted at a secondary site.

Conceptually, assembly of the tablets could take place at a retail pharmacy, using small tabletop machines, as shown in Fig. 8. However, there are substantial issues to address in managing a network of tens of thousands of machines across a large territory, such as the US, given the criticality of the operation of the machine to final product quality. A trend in healthcare provision in the US in recent years has been the development of large distribution sites, operated by pharmacy benefit management organizations such as Medco. These sites would be suitable locations for final assembly and would provide ready access to existing mail distribution operations for chronic medications. The provision of tablet elements to these sites and final distribution via mail would avoid the supply chain issues that are considered by some observers to hamper the acceptance by the market of combination tablets. Naturally, the implementation of such an approach would require industrial-scale selection of the tablet elements and the joining (i.e., bonding) of

these units. In the scenario that is outlined above, at no point would the wholesalers or distributors need to stock or handle multiple variants of the same actives—i.e., as both single tablets and as combinations—in order to fulfill supply.

The issue of complexity is at the heart of this matter, as it would be important to avoid eliminating one set of costs incurred by complexity for a different set of activities and expenses. It has become a widespread practice in many territories for insurers (whether government-controlled or private) to restrict access to certain drugs within a therapeutic class, by refusing to supply certain drugs as part of a specific health insurance program or by charging very substantial additional fees for those drugs that are not included on approved "formulary lists." Given the prevalence of this practice, and in light of the care that has been taken to evaluate the need for maximal flexibility in the development of machine design concepts, it is likely to be feasible for this polypill approach to be implemented for a large proportion of a given formulary list. While it may be difficult to produce all medicines for all patients using this approach, many of the potential benefits might be provided by supplying the majority of medication for a large number of patients using this platform.

It is worth noting that the production of a range of dose elements that can be assembled into a polypill may require the use of a set of compression blends in the secondary manufacturing site, rather than a single compression (i.e., tabletting) powder blend. However, this requirement would also exist in the case of the production of standard tablets (for those drug substances that require multiple blends), and so no additional work would be required.

The management of the blister-packing process, as described above, would be complex but would allow for notable patient benefits to be provided. Such a development would be in line with trends within the industry to apply increasingly sophisticated management to blister-packing processes, for instance in connection with product identification and tracking initiatives.

State of the Technology

The technology (Fig. 4) has been developed to the point that prototype machines (which would be suitable for clinical trial manufacturing) have been constructed, validated, and operated, in vivo pharmacokinetic testing has been conducted in dogs (in order to show that the multiple elements behave as though they were ingested as separate tablets), and designs have been developed for commercial machines that could operate in major distribution sites. It is predicted that each large machine, which would be capable of producing 300,000 individualized combination tablets in 24 h, would cost approximately £1 M.

It is envisaged that this approach could be used to provide three actives in a single combination tablet, but it is unlikely to be possible to deliver more, due to size constraints and machine design considerations. The size of the tablet elements would be limited, and formulation would need to take this size constraint into account. In this sense, the physical volume of the drug substance (i.e., of the active pharmaceutical)

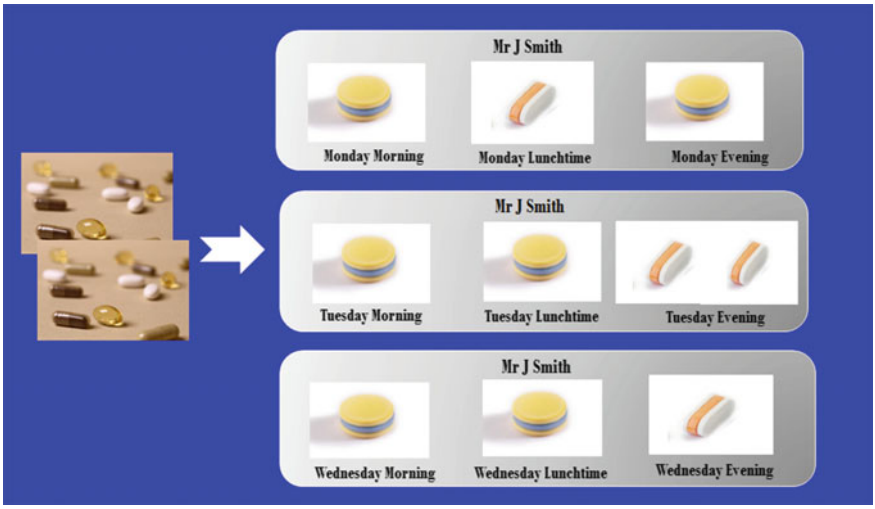

Fig. 4 With the GSK polypill technology, blister packs could be produced containing varying daily dosing regimens, if required (Image courtesy of GlaxoSmithKline)

material would become one of the many constraints that formulators would need to take into account, but this would be unlikely to cause major difficulties. There is a limit to the size of a tablet that will be acceptable for provision to elderly patients, and various studies have been conducted on this topic, both by academics and pharmaceutical firms. (Stegemann et al. [43] provide a comprehensive review of the issues that the elderly encounter frequently in connection with swallowing.) However, despite the criticality of this issue, tablets within the range of sizes that the industry currently provides for patients would allow ample scope for formulation, particularly given the moderate doses of many common medicines. (Naturally, it may be necessary to work below the maximum sizes that are commonly produced, as some tablets are of a substantial size; one Augmentin formulation, for example, has been commercialized with a 18 mm by 7 mm "caplet"-shaped tablet; [44].) It is clear, however, that there will be an upper dose limit, and that it may be impossible to deliver very large doses (e.g. 1 g) in a combination tablet of an acceptable size.

In any dose form that relies on the joining of tablet layers, the strength of the bond between the layers prior to ingestion by the patient, and the behavior of the dose form in vivo, are both critical characteristics. The polypill tablets that have been developed using this approach have proven to be very robust, with the bond remaining intact for several years on storage and proving resistant in friability testing. Although further development would be required, the prototype dose forms appear to avoid major delamination issues. Based on development data, the bond appears to come part readily once the dose form is in stomach media, which fact suggests that the critical bonding process may be suitable for purpose.

In terms of potential large-scale operation, considerable design effort has taken place to establish how a commercial machine might operate (Figs. 5 and 6). The

Fig. 5 Pilot-scale production equipment for the GSK polypill technology (Image courtesy of GlaxoSmithKline)

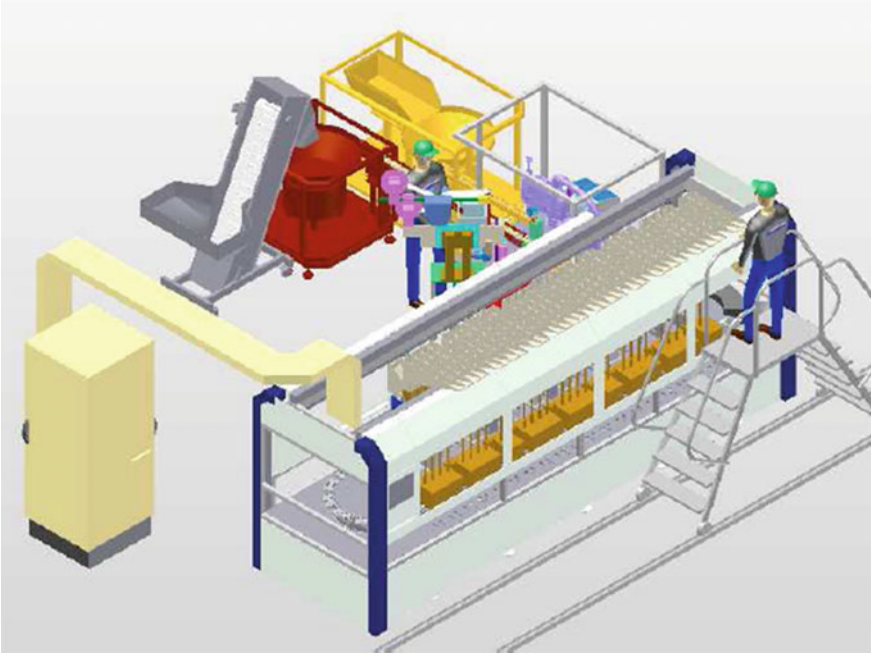

Fig. 6 Initial designs for large-scale polypill assembly machines have been developed that would allow mail-order distribution (Image courtesy of GlaxoSmithKline)

envisaged designs, which were developed by GSK in conjunction with 3PInnovation Ltd., utilize standard tablet handling systems to allow construction of individual tablet assemblies at high throughputs, within a machine size that would be practical for end users. These design approaches allow for variation in the size and shape of final machine to suit installation requirements, provide the potential for high-throughput rates, and enable assembly to take place with a variable number of actives. The modular machine layout and configuration have been designed with 30 actives in mind, but more could be accommodated.

Pathways to Adoption

At the time of writing (2016), a number of industrial companies have expressed interest in collaborating in a consortium to develop the technology and to consider the potential of this approach, and a number of non-governmental organizations have signaled interest in the possibility of utilizing this technology to improve adherence rates and to improve healthcare for patients with chronic diseases. It seems logical that a change on this scale would require the cooperation and involvement of a number of pharmaceutical companies, both producers of innovative medicines and generic manufacturers. The system would need to be a common standard, an "operating system for the industry," and to be independent of any one organization (Fig. 7). A proprietary standard, accessed by only one manufacturer, would not allow the production of combination medicines from different manufacturers, and would be unlikely to be adopted by pharmacy benefit managers. The most likely initial application of the technology would be to commonly prescribe generic medications for cardiovascular and metabolic conditions; it would be possible to reformulate these generics into the standard tablet elements that this system requires with only moderate effort.

Naturally, these elements would need to be shown to be bioequivalent to reference dose forms, and the total cost of a set of bioequivalence studies for a range of generic drugs would be substantial (as such studies cost up to a few hundred thousand dollars). This cost, however, would need to be assessed in the context of the substantial potential benefits that the system might provide, which might outweigh by a very substantial margin the costs of assessing bioeqivalence.

It is clear that the regulatory position of the technology would need to be explored with the appropriate authorities. Given the fact that the tablet elements would be bioequivalent to reference dose forms, and that assembly of each tablet would be on a named patient basis, it is possible that this approach may be construed to be patient-specific extemporaneous compounding. Whatever the most appropriate regulatory treatment may be, it is to be hoped that the industry and regulators would welcome the chance to apply a novel technology to provide patient benefits, and would work to find an appropriate regulatory pathway for such an approach.

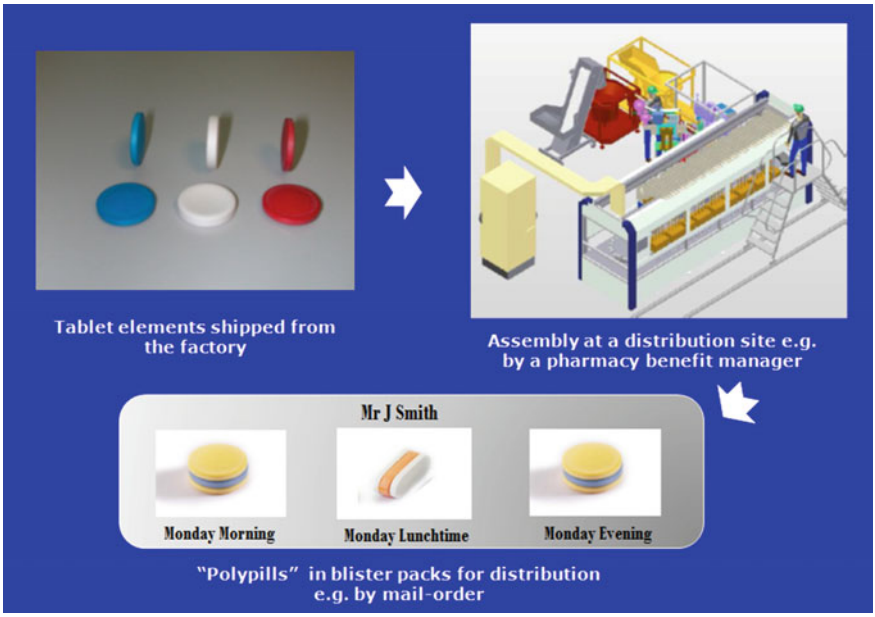

Fig. 7 The assembly of individualised polypills at distribution sites could reduce the pill burden for elderly patients and help to improve treatment adherence rates for common chronic diseases (Image courtesy of GlaxoSmithKline)

The likely path to adoption would be for the technology to be evaluated in a "use" trial in a small patient group that was receiving treatment for a suitable indication, such as hypertension, in order to investigate whether or not the use of the approach could provide improvements in patient outcomes. If such an initial trial were successful, a "real world" outcomes trial would be likely to be required, in order to reassure all parties involved that the approach could have a significant effect on healthcare outcomes in patients on multiple chronic medications. The approach is predicated on the known fact that adherence in real use situations is far from perfect, so it would make sense to test the utility of the approach in such a situation, by provision of combination tablets, rather than in a clinical trial setting where higher adherence rates are more likely to be obtained.

Provision of these "polypills" would reduce the number of pills that a patient must take, thereby facilitating the potential for an improvement in adherence rates and healthcare outcomes. The benefits of such an approach may be particularly notable for chronic and widespread disease conditions such as hypertension and diabetes, and, given this context, the initial application of the approach is likely to involve primarily generic medicines. If the approach could raise adherence rates modestly, the potential benefits to healthcare systems from widespread adoption of the approach might be as large as hundreds of millions of pounds a year, in the form of reduced healthcare costs; these savings would arise due to the reduction in the

incidence of expensive hospitalisations (and similar medical interventions) that would be a consequence of improved adherence. If the technology was developed fully, it is likely also to have application in oncology and psychiatry, given the prevalence of combination medication in these fields of medicine.

As an additional potential benefit, the creation of bespoke patient packs, with individualised tablets, would open up new possibilities in terms of managing and utilizing healthcare data. Critical aspects of the final system design that would need to be addressed would be the integration into broad-scale healthcare IT structures, machine and system control approaches, database management, and the intelligent use of these data sources to improve patient outcomes, e.g., through error reduction. In this regard, the provision of medications through this system and the associated management of individualised records (while being challenging in its own right) might assist in the tracking and monitoring of medicines that a patient is being prescribed; such an approach might enable the development of systems to alert automatically healthcare professionals, should drugs with the potential to cause adverse events through interactions be prescribed in a polypharmacy situation. The initiative offers a new approach to production, potentially enabling local, and distributed assembly which is close to the patient. At the time of writing (2016), a number of organizations who are interested to assist in the development of this large-scale personalisation technology are evaluating how best to progress this initiative, in order to provide a viable approach to reduce the pill burden for elderly patients and to improve adherence rates and health outcomes.

Liquid Dispensing Technology

The Processing of Highly Active Materials in the Pharmaceutical Industry

In the 1990s, the pharmaceutical engineering community had to come to terms with some new challenges: to develop approaches to process highly active drug substances, and to understand how to deal with compounds with a hitherto largely unknown potency. The arrival in the development pipelines of many large companies of multiple actives with such high potencies required the industry to adopt new ways of thinking and to refine existing approaches (as described by Stracey in [45, 46] articles). There appeared to be a step change in the potencies of molecules that many pharmaceutical companies were dealing with, and the consequent dramatic lowering of the allowable occupational exposure limits caused prior approaches to be challenged (as noted by Marie et al. [47], Wollowitz [48]). Standard approaches to containment had to be revised substantially: when the amount of active dust left on a traditional powder valve surface could be enough to exceed the acceptable safety limits, it was clear that processes must be rethought and new equipment and processes explored. One response to this challenge was to

adopt highly engineered powder handling facilities, to enable serial powder dilution and to facilitate standard tabletting processes (as noted by Rehbaum [49] and Mezger [50]). In a notable development, industry guidelines on the measurement of particulate emission, in connection with the processing of highly active compounds, were published in 2012 by the International Society of Pharmaceutical Engineers (or "ISPE") [51]. In this type of facility, great care must be taken to consider all points of ingress, egress, and potential contamination (as described by Margarita [52]. Air-locks and glove boxes are standard, and process and facility utilities such as air-handling systems must be designed with scrupulous care to avoid accidental exposure of operators to the active in the facility or inadvertent discharge of active from the facility to the external environment. Such extensive engineering controls and systems require considerable capital expenditure for manufacturing plant design and construction, and such facilities may cost up to £150 M ($225 M) to construct [53]. From a pharmaceutics perspective, high-active product development also poses challenges. The formulation approach that is often employed in developing manufacturing processes for highly potent substances is to use serial powder dilution, in order that a blend of powder with a small amount of active drug in a large mass of excipients is created; as noted by Zheng, this approach can create significant issues in achieving satisfactory blend strength and tablet dose consistency [54].

The Liquid Dispensing Technology

In a different response to this industry-wide challenge, GSK decided to develop a process that aimed to obviate some of the most difficult containment challenges in dealing with highly potent molecules. Over the course of ten years, the liquid dispensing technology ("LDT") was developed to enable the production of highly accurate low-dose tablets from highly potent active pharmaceutical ingredients, to ensure operator safety, and to significantly reduce capital expenditures for secondary processing plant for highly active molecules (as noted by Clarke in [55, 56] conference presentations; and as described by Clarke and Doughty [57]).

The technology deposits a 5–20 μl droplet of active drug in solution onto a carrier tablet, which may be a placebo or a tablet that contains another active ingredient. The deposited active is formulated as a solution in an organic solvent, with a film-forming polymer and other excipients. The droplet is imaged in-flight, and the volume of the droplet is calculated from the photographic image using a sophisticated algorithm. As the concentration of the feed solution is measured continuously, the amount of active that has been deposited can be calculated for each individual dose form. The tablets are handled using a horizontal array platen, and the row and column identity of the well on the platen is linked to the specific tablet record in the machine control system.

Upon evaporation of the solvent, the active material forms an adherent film on the surface of the carrier tablet binding the dose to the tablet. At low doses, the active is typically in the amorphous solid state form in the film while at higher doses, the solid state of the active may be crystalline, partly crystalline and partly amorphous, or amorphous, depending upon the properties of the active. The physical state of the active in the film typically does not change over time or during accelerated stability conditions.

During the processing, the tablet is heated gently (typically to 30–40 °C at the tablet surface) for 10–15 min and the organic solvent is evaporated. Only a very small volume of organic solvent (5–20 μl) is required to solubilise the low active dose. As the initial droplet size is small, only a very modest amount of organic solvent must be removed, and the solvent vapor can be removed in a standard secondary plant air-handling system without creating an explosion hazard. Given the low amount of solvent, the evaporation demand is very limited, and harsher process conditions are not required. Thermal degradation of the active is unlikely to occur, given these conditions, even with thermally sensitive actives. In normal product development activities, oral tablets are typically stored (for accelerated stability) for six months at an elevated temperature and humidity level, i.e., at 40 °C and at 75 % relative humidity. In light of this comparison, it can be seen that the processing conditions are quite mild and are analogous to those employed in standard aqueous film coating processes (Fig. 8).

The polymer in the formulation has a number of functions: it enables droplet formation by increasing the viscosity and surface tension of the liquid and it entraps the drug substance in a polymer film that adheres to the tablet surface. Once the solvent has evaporated, the film prevents the release of the active as dust. After deposition and evaporation, the tablets are subjected to a near-infrared identity

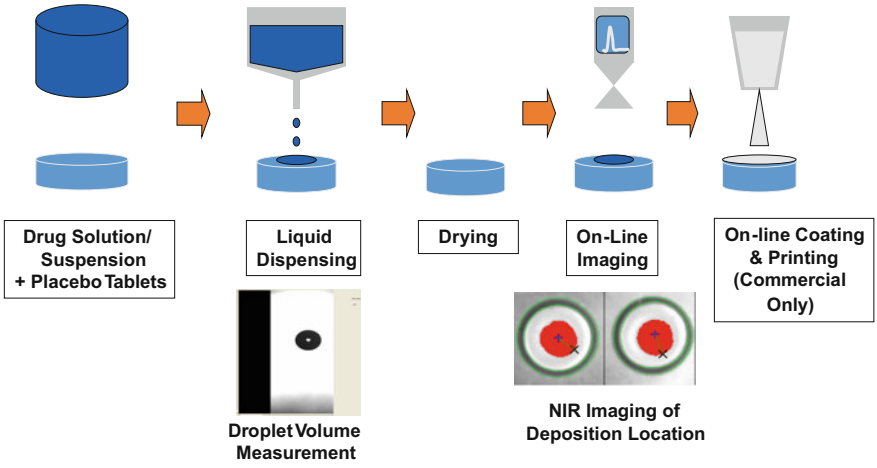

Fig. 8 Schematic diagram of the liquid dispensing technology, which enables "shirt-sleeve" manufacturing of low-dose and potent actives (Image courtesy of GlaxoSmithKline)

check, in order to verify that the active drug substance is present on the tablet surface. Following this check step, the tablets are over printed using a pad-printing system, in order to ensure acceptable cosmetic properties. In a final station on the machine, a printing process can add identification lettering, if this is required.

The system is designed for the low doses that are typical of many (though not all) highly active drug substances. The system works very well, with excellent dose reproducibility, at around 0.2 μg up to 3 mg; higher doses can be accommodated by inverting the tablets on the platens in a tablet handling process and dosing onto the other side of the placebo carrier tablet. However, there is a limit to total dosing of around 6–8 mg, with the maximum dose achievable being dependent on the properties of the active.

The machine is capable of highly accurate dose deposition, delivering relative standard deviation ("RSD") values of around 0.3 % in trials with 250,000 tablets, and providing a process capability, in these tests, of 3.22, above the value of 1.5 that is considered to represent a highly capable process [58]. The corresponding "sigma-level" from this work was 9.66 (i.e., one defective tablet in every thousand million that are produced), which is substantially above the low defect rate implied by a level of six (for "six-sigma" manufacturing, i.e., one defective tablet in every million that are produced).

A significant innovation offered by this process is the imaging and measurement of the volume of every droplet dispensed and, therefore, by calculation, the measurement of the actual dose quantity for every tablet produced. The fact that the dose quantity record is created and retained for each individual tablet means that this technology provides a novel capability: the real batch size, on a continuous process, is of one tablet. Any tablet that is dosed with a quantity that is not within preestablished limits, as assessed by the in-flight image that is recorded and analyzed for each tablet (for example, within a range of ±5 % of the target dose) is rejected. The individual tablets that are out of specification are removed using a "pick and place" capability, which is provided by means of vacuum.

GlaxoSmithKline has dosed tablets, using this liquid dispensing technology, for phase I to phase IIb trials for multiple drug products. A pilot machine, which is operated with a typical batch size of approximately 35,000 tablets and which is housed in a research and development facility, was used for this purpose.

Commercial Manufacturing

A phase III clinical supply and commercial launch unit (Fig. 9) has been installed by GlaxoSmithKline at its Barnard Castle site in the North East of England. This facility cost a fraction of the projected capital cost of a standard powder dilution facility for similar production volumes, according to company estimates. The commercial machine has the dimensions of a small packaging line, and platens are passed along the line, stopping at specific locations (or "stations") for processing to occur.

Fig. 9 The phase III clinical trial supply and commercial launch facility for the liquid dispensing technology, at GSK's Barnard Castle (UK) site (Image courtesy of GlaxoSmithKline)

The line is designed to be scale-independent and to be operated as a continuous process. Three scales of machine have been developed: a laboratory unit, a clinical manufacturing (or pilot plant scale) unit, and a commercial machine. The deposition process onto the tablet is the same regardless of the scale of the machine; consequently, the manufacturing process requires no scale-up, as all product critical aspects of tablet manufacturing are the same on all scales of machine. On the larger machines, more nozzles operate at higher speeds, but the deposition process is identical to that utilized on the smaller machines. The process is designed to be operated on a 24-h 7-day a week basis, and the passage of platens on a production line system, similar in size to a small packaging line (for the commercial scale machine) enables continuous operation. GlaxoSmithKline set a performance benchmark of 80,000 tablets per hour as being the minimum required for commercial operation, as it was considered that this processing throughput would allow economical manufacturing of a range of moderate volume products.

The system provides dose verification on an individual tablet basis. Due to this fact, GSK has suggested that the system could be operated as a "real-time release" process (as described by the European Medicines Agency [59], Moore [60]), with no additional at-line or off-line testing. The system is designed for immediate-release dose forms, and, given the low doses and the fact that the drug is in a film on the tablet surface, dissolution should be rapid; dissolution testing may be avoided, by International Council for Harmonization ("ICH") regulations, if the active is sufficiently soluble in biologically relevant media. Consequently, additional testing beyond the approaches that are embedded in the line is considered potentially to be unnecessary.

The feed solution is pumped to the nozzle heads using a peristaltic pump, and the tubing can be disposed of at the end of the run. Due to the design of the system, very few parts need to be disposed of or cleaned. The only part that requires cleaning is the stainless steel support for the pump ceramic piston/cylinder (which costs less that £1000), and which is typically dedicated to a single product in order to avoid routine cleaning verification. This assembly is small enough to fit into a coffee cup and can be readily cleaned. The platens are not exposed to any significant active contamination, as the drug substance is confined to the droplets, and the transport trays can be cleaned in a standard secondary parts washer. On the commercial line, four dosing nozzles operate in parallel, enabling the throughput of 80,000 tablets per hour to be obtained. The use of four systems requires that four pump piston/cylinder assemblies need to be cleaned. Tubing is an expendable item and is disposed of at the end of a run.

The system allows for "shirt-sleeve" processing of highly potent actives: operators do not need to wear any protective clothing, such as breathing equipment (or "respirators"), and can move freely around the processing machine. In addition to these operator advantages, the technology significantly reduces not only the installed capital cost of high-active's facilities, but also the environmental burden of such manufacturing processes. There is minimal need for washing water, and consequent minimal production of wastewaters, compared to standard high-active tablet manufacturing, and no need to change high-efficiency particulate air ("HEPA") filters and other elements in air-handling systems after a batch. The application of single-use plastic tubing for manufacturing minimizes cleaning and solid waste, and avoids a number of major sources of environmental release risks through the elimination of powder processing. The total solvent volume (which is typically of ethanol or methanol) that is evaporated is less than 20 l per day at full production rate and this discharge is below permitted levels at most secondary sites.

Manufacturing "Patient-Friendly" Medicines Using This Novel Approach

The system can be used to manufacture dose forms that are suitable for elderly patients by deposition of a low-dose active onto an orally dispersible tablet. This approach enables the production of a low dose drug and a high dose drug in combination in a format that disintegrates rapidly and provides ease of ingestion. The flexibility of the liquid dispensing system also enables a number of dose strengths to be manufactured in quick succession. Changing either the concentration in the feed solution or the droplet size enables dose strength to be adjusted readily; although the line may be stopped to make a clear break in production, very little time is required to effect the necessary changes, and a series of dose strengths can be produced with minimal setup time. As the system is designed for real-time release, there is no need for "down time" on the line for quality checks to be

completed. This system, therefore, minimizes the inefficiencies that are common in tablet production, and can produce a series of dose strengths in rapid succession, at reasonable cost.

For some of the compounds for which formulations have been developed using this approach, the liquid dispensing technology appears to have provided some tablet stability benefits when compared with conventional powder dilution approaches. In standard high-active tabletting processes, a small amount of active is distributed in a large bulk of excipients. This creates a large exposure of the active to the excipient materials, and subjects the active material to considerable processing strains. The rapidity of the liquid dispensing process and the fact that the active ingredient is processed in a confined and constrained manner appears to enable the stability of some labile high-active materials to be enhanced.

Operating costs for the line are modest. The process replaces many steps in tablet production with highly active compounds, and so eliminates a large part of the necessary capital-intensive plant infrastructure and the majority of the activities that require labor. In addition, the online testing approaches eliminate the need for off-line testing, and the costs associated with these activities, and remove the need to halt the process at an intermediate step, while off-line test data is obtained. Two operators typically staff the line, and manufacturing costs are comparable to those for production of a standard immediate-release tablet. It is true that a placebo tablets are input materials to the process and must be produced in advance; however, as there is no active in these tablets, these placebo materials can be produced in bulk at very low cost. As noted above, capital costs for the technology are very significantly lower than those for powder-based tablet production facilities for highly active compounds.

Capabilities and Potential Applications of the Technology

The liquid dispensing technology is a novel platform for the manufacturing of highly potent compounds, which provides a method of producing oral dose forms at doses as low as 0.1–0.5 μg (with very high levels of accuracy), in a low-cost, "shirt-sleeve" environment. This approach provides a potential method of formulating unstable, low-dose actives; the rapidity of the processing can limit degradation and enhance product stability, compared to conventional approaches, for some low-dose compounds. Each tablet is dose-checked individually, enabling a "quality by design" manufacturing approach, and real-time release appears to be a viable possibility. Critically, the technology greatly reduces capital plant costs, in comparison to powder dilution tabletting approaches, enables production of dose forms at a standard secondary tabletting cost, and has been developed to a commercial manufacturing scale.

The technology can be used to provide low dose orally dispersible formulations that minimise ease of swallowing for pediatric and elderly patients, and to provide a very high level of quality assurance with regard to dose levels for products for which dose is both critical to patient treatment and difficult to guarantee using standard technologies. At the time of writing (2016), the technology has been made available on a commercial basis to the broader industry, and given the unique characteristics of the approach, it is to be hoped that the industry will embrace the technology's distinctive capabilities.

Conclusions

There are significant challenges in developing patient-friendly drug products for elderly patients, due to the range of conditions and disease states that must be addressed. In this regard, it is interesting to consider the related but differing challenges of formulating age-appropriate formulations for young patients and for the elderly. While there are many stages of development and growth to recognize when formulating medicines for children and young adults, pediatric drug product design at least offers some clear pathways, due to the accepted categorisations of stages of development. In the sphere of medicines for the elderly, a large array of disease conditions, visual and cognitive capabilities, and physical manipulation skills must be taken into account. One can be encouraged that interest in both pediatric and geriatric medication and treatment is now an accepted topic of debate in the pharmaceutics community, with support and engagement from professional bodies and regulators.

Primary manufacturing relies on chemical transformations of materials, whereas secondary production is dominated by physical aspects of material processing. Chemistry remains important, naturally, but the physical properties of the active drug material will always be a fundamental consideration in drug product development. There is a close interaction in the secondary formulation domain between product development and manufacturing process selection and optimisation, and a limited set of accepted formulation approaches that are available with which to develop products for elderly patients. This document aims to suggest that, within the limited palette of techniques that are known to the industry, new approaches are possible.

The issue of manufacturing engineering (or "industrial engineering") is not normally commented on in formulation reviews. Nonetheless, the fashion with which the industry operates the large part of its capital assets, and the low efficiencies and utilization rates that are achieved, is worthy of comment. It is in this environment that any new technique must be implemented. In secondary manufacturing, overhead charges usually dominate all other costs, and direct expenses of production account for only a small percentage of total manufacturing costs.

Naturally, in any overhead allocation system, there is some subjectivity as to the optimal approach. However, applying overhead on the basis of machine hours used by a process provides a logical and rational approach that enables the development of an understanding of secondary costs and of the key factors that affect these. The extensive time demands of machine setup, cleaning and quality assurance activities, all of which are completely necessary, add substantially to manufacturing time and cost. In the environment of a modern secondary plant, due to the complexity and cost that these activities create, it does not seem reasonable to believe that more than 5–6 dose strengths of an active could be produced routinely across ranges of products.

The polypill technology that GlaxoSmithKline has developed offers a means to create combination tablets on an individual patient basis, to offer the potential to improve adherence, at least to a modest degree, and to affect positively health outcomes. While the technology is at a proof of concept stage and requires significant further development, the approach of assembly at local distribution sites would enable greater patient customisation to be provided without changing fundamentally the activities of the industry's large installed capital base of secondary manufacturing facilities. Such an approach could only be brought to a commercial realization with the engagement of many companies and stakeholders, but it offers the potential to reduce the significant pill burden that many patients, including many elderly ones, face on a daily basis. Many industries have moved to a greater degree than the pharmaceutical industry to adopt approaches that provide both personalisation of products, through approaches such as the postponement of complexity, and distributed manufacturing, which allows final assembly to take place close to the site of use. This polypill approach offers the potential to enable the industry to adopt some of the mass customisation and localized assembly approaches that other industries have applied, in order to enable individualised tablets to be delivered to patients, and to provide some modest adherence benefits.

Adherence is a complex, multifaceted issue. In recent years, many technological solutions to assist with adherence have been suggested that utilize mobile telephone or computing systems. (Recent papers by Varshney [61] and by Klein, Mogles and van Wissem [62] and Walker and Hayes [63] exemplify this literature and this approach to adherence improvement). In contrast to these approaches, the polypill technology offers the potential to improve adherence, to a small but notable extent, through alteration of the presentation of the dose form itself, and to address one element of the causes of non-adherence at source. Clearly, there are many challenges to the adoption of such an approach, yet the potential benefits are sufficiently significant that it is to be hoped that industry and other stakeholders will pursue this novel approach.

In evaluating the set of tablet variants and other dose forms that can be employed to develop oral dose forms for elderly patients, the physical constraints of the dose to be delivered, and the physiological requirements of delivery to a wide range of patients, limit the approaches available. In an industry that has seen only modest

levels of innovation with regard to production techniques, new approaches that have been developed to commercial scale are to be welcomed.

The liquid dispensing technology offers a means to provide dose verification on an individual tablet basis, and to manufacture and to assure quality with a batch size of one dose form, with full data recording. The approach enables highly active compounds to be processed safely in a "shirt-sleeve" environment, avoids powder handling of potent molecules, and substantially reduces plant capital costs for secondary high-active manufacturing facilities. Real-time release, without additional quality checks, of immediate-release products appears to be possible using this process, due to the online feed concentration, imaging and NIR systems employed, and doses as low as 0.1 μg can be delivered with very high accuracy, far exceeding the capability of standard tabletting approaches. The technology offers the potential for combination with orally dispersible tablet approaches to provide flexible manufacturing of a wide range of dose strengths of tablets of highly potent molecules, in dose forms that will be acceptable to many elderly patients.

The industry has placed significant emphasis over the last decade in understanding the requirements of both pediatric and geriatric patients and in considering how existing technologies can be deployed, adapted, or extended in order to meet better the requirements of these patient groups. (Articles by Liu et al. [64], Orla-Gul et al. [65], Ribera Casado [66], Perrie et al. [67] and Stegemann et al. [68] describe the challenges that must be faced, and recent industry developments.) This move to "patient-centered" product development is encouraging and welcome. Despite the many challenges of product formulation and secondary manufacturing, it is to be hoped that the industry will seek to explore novel approaches for formulation and production, and to develop promising approaches to commercial manufacturing scale, in order to address the needs of these patient groups. Advanced manufacturing technologies that apply sophisticated information technology systems (for example, to deliver performance prediction and item tracking) and mass customisation (often through postponement of complexity) have become common in other manufacturing industries. Despite some notable advances in recent years, there is considerable potential for the pharmaceutical industry to adopt such approaches. It is to be hoped that the industry will seek to develop and to apply innovative technologies, in order to provide medicines that are easier to use, that are more acceptable to the patient, and that, ultimately, help to provide better healthcare in everyday ("real world") use.

Acknowledgments The authors are pleased to acknowledge the dedicated work, on the part of many skilled scientists and engineers at GlaxoSmithKline and its development partners, to develop these novel technologies. The authors gratefully note the significant contribution of Dr Richard Kirsh to the development of the polypill approach.

The authors gratefully thank D. Dinner, D. Elder, T. Ernest and S. Sharpe for graciously and kindly providing comments on a draft version of this chapter.

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Part V
Drug Therapy in Older Adults

Prescribing to Older Adults

Sunny A. Linnebur

Abstract This chapter focuses on methods of appropriate prescribing of drugs to older adults. Pharmacokinetic changes observed in older adults which affect drug absorption, distribution, metabolism, and excretion are discussed. Pharmacodynamic changes associated with aging are also discussed as they relate to drug therapy. Recommendations on appropriate prescribing and deprescribing are highlighted and related to preventing adverse drug events. Tables from the updated 2015 American Geriatrics Society Beers Criteria are included for your reference.

Keywords Prescribing · Pharmacokinetics · Pharmacodynamics · Adverse drug events · Deprescribing · Beer's criteria

Introduction

Prescribing drugs to older adults is a complex process that requires care and attention by the practitioner. Adverse drug events occur more frequently in older adults than in younger adults, due to many factors including inappropriate prescribing, pharmacokinetic, and pharmacodynamic changes that occur with aging, lack of clinical data in older adults, and polypharmacy. Clinicians wishing to treat a new symptom with a drug should always evaluate current drugs as a potential cause for the new symptom prior to initiating a new drug. This thought process and other principles of prescribing to older adults may help to prevent drug-related problems and adverse events which can occur in older adults.

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S. Stegemann (ed.), *Developing Drug Products in an Aging Society*,
AAPS Advances in the Pharmaceutical Sciences Series 24,
DOI 10.1007/978-3-319-43099-7_24

Pharmacokinetic Changes Associated with Aging and the Impact on Prescribing

Most drugs taken or used by older adults are not absorbed, distributed, metabolized, or eliminated in the same manner that they are in younger adults. Drug absorption is particularly affected by the pH and motility of the gastrointestinal tract. As older adults age they often produce less gastric acid, increasing their gastric pH. This can also occur due to the consumption of acid reducing drugs, like antacids, histamine-H_2 receptor antagonists, or proton pump inhibitors. Drugs that are weakly acidic (e.g., warfarin, penicillin) have the potential for reduced absorption in this scenario, while drugs that are weakly basic (e.g., propranolol, amitriptyline) may have increased absorption. Often these small changes are not clinically relevant because most drugs are absorbed via passive diffusion. In contrast, some drugs (e.g., calcium carbonate, itraconazole, ketoconazole) rely heavily on an acidic environment for active transport and may have clinically relevant reductions in bioavailability in the setting of increased gastric pH. Older adults can take alternative agents (e.g., Calcium citrate and terbinafine) which do not rely on an acidic environment for absorption. Moreover, in the setting of increased gastric pH, drugs that are enteric coated (e.g., aspirin, bisacodyl) may dissolve in the stomach instead of the small intestine, causing adverse effects like upset stomach or cramping. Decreased gastric emptying rate and motility can also occur as adults age or have comorbidities like diabetes. Certain medications, like anticholinergic drugs, can also contribute to slowing of the gastrointestinal (GI) tract. This can increase the time to maximal drug concentrations (Tmax) and sometimes decrease the maximal drug concentrations (Cmax). Slowing of GI transit can also increase adverse effects of certain drugs. For example, potassium chloride sustained release tablets taken concomitantly with anticholinergic drugs can potentially increase gastric irritation, leading to esophageal ulcers and other adverse effects [1]. To avoid these effects, liquid potassium could be utilized and the patient should avoid laying or sitting down immediately after taking potassium. Additional gastrointestinal medications, like cholestryramine and sucralfate, if taken at the same time as other medications can reduce absorption of concomitant medications in older adults. Separating administration of cholestyramine and sucralfate from other medications by 2–3 h can usually prevent this. Overall, changes in drug absorption can mean that pharmacologic effects may take longer in older adults, certain drugs may not be as effective, or adverse effects may increase.

Once the drug is absorbed in the small intestine, distribution of the drug occurs and can be much different in an older adult compared to a younger adult. First, older adults typically have a decrease in total body water and lean muscle mass and an increase in adipose tissue compared to younger adults. Thus, volume of distribution can change greatly in an older adult. Drugs which are highly water soluble (e.g., digoxin, gentamicin) have a reduced volume of distribution, which can translate to being less effective or necessitating a lower dose. In contrast, drugs which are more lipid soluble (e.g., chlordiazepoxide, diazepam) typically have an increased volume

of distribution and cause more toxicity. Initial doses of highly lipid soluble drugs should be lower in older adults, or the dosing interval should be increased, to account for reduced clearance of these drugs. Next, older adults who are frail or malnourished may have altered plasma proteins, specifically decreased albumin and potentially increased α-1 acid glycoprotein. Changes in plasma proteins may cause clinically relevant effects in free (active) drug concentrations for drugs which are highly protein bound (e.g., warfarin, phenytoin, lidocaine). For example, total serum concentrations of phenytoin need to be interpreted differently if the patient has low albumin concentrations. An adjusted phenytoin level is calculated from the following equation: measured total phenytoin concentration in mcg/mL divided by [(0.2 × albumin in g/dL) + 0.1]. Alternatively, free drug concentrations can be monitored in older adults so as to avoid unpredictable drug concentrations from acute or chronic changes in plasma proteins from aging or illness.

Drug metabolism primarily occurs in the liver through two main pathways: phase I (oxidation, reduction, hydrolysis) and phase II (glucuronidation, acetylation, and sulfation). Age-related reductions occur in phase I metabolism, but phase II metabolism is maintained throughout the aging process. Data are conflicting regarding the effects of aging on drug metabolism through the cytochrome P450 system. In general, it is reasonable for clinicians to utilize lower doses of drugs metabolized through phase I reactions (e.g., chlordiazepoxide, diazepam), while drugs metabolized though phase II reactions (e.g., lorazepam, oxazepam, temazepam) do not require dosing adjustment for metabolism purposes. Drug–drug interactions from inhibition or induction of hepatic enzymes occur similarly in older adults as compared to younger adults. However, as one ages, hepatic volume and blood flow typically decrease and first-pass metabolism of high extraction drugs (e.g., lidocaine, propranolol, nitrates, phenobarbital) is also reduced, leading to increased bioavailability and potentially increased adverse effects if the dose is not reduced.

Reduced elimination of drugs through the kidneys is one of the most important pharmacokinetic changes that occurs in older adults. Although data are not available to longitudinally assess the effects of aging on drug elimination, it is well known that reductions in kidney function (glomerular filtration rate, renal plasma flow, and tubular secretion) occur in older adults due to the effects of aging on the number of functioning nephrons. These negative effects can be compounded by common comorbidities, such as hypertension and diabetes, which can also lead to kidney impairment. Unfortunately, there is not a perfect way to easily determine the glomerular filtration rate in an older adult. As such, estimations of kidney function are recommended to be utilized, with the most common equation being the Cockcroft-Gault equation.

$$\text{Cockcroft-Gault Equation: } \frac{[(140 - \text{age in years}) \times (\text{body weight in kg})]}{[(72) \times (\text{serum creatinine in mg/dL})]} \times 0.85 \text{ if female}$$

In the United States, most drug labeling approved by the Food and Drug Administration recommends dose adjustments based upon this equation. Drug

doses are typically recommended to be lower if the creatinine clearance (CrCl) is less than 50–60 mL/min. All clinicians prescribing for older adults should assess the patient's CrCl prior to prescribing in order to utilize the most appropriate dose, especially if it is a drug which is highly eliminated by the kidneys (e.g., digoxin, metoclopramide, ranitidine, enoxaparin, dabigatran, gabapentin, sitagliptan). It is important to recognize that this equation is an estimate of kidney function and that the serum creatinine concentration and body weight utilized in the equation may not be reliable. For example, older adults typically have a decrease in lean muscle mass and as such their serum creatinine may be low, leading to an overestimation of the CrCl. Rounding of serum creatinine in the equation (e.g., to 1.0 mg/dL) is sometimes done by clinicians but is not supported by data. The variable of body weight in the equation is also something that is controversial. Ideal body weight [(2.3 × height in inches > 5 ft) + 45.5 kg for women and 50 kg for men] is typically utilized in the equation, but in the case of a frail older adult, the actual body weight may be lower and should be used. If the patient is obese, the adjusted body weight [0.4(actual body weight in kg − ideal body weight in kg) + ideal body weight in kg] is often utilized. Because there is no universal method to 100 % accurately calculate the glomerular filtration rate, patients with significant kidney impairment should be monitored closely for drug efficacy and tolerability after being prescribed drugs that are renally eliminated. Although some drugs are excreted through the biliary system, there are no data to support reduced biliary excretion due to aging. Thus, dose adjustments are not necessary.

Pharmacodynamic Changes Associated with Aging and the Impact on Prescribing

Pharmacodynamic changes associated with aging, or altered sensitivity to certain drugs, can compound pharmacokinetic changes in older adults making prescribing more challenging. The organ systems most affected by pharmacodynamic changes are the cardiovascular system and the central nervous system [2]. Within the cardiovascular system, β-adrenergic receptor and baroreceptor function is typically reduced. This results in a blunted response to β-agonist (e.g., albuterol) and β-antagonist (e.g., metoprolol) therapies and reduced reflex cardiovascular effects (e.g., tachycardia when blood pressure is low). As such, older adults utilizing drugs that bind at β-receptors should be monitored closely for efficacy, and those taking drugs affecting blood volume or vasodilation (e.g., diuretics, angiotensin receptor blockers, nitrates) should be monitored closely for orthostatic hypotension. Within the central nervous system, several changes can occur with aging that predispose older adults to increased effects and toxicity from drugs which cross the blood–brain barrier. Specifically, as the brain ages there is less reserve capacity and ability to recover from drug effects. In addition, the permeability of the blood brain barrier is increased. Data indicate that older adults are much more sensitive to the effects of

benzodiazepines (e.g., alprazolam and diazepam) and anticholinergic drugs (e.g., oxybutynin and diphenhydramine) [3–5]. As such, these drugs should be avoided in older adults if possible. If they must be utilized, the lowest doses possible should be utilized.

It is often difficult to differentiate the pharmacokinetic changes affecting a drug from the pharmacodynamics changes. For example, diazepam is highly toxic to older adults due to pharmacokinetic and pharmacodynamics changes/effects (increased volume of distribution due to high lipophilicity, reduced metabolism through the Phase I system, active metabolite, long half-life, and increased sensitivity in the central nervous system). With a drug like this, it is best to avoid it altogether and if necessary prescribe a benzodiazepine such as lorazepam, which is hydrophilic, metabolized through Phase II metabolism, and has a shorter half-life. Pharmacodynamic changes could still affect the response to lorazepam and thus lead to adverse events, but the potential for drug toxicity due to pharmacokinetic changes would be less than with diazepam [3]. Digoxin is another example of a drug which causes toxicity due to pharmacokinetic changes (reduced volume of distribution and renal clearance) and pharmacodynamic changes (increased sensitivity) due to aging or reduced kidney function [6]. Digoxin also interacts with many other pharmacologic agents. It may be helpful to monitor serum digoxin concentrations, but older adults may suffer from digoxin toxicity even with drug concentrations in the therapeutic range.

Principles of Prescribing to Avoid Adverse Drug Events

Data indicate that at least 25 % of adverse drug events are preventable [7]. Strategies to prevent drug-related problems and adverse drug events can be implemented at the prescribing and monitoring stages [8]. Adverse drug events may occur due to a variety of reasons, but are commonly due to the patient taking unnecessary medications, inappropriate medications, overuse of medications, or nonadherence.

Prior to prescribing a medication, it is important for the clinician to first evaluate if the new symptom or condition is caused or exacerbated by the patient's current drug therapy (Table 1). Due to the previously described pharmacokinetic and pharmacodynamic changes associated with aging, it is common for drug therapy to cause adverse effects in older adults. Often these adverse effects (e.g., diarrhea from metformin or donepezil) are manageable with time, but the patient may require a slower dose titration or a reduction in the dose of the drug to allow for the patient to tolerate the drug. In other situations, the drug therapy may need to be stopped in order to avoid a prescribing cascade. For example, a patient with dementia is initiated on donepezil and it causes muscarinic stimulation which results in new symptoms of overactive bladder. The initial thought may be to prescribe an antimuscarinic agent to treat the urinary incontinence. Next, the antimuscarinic agent causes further memory decline, so another drug for dementia is added. Also,

Table 1 Principles of prescribing to older adults

Consider BEFORE prescribing	Consider DURING prescribing	Consider AFTER prescribing
Is this new symptom a side effect of any drugs the patient is currently taking?	Is this the right drug for this patient? Have the risks of the drug been weighed against the benefits of the drug for this patient?	Has both the patient and/or caregiver been educated about the proper use and side effects of the drug?
Is the problem/symptom treatable with a drug(s) or could any nondrug alternatives be tried before drug therapy?	Is this the right drug for this patient? Does this drug interact with any other diseases/conditions the patient may have? Does the drug interact with any other drugs the patient may be taking?	Is the drug having the desired therapeutic effect?
	Is this the right dose for this patient? Has the dose been adjusted for age, renal function, hepatic function, or other parameters? Start with a low dose and increase slowly	Is the drug causing an unwanted adverse effect?
	Can the patient afford the drug?	What is the appropriate duration of treatment?
		When can the drug be stopped?
		Does the patient still need every drug they are taking?

the antimuscarinic agent could contribute to constipation, dry mouth, and dizziness, all of which may lead to further drug therapy. Another example of a prescribing cascade is a patient who has hypertension and is initiated on amlodipine. The patient then develops peripheral edema (a common side effect) and is initiated on furosemide. Next comes hypokalemia and a prescription for potassium chloride. In both of these patient scenarios, the patient's initial drug therapy (donepezil and amlodipine, respectively) could be dose-reduced or discontinued in favor of a different drug which will not precipitate the same adverse effect. Avoiding unnecessary drugs to treat the side effect of another drug is important in preventing further adverse drug events. In addition, discontinuation of unnecessary drugs which do not have a valid medical indication is also important [9]. Keeping medication lists updated and including indications for drugs helps to further prevent the use of unnecessary drug therapy.

The next review prior to prescribing is whether the problem or symptom is treatable with a drug. In many cases, nonpharmacologic therapies, such as exercise, diet, sleep hygiene, biofeedback, counseling, acupuncture, pelvic floor exercises, etc., may be safer and more effective than a drug.

If a drug therapy is warranted, in the prescribing process it is important to weigh the risks of the drug against the benefits of the drug for that patient. With certain drugs the risks often outweigh the benefits. This type of medication is labeled a "potentially inappropriate medication" or "PIM" for older adults. Lists of PIMs can be found in The American Geriatrics Society (AGS) [10] Updated Beers Criteria for Potentially Inappropriate Medication Use in Older Adults and the STOPP/START criteria for potentially inappropriate prescribing in older people: version 2 [10, 11]. The documents contain lists of PIMs to avoid in all older adults if possible, to avoid in patients with certain conditions or diseases or at certain doses, and to use with caution (Table 2). The use of potentially inappropriate drugs included on both the AGS Beers Criteria and the STOPP list has been associated with increased mortality, increased healthcare resources, adverse events, and other poor health outcomes. Thus, avoiding PIMs at the time of prescribing is ideal.

Strategies to avoiding PIMs at the time of prescribing can be implemented at the population level by integrating either the AGS Beers Criteria or the STOPP lists into the electronic health record. Decision support can help reduce PIM prescribing at the point of order entry by providing the clinician with more information about the risks of the drug therapy they are attempting to select. In the future, decision support could also provide drug alternatives to PIMs. Process redesign can also help to guide the implementation of decision support tools into the workflow in the best possible way so as to avoid adding additional time to the workflow. Another way to reduce the burden on clinicians is to implement decision support for specific patient groups (e.g., based upon age, comorbidities, or number of medications) in the electronic health record. Targeting specific groups of patients may also increase the likelihood of positively impacting patient care.

During the prescribing process (Table 1), it is also important to evaluate if the proposed drug interacts with the patient's other drugs or diseases/conditions. Drug–drug interactions are common in older adults due to their higher propensity for polypharmacy, but not all of them are clinically relevant. Many of the clinically relevant drug–drug interactions occur with anti-infective agents (e.g., sulfonylureas, macrolides, and fluoroquinolones) [12]. For those interactions which are not from anti-infective agents, the 2015 AGS Beers Criteria provides a table (Table 3) of clinically important interactions to avoid in older adults [10]. Drug-disease interactions are often a bigger concern for older adults with comorbidities, and the 2015 AGS Beers Criteria provides a list of PIMs (Table 4) based upon the patients other diseases/conditions [10]. At the clinician level, becoming familiar with these tables and screening for the interactions can help to reduce inappropriate prescribing in older adults and the avoidance of adverse drug events. Screening for these interactions at the pharmacy can also provide a second check to verify appropriateness for the patient.

After the drug has been selected for the patient, it is important to verify that the dose is appropriate. In most instances, older adults should be treated with a "start low and go slow" approach. Utilizing the lowest dose and titrating slowly can help to prevent side effects in older adults. In addition, it is important to verify that the dose is adjusted for renal or hepatic impairment if necessary. The 2015 AGS Beers

Table 2 2015 American geriatrics society beers criteria for potentially inappropriate medication use in older adults (reprinted with permission)

Organ system, therapeutic category, drugs	Rationale	Recommendation	Quality of evidence	Strength of recommendation
Anticholinergics				
First-generation antihistamines	Highly anticholinergic; clearance reduced with advanced age, and tolerance develops when used as hypnotic; risk of confusion, dry mouth, constipation, and otter anticholinergic effects or toxicity	Avoid	Moderate	Strong
Brompheniramine				
Carbinoxamine				
Chlorpheniramine				
Clemastine				
Cyproheptadine	Use of diphenhydramine in situations such as acute treatment of severe allergic reaction may be appropriate			
Dexbrompheniramine				
Dexchlorpheniramine				
Dimenhydrinate				
Diphenhydramine (oral)				
Doxylamine				
Hydroxyzine				
Meclizine				
Promethazine				
Triprolidine				
Antiparkinsonian agents	Not recommended for prevention of extrapyramidal symptoms with antipsychotics; more effective agents available for treatment of Parkinson disease	Avoid	Moderate	Strong
Benztropine (oral)				
Trihexyphenidyl				

(continued)

Table 2 (continued)

Organ system, therapeutic category, drugs	Rationale	Recommendation	Quality of evidence	Strength of recommendation
Antispasmodics	Highly anticholinergic, uncertain effectiveness	Avoid	Moderate	Strong
Atropine (excludes ophthalmic)				
Belladonna alkaloids				
Clidinium-Chlordiazepoxide				
Dicyclomine				
Hyoscyamine				
Propantheline				
Scopolamine				
Antithrombotics				
Dipyridamole, oral short-acting (does not apply to the extended-release combination with aspirin)	May cause orthostatic hypotension; more effective alternatives available; intravenous form acceptable for use in cardiac stress testing	Avoid	Moderate	Strong
Ticlopidine	Safer, effective alternatives available	Avoid	Moderate	Strong
Anti-infective				
Nitrofurantoin	Potential for pulmonary toxicity, hepatoxicity, and peripheral neuropathy, especially with long-term use; safer alternatives available	Avoid in individuals with creatinine clearance <30 mL/min or for long-term suppression of bacteria	Low	Strong
Cardiovascular				
Peripheral alpha-1 blockers	High risk of orthostatic hypotension: not recommended as routine treatment for hypertension; alternative agents have superior risk-benefit profile	Avoid use as an antihypertensive	Moderate	Strong
Doxazosin				
Prazosin				
Terazosin				

(continued)

Table 2 (continued)

Organ system, therapeutic category, drugs	Rationale	Recommendation	Quality of evidence	Strength of recommendation
Central alpha agonists	High risk of adverse CNS effects; may cause bradycardia and orthostatic hypotension; not recommended as routine treatment for hypertension	Avoid clonidine as first-line antihypertensive Avoid others as listed	Low	Strong
Clonidine				
Guanabenz				
Guanfacine				
Methyldopa				
Reserpine (>0.1 mg/d)				
Disopyramide	Disopyramide is a potent negative inotrope and therefore may induce heart failure in older adults; strongly anticholinergic; other antiarrhythmic drugs preferred	Avoid	Low	Strong
Dronedarone	Worse outcomes have been reported in patients taking dronedarone who have permanent atrial fibrillation or severe or recently decompensated heart failure	Avoid in individuals with permanent atrial fibrillation or severe or recently decompensated heart failure	High	Strong
Digoxin	Use in atrial fibrillation: should not be used as a first-line agent in atrial fibrillation, because more effective alternatives exist and it may be associated with increased mortality	Avoid as first-line therapy for atrial fibrillation	Atrial fibrillation: moderate	Atrial fibrillation: Strong
	Use in heart failure: questionable effects on risk of hospitalization and may be associated with increased mortality in older adults with heart failure; in heart failure, higher dosages not associated with additional benefit and may increase risk of toxicity	Avoid as first-line therapy for heart failure	Heart failure: low	Heart failure: Strong
	Decreased renal clearance of digoxin may lead to increased risk of toxic effects; further dose reduction may be necessary in patients with Stage 4 or 5 chronic kidney disease	If used for atrial fibrillation or heart failure, avoid dosages >0.125 mg/d	Dosage >0.125 mg/d: moderate	Dosage >0.125 mg/d: Strong

(continued)

Table 2 (continued)

Organ system, therapeutic category, drugs	Rationale	Recommendation	Quality of evidence	Strength of recommendation
Nifedipine, immediate release	Potential for hypotension; risk of precipitating myocardial ischemia	Avoid	High	Strong
Amiodarone	Amiodarone is effective for maintaining sinus rhythm but has greater toxicities than other antiarrhythmics used in atrial fibrillation; it may be reasonable first-line therapy in patients with concomitant heart failure or substantial left ventricular hypertrophy if rhythm control is preferred over rate control	Avoid amiodarone as first-line therapy for atrial fibrillation unless patient has heart failure or substantial left ventricular hypertrophy	High	Strong
Central nervous system				
Antidepressants, alone or in combination	Highly anticholinergic, sedating, and cause orthostatic hypotension; safety profile of low-dose doxepin ($\leq$6 mg/d) comparable with that of placebo	Avoid	High	Strong
Amitriptyline				
Amoxapine				
Clomipramine				
Desipramine				
Doxepin >6 mg/d				
Imipramine				
Nortriptyline				
Paroxetine				
Protriptyline				
Trimipramine				

(continued)

Table 2 (continued)

Organ system, therapeutic category, drugs	Rationale	Recommendation	Quality of evidence	Strength of recommendation
Antipsychotics, first-(conventional)and second-(atypical) generation	Increased risk of cerebrovascular accident (stroke) and greater rate of cognitive decline and mortality in persons with dementia. Avoid antipsychotics for behavioral problems of dementia or delirium unless nonpharmacological options (e.g., behavioral interventions) have failed or are not possible ***and*** the older adult is threatening substantial harm to self or others	Avoid, except for schizophrenia, bipolar disorder, or short-term use as antiemetic during chemotherapy	Moderate	Strong
Barbiturates	High rate of physical dependence, tolerance to sleep benefits, greater risk of overdose at low dosages	Avoid	High	Strong
Amobarbital				
Butabarbital				
Butalbital				
Mephobarbital				
Pentobarbital				
Phenobarbital				
Secobarbital				
Benzodiazepines	Older adults have increased sensitivity to benzodiazepines and decreased metabolism of long-acting agents; in general, all benzodiazepines increase risk of cognitive impairment, delirium, falls, fractures, and motor vehicle crashes in older adults	Avoid	Moderate	Strong
Short- and intermediate-acting				
Alprazolam				
Estazolam				
Lorazepam				
Oxazepam				
Temazepam				
Triazolam				

(continued)

Table 2 (continued)

Organ system, therapeutic category, drugs	Rationale	Recommendation	Quality of evidence	Strength of recommendation
Long-acting	May be appropriate for seizure disorders, rapid eye movement sleep disorders, benzodiazepine withdrawal, ethanol withdrawal, severe generalized anxiety disorder, and periprocedural anesthesia			
Clorazepate				
Chlordiazepoxide (alone or in combination with amitriptyline or clidinium)				
Clonazepam				
Diazepam				
Flurazepam				
Quazepam				
Meprobamate	High rate of physical dependence; very sedating	Avoid	Moderate	Strong
Nonbenzodiazepine, benzodiazepine receptor agonist hypnotics	Benzodiazepine receptor agonists have adverse events similar to those of benzodiazepines in older adults (e.g., delirium, falls, fractures); increased emergency department visits and hospitalizations; motor vehicle crashes; minimal improvement in sleep latency and duration	Avoid	Moderate	Strong
Eszopiclone				
Zolpidem				
Zaleplon				

(continued)

Table 2 (continued)

Organ system, therapeutic category, drugs	Rationale	Recommendation	Quality of evidence	Strength of recommendation
Ergoloid mesylates (dehydrogenated ergot alkaloids) Isoxsuprine	Lack of efficacy	Avoid	High	Strong
Endocrine				
Androgens	Potential for cardiac problems; contraindicated in men with prostate cancer	Avoid unless indicated for confirmed hypogonadism with clinical symptoms	Moderate	Weak
Methyltestosterone				
Testosterone				
Desiccated thyroid	Concerns about cardiac effects; safer alternatives available	Avoid	Low	Strong
Estrogens with or without progestins	Evidence of carcinogenic potential (breast and endometrium); lack of cardioprotective effect and cognitive protection in older women.	Avoid oral and topical patch. Vaginal cream or tablets: acceptable to use low-dose intravaginal estrogen for management of dyspareunia, lower urinary tract infections, and other vaginal symptoms	Oral and patch: high Vaginal cream or tablets: moderate	Oral and patch: strong Topical vaginal cream or tablets: weak
	Evidence indicates that vaginal estrogens for the treatment of vaginal dryness are safe and effective; women with a history of breast cancer who do not respond to nonhormonal therapies are advised to discuss the risk and benefits of low-dose vaginal estrogen (dosages of estradiol <25 μg twice weekly) with their healthcare provider			
Growth hormone	Impact on body composition is small and associated with edema, arthralgia, carpal tunnel syndrome, gynecomastia, impaired fasting glucose	Avoid, except as hormone replacement after pituitary gland removal	High	Strong

(continued)

Table 2 (continued)

Organ system, therapeutic category, drugs	Rationale	Recommendation	Quality of evidence	Strength of recommendation
Insulin, sliding scale	Higher risk of hypoglycemia without improvement in hyperglycemia management regardless of care setting; refers to sole use of short- or rapid-acting insulins to manage or avoid hyperglycemia in absence of basal or long-acting insulin; does not apply to titration of basal insulin or use of additional shod short- or rapid-acting insulin in conjunction with scheduled insulin (i.e., correction insulin)	Avoid	Moderate	Strong
Megestrol	Minimal effect on weight; increases risk of thrombotic events and possibly death in older adults	Avoid	Moderate	Strong
Sulfonylureas, long-duration Chlorpropamide	Chlorpropamide: prolonged half-life in older adults; can cause prolonged hypoglycemia; causes syndrome of inappropriate antidiuretic hormone secretion	Avoid	High	Strong
Glyburide	Glyburide: higher risk of severe prolonged hypoglycemia in older adults			
Gastrointestinal				
Metoclopramide	Can cause extrapyramidal effects, including tardive dyskinesia; risk may be greater in frail older adults	Avoid, unless for gastroparesis	Moderate	Strong
Mineral oil, given orally	Potential for aspiration and adverse effects; safer alternatives available	Avoid	Moderate	Strong

(continued)

Table 2 (continued)

Organ system, therapeutic category, drugs	Rationale	Recommendation	Quality of evidence	Strength of recommendation
Proton pump inhibitors	Risk of *Clostridium difficile* infection and bone loss and fractures	Avoid scheduled use for >8 weeks unless for high-risk patients (e.g., oral corticosteroids or chronic NSAID use), erosive esophagitis, Barrett's esophagitis, pathological hypersecretory condition, or demonstrated need for maintenance treatment (e.g., due to failure of drug discontinuation trial or H_2 blockers)	High	Strong
Pain medications				
Meperidine	Mot effective oral analgesic in dosages commonly used; may have higher risk of neurotoxicity, including delirium, than other opioids; safer alternatives available	Avoid, especially in individuals with chronic kidney disease	Moderate	Strong
Non-cyclooxygenase-selective	Increased risk of gastrointestinal bleeding or peptic ulcer disease in high-risk groups, including those aged >75 or taking oral or parenteral corticosteroids, anticoagulants, or antiplatelet agents; use of proton pump inhibitor or misoprostol reduces but does not eliminate risk. Upper gastrointestinal ulcers, gross bleeding, or perforation caused by NSAIDs occur in approximately 1 % of patients treated for 3–6 months and in ~2–4 % of patients treated for 1 year; these trends continue with longer duration of use	Avoid chronic use, unless other alternatives are not effective and patient can take gastroprotective agent (proton pump inhibitor or misoprostol)	Moderate	Strong

(continued)

Table 2 (continued)

Organ system, therapeutic category, drugs	Rationale	Recommendation	Quality of evidence	Strength of recommendation
NSAIDs, oral:				
Aspirin >325 mg/d				
Diclofenac				
Diflunisal				
Etodolac				
Fenoprofen				
Ibuprofen				
Ketoprofen				
Meclofenamate				
Mefenamic acid				
Meloxicam				
Nabumetone				
Naproxen				
Oxaprozin				
Piroxicam				
Sulindac				
Tolmetin				
Indomethacin	Indomethacin is more likely than other NSAIDs to have adverse CNS effects. Of all the NSAIDs, indomethacin has the most adverse effects. Increased risk of gastrointestinal bleeding, peptic ulcer disease, and acute kidney injury in older adults	Avoid	Moderate	Strong
Ketorolac, includes parenteral				

(continued)

Table 2 (continued)

Organ system, therapeutic category, drugs	Rationale	Recommendation	Quality of evidence	Strength of recommendation
Pentazocine	Opioid analgesic that causes CNS adverse effects, including confusion and hallucinations, more commonly than other opioid analgesic drugs; is also a mixed agonist and antagonist; safer alternatives available	Avoid	Low	Strong
Skeletal muscle relaxants	Most muscle relaxants poorly tolerated by older adults because some have anticholinergic adults because some have anticholinergic adverse effects, sedation, increased risk of fractures; effectiveness at dosages tolerated by older adults questionable	Avoid	Moderate	Strong
Carisoprodol				
Chlorzoxazone				
Cyclobenzaprine				
Metaxalone				
Methocarbamol				
Orphenadrine				
Genitourinary desmopressin	High risk of hyponatremia; safer alternative treatments	Avoid for treatment of nocturia or nocturnal polyuria	Moderate	Strong

The primary target audience is practicing clinicians. The intentions of the criteria are to improve the selection of prescription drugs by clinicians and patients; evaluate patterns of drug use within populations; educate clinicians and patients on proper drug usage; and evaluate health outcome, quality of care, cost, and utilization data

CNS Central nervous system; *NSAIDs* nonsteroidal anti-inflammatory drugs

Table 3 2015 American geriatrics society beers criteria for potentially clinically important non-anti-infective drug–drug interactions that should be avoided in older adults (reprinted with permission)

Object drug and class	Interacting drug and class	Risk rationale	Recommendation	Quality of evidence	Strength of recommendation
ACEIs	Amiloride or triamterene	Increased risk of Hyperkalemia	Avoid routine use; reserve for patients with demonstrated hypokalemia while taking an ACEI	Moderate	Strong
Anticholinergic	Anticholinergic	Increased risk of Cognitive decline	Avoid, minimize number of anticholinergic drugs (Table 7)	Moderate	Strong
Antidepressants (i.e.,TCAs and SSRIs)	≥ 2 other CNS-active drugs[a]	Increased risk of Falls	Avoid total of ≥ 3 CNS-active drugs[a]; minimize number of CNS-active drugs	Moderate	Strong
Antipsychotics	≥ 2 other CNS-active drugs[a]	Increased risk of Falls	Avoid total of ≥ 3 CNS-active drugs[a]; minimize number of CNS-active drugs	Moderate	Strong
Benzodiazepines and nonbenzodiazepine, benzodiazepine receptor agonist hypnotics	≥ 2 other CNS-active drugs[a]	Increased risk of Falls and fractures	Avoid total of ≥ 3 CNS-active drugs[a]; minimize number of CNS-active drugs	High	Strong
Corticosteroids, oral or parenteral	NSAIDs	Increased risk of pepticulcer disease or gastrointestinal bleeding	Avoid; if not possible, provide gastrointestinal protection	Moderate	Strong
Lithium	ACEIs	Increased risk of lithium toxicity	Avoid, monitor lithium concentrations	Moderate	Strong
Lithium	Loop diuretics	Increased risk of lithium toxicity	Avoid, monitor lithium concentrations	Moderate	Strong

(continued)

Table 3 (continued)

Object drug and class	Interacting drug and class	Risk rationale	Recommendation	Quality of evidence	Strength of recommendation
Opioid receptor agonist analgesics	$\geq$2 other CNS-active drugs[a]	Increased risk of Falls	Avoid total of $\geq$3 CNS-active drugs[a]; minimize number of CNS drugs	High	Strong
Peripheral Alpha-1 blockers	Loop diuretics	Increased risk of urinary incontinence in older women	Avoid in older women, unless conditions warrant both drugs	Moderate	Strong
Theophylline	Cimetidine	Increased risk of theophylline toxicity	Avoid	Moderate	Strong
Warfarin	Amiodarone	Increased risk of bleeding	Avoid when possible; monitor international normalized ratio closely	Moderate	Strong
Warfarin	NSAIDs	Increased risk of bleeding	Avoid when possible; if used together, monitor for bleeding closely	High	Strong

[a]Central nervous system (*CNS*)-active drugs: antipsychotics; benzodiazepines; nonbenzodiazepine, benzodiazepine receptor agonist hypnotics; tricyclic antidepressants (*TCAs*); selective serotonin reuptake inhibitors (*SSRIs*); and opioids

ACEI Angiotensin-converting enzyme inhibitor; *NSA1D* nonsteroidal anti-inflammatory drug

Table 4 2015 American Geriatrics Society Beers Criteria for potentially inappropriate medication use in older adults due to drug-disease or drug-syndrome interactions that may exacerbate the disease or syndrome (reprinted with permission)

Disease or syndrome	Drug(s)	Rationale	Recommendation	Quality of evidence	Strength of recommendation
Cardiovascular					
Heart failure	NSAIDs and COX-2 inhibitors Nondihydropyridine CCBs (diltiazem, verapamil)—avoid only for heart failure with reduced ejection fraction Thiazolidinediones (pioglitazone, rosiglitazone) Cilostazol Dronedarone (severe or recently decompensated heart failure)	Potential to promote fluid retention and exacerbate heart failure	Avoid	NSAIDs: moderate CCBs: moderate Thiazolidinediones: high Cilostazol: low Dronedarone: high	Strong
Syncope	AChEIs Peripheral alpha-1 blockers Doxazosin Prazosin Terazosin Tertiary TCAs Chlorpromazine Thioridazine Olanzapine	Increases risk of orthostatic hypotension or bradycardia	Avoid	Peripheral alpha-1 blockers: high TCAs, AChEIs, antipsychotics moderate	AChEIs, TCAs: strong Peripheral alpha-1 blockers, antipsychotics: weak
Central nervous system					
Chronic seizures or epilepsy	Bupropion Chlorpromazine Clozapine Maprotiline Olanzapine Thioridazine Thiothixene Tramadol	Lowers seizure threshold; may be acceptable in individuals with well-controlled seizures in whom alternative agents have not been effective	Avoid	Low	Strong

(continued)

Table 4 (continued)

Disease or syndrome	Drug(s)	Rationale	Recommendation	Quality of evidence	Strength of recommendation
Delirium	Anticholinergics (see Table 7 for full list) Antipsychotics Benzodiazepines Chlorpromazine Corticosteroids[3] H_2-receptor antagonists Cimetidine Famotidine Nizatidine Ranitidine Meperidine Sedative hypnotics	Avoid in older adults with or at high risk of delirium because of the potential of inducing or worsening delirium. Avoid antipsychotics for behavioral problems of dementia or delirium unless nonpharmacological options (e.g., behavioral interventions) have failed or are not possible *and* the older adult is threatening substantial harm to self or others. Antipsychotics are associated with greater risk of cerebrovascular accident (stroke) and mortality in persons with dementia.	Avoid	Moderate	Strong
Dementia or cognitive impairment	Anticholinergics (see Table 7 for full list) Benzodiazepines H_2-receptor antagonists Nonbenzodiazepine, benzodiazepine receptor agonist hypnotics Eszopicione Zolpidem Zaieplon Antipsychotics, chronic and as-needed use	Avoid because of adverse CNS effects Avoid antipsychotics for behavioral problems of dementia or delirium unless nonpharmacological options (e.g., behavioral interventions) have failed or are not possible a/icf the older adult is threatening substantial harm to self or others. Antipsychotics are associated with greater risk of cerebrovascular accident (stroke) and mortality in persons with dementia	Avoid	Moderate	Strong

(continued)

Table 4 (continued)

Disease or syndrome	Drug(s)	Rationale	Recommendation	Quality of evidence	Strength of recommendation
History of falls or fractures	Anticonvulsants Antipsychotics Benzodiazepines Nonbenzodiazepine, benzodiazepine receptor agonist hypnotics Eszopicione Zaieplon Zolpidem TCAs SSRIs Opioids	May cause ataxia, impaired psychomotor function, syncope, additional falls; shorter-acting benzodiazepines are not safer than long-acting ones If one of the drugs must be used, consider reducing use of other CNS-active medications that increase risk of falls and fractures (i.e., anticonvulsants, opioid-receptor agonists, antipsychotics, antidepressants, benzodiazepine-receptor agonists, other sedatives and hypnotics) and implement other strategies to reduce fall risk	Avoid unless safer alternatives are not available; avoid anticonvulsants except for seizure and mood disorders Opioids: avoid, excludes pain management due to recent fractures or joint replacement	High Opioids: moderate	Strong Opioids: strong
Insomnia	Oral decongestants Pseudoephedrine Phenylephrine Stimulants Amphetamine Armodafinil Methylphenidate Modafinil Theobromines Theophylline Caffeine	CNS stimulant effects	Avoid	Moderate	Strong

(continued)

Table 4 (continued)

Disease or syndrome	Drug(s)	Rationale	Recommendation	Quality of evidence	Strength of recommendation
Parkinson disease	All antipsychotics (except aripiprazole, quetiapine, clozapine) Antiemetics Metoclopramide Prochlorperazine Promethazine	Dopamine-receptor antagonists with potential to worsen parkinsonian symptoms Quetiapine, aripiprazole, clozapine appear to be less likely to precipitate worsening of Parkinson disease	Avoid	Moderate	Strong
Gastrointestinal					
History of gastric or duodenal ulcers	Aspirin (>325 mg/d) Non-COX-2 selective NSAIDs	May exacerbate existing ulcers or cause new or additional ulcers	Avoid unless other alternatives are not effective and patient can take gastroprotective agent (i.e., proton-pump inhibitor or misoprostol)	Moderate	Strong
Kidney and urinary tract					
Chronic kidney disease Stages IV or less (creatinine clearance <30 mL/min)	NSAIDs (non-COX and COX-selective, oral and parenteral)	May increase risk of acute kidney injury and further decline of renal function	Avoid	Moderate	Strong
Urinary incontinence (all types) in women	Estrogen oral and transdermal (excludes intravaginal estrogen) Peripheral alpha-1 blockers: Doxazosin Prazosin Terazosin	Aggravation of incontinence	Avoid in women	Estrogen: high Peripheral alpha-1 blockers: moderate	Estrogen: strong Peripheral alpha-1 blockers: strong

(continued)

Table 4 (continued)

Disease or syndrome	Drug(s)	Rationale	Recommendation	Quality of evidence	Strength of recommendation
Lower urinary tract symptoms, benign prostatic hyperplasia	Strongly anticholinergic drugs, except antimuscarinics for urinary incontinence (see Table 7 for complete list)	May decrease urinary flow and cause urinary retention	Avoid in men	Moderate	Strong

The primary target audience is the practicing clinician. The intentions of the criteria are to improve selection of prescription drugs by clinicians and patients; evaluate patterns of drug use within populations; educate clinicians and patients on proper drug usage; and evaluate health outcome, quality of care, cost, and utilization data

[a]Excludes inhaled and topical forms. Oral and parenteral corticosteroids may be required for conditions such as exacerbations of chronic obstructive pulmonary disease but should be prescribed in the lowest effective dose and for the shortest possible duration

CCB Calcium channel blocker; *AChEI* acetylcholinesterase inhibitor; *CNS* central nervous system; *COX* cyclooxygenase; *NSAID* nonsteroidal anti-inflammatory drug; *SSRIs* selective serotonin reuptake inhibitors; *TCA* tricyclic antidepressant

Table 5 2015 American Geriatrics Society Beers Criteria for Non-anti-infective Medications that should be avoided or have their dosage reduced with varying levels of kidney function in older adults (reprinted with permission)

Medication class and medication	Creatinine clearance, mL/min, at which action required	Rationale	Recommendation	Quality of evidence	Strength of recommendation
Cardiovascular or hemostasis					
Amiloride	<30	Increased potassium, and decreased sodium	Avoid	Moderate	Strong
Apixaban	<25	Increased risk of bleeding	Avoid	Moderate	Strong
Dabigatran	<30	Increased risk of bleeding	Avoid	Moderate	Strong
Edoxaban	30–50	Increased risk of bleeding	Reduce dose	Moderate	Strong
	<30 or >95		Avoid		
Enoxaparin	<30	Increased risk of bleeding	Reduce dose	Moderate	Strong
Fondaparinux	<30	Increased risk of bleeding	Avoid	Moderate	Strong
Rivaroxaban	30–50	Increased risk of bleeding	Reduce dose	Moderate	Strong
	<30		Avoid		
Spironolactone	<30	Increased potassium	Avoid	Moderate	Strong
Triamterene	<30	Increased potassium, and decreased sodium	Avoid	Moderate	Strong
Central nervous system and analgesics					
Duloxetine	<30	Increased Gastrointestinal adverse effects (nausea, diarrhea)	Avoid	Moderate	Weak
Gabapentin	<60	CNS adverse effects	Reduce dose	Moderate	Strong
Levetiracetam	≤ 80	CNS adverse effects	Reduce dose	Moderate	Strong
Pregabalin	<60	CNS adverse effects	Reduce dose	Moderate	Strong
Tramadol	<30	CNS adverse effects	Immediate release: reduce dose	Low	Weak
			Extended release: avoid		
Gastrointestinal					
Cimetidine	<50	Mental status changes	Reduce dose	Moderate	Strong
Famotidine	<50	Mental status changes	Reduce dose	Moderate	Strong
Nizatidine	<50	Mental status changes	Reduce dose	Moderate	Strong
Ranitidine	<50	Mental status changes	Reduce dose	Moderate	Strong
Hyperuricemia					
Colchicine	<30	Gastrointestinal, neuromuscular, bone marrow toxicity	Reduce dose; monitor for adverse effects	Moderate	Strong
Probenecid	<30	Loss of effectiveness	Avoid	Moderate	Strong

CNS Central nervous system

Criteria provides a table (Table 5) of recommendations for older adults for renal dose adjustment of non-anti-infective medications [10]. Of note, many anti-infective agents require renal dose adjustment, but are not included in the table.

Finally, during the prescribing process it is important to assess if the patient has access to the particular drug or if they can afford the drug. In the United States, this may mean reviewing their Medicare Part C or D formulary, or the state Medicaid formulary. Drugs which are expensive may not be covered by the patient's insurance plan and the patient may not be able to access the drug without a prior authorization or justification provided by the prescriber. Alternatively, the drug may be covered but may be too expensive for the patient to afford, or the drug cost may cause them to reach their coverage gap. If the intent is for the patient to continue the drug long term, drug coverage and pricing can be a barrier to adherence. In Europe, drug coverage may be limited to the particular national formulary of the country of origin. Cost may not be as much of a concern for older adults if the drug is covered by the national formulary.

After prescribing the drug (Table 1), the clinician and/or pharmacist should provide the patient and/or caregiver education regarding the proper use and side effects of the drug. Education will help to ensure the older adult utilizes the drug appropriately and avoids adverse events. The clinician will also typically need to follow up with the patient to monitor for effectiveness and side effects. If the drug dosing is being tapered up to improve tolerability or for effectiveness, it is important that titrations continue and are not overlooked. For example, the doses of galantamine and rivastigmine for Alzheimer's disease are titrated to improve tolerability. If not titrated to the minimum effective dose (galantamine 16 mg daily or rivastigmine 9.5 mg patch daily) the drugs will not likely provide benefit. Similarly, treatments with multiple available dosages (e.g., statins, glucagon-like peptide-1 agonists, omega 3-fatty acids) are likely futile if the dose is not at an effective dose. Treatment duration should be reevaluated regularly to ensure it is appropriate. Some drugs, such as proton pump inhibitors and albuterol, are often initiated while a patient is admitted to the hospital and are continued as an outpatient without indication. Reevaluating treatment duration helps to detect this type of drug-related problem and prevent unnecessary drug use. Moreover, as older adults become frailer, some chronic treatments may not be necessary or may not improve quality of life and can be discontinued. For example, data indicate that statins can be safely stopped in older adults with advanced, life-limiting illness [13]. Until future research is available, discussions about continuing or discontinuing drug therapy should be patient specific.

Finally, it is important for the clinician to balance polypharmacy with underuse of drugs. Patients with multiple chronic illnesses may be prescribed numerous drugs as part of the standard of care (e.g., myocardial infarction and use of antiplatelet agents, β-antagonists, angiotensin converting enzyme inhibitors, nitroglycerin, and statins). However, it is still important for the clinician to evaluate if the patient is a candidate for preventive drugs such as bisphosphonates and calcium/vitamin D, or for the clinician to treat untreated conditions such as depression and chronic pain.

Deprescribing

Deprescribing requires just as much time and attention by the clinician as the initial prescribing process, and is outlined by Scott et al. [9]. Five steps will help ensure a thorough review of the patient's drugs and a plan of action that is safe for the patient. If a drug which an older adult is prescribed is not necessary or can be stopped, it is important for the clinician to evaluate how to stop the drug safely. Some drugs (e.g., anticonvulsants, benzodiazepines, opioids, β-antagonists, clonidine, and estrogens) require tapering in order to prevent withdrawal, rebound clinical effects, or other adverse events. Others can be stopped abruptly without consequences. If the patient is experiencing adverse effects, the negative effects may outweigh the risks of withdrawal and the drug can be stopped abruptly. Discontinuing one drug at a time is recommended to help ascribe the results to the correct drug. If withdrawal symptoms occur or initial symptoms reoccur, the drug can be restarted.

Stopping a drug also requires communication in the electronic health record, to the patient, to the caregiver, and to the pharmacy. An updated medication list may need to be provided to the patient and/or caregiver, and the order may need to be deactivated at the pharmacy. In the event that the patient has automatic refills at the pharmacy, the active order can continue to be filled at the pharmacy and the patient may purchase and unknowingly take the drug. This is a simple step which can prevent severe consequences.

Summary

Older adults are treated with a disproportionate amount of prescription drugs. Unfortunately, pharmacokinetic and pharmacodynamic changes in older adults predisposes them to suffering adverse drug events. Electronic order entry systems with decision support may help to reduce the amount of potentially inappropriate medications prescribed to older adults. However, clinicians should still be aware of general drugs to avoid in older adults and ways to improve prescribing. Overall, evaluating, prescribing, monitoring, and deprescribing in older adults is a complex process that requires attention to detail and a considerable amount of time.

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Multimorbidity and Polypharmacy

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Abstract As individuals age, the likelihood of developing more than one chronic condition increases. The presence of more than one disease, or multimorbidity, often leads to treatment with multiple medications (polypharmacy). Unfortunately, polypharmacy may predispose older adults to a number of adverse consequences, including adverse drug reactions, potentially inappropriate prescribing/medications, nonadherence, functional status decline, geriatric syndromes, and mortality. This chapter will focus on the prevalence of multimorbidity among older adults, the epidemiology of polypharmacy in this population, and the negative clinical outcomes associated with the use of multiple medications.

Keywords Older adult · Polypharmacy · Multimorbidity · Potentially inappropriate prescribing

Introduction

As individuals age, the likelihood of developing more than one chronic condition increases. The presence of more than one disease, or multimorbidity, often leads to treatment with multiple medications (polypharmacy). Unfortunately, polypharmacy may predispose older adults to a number of adverse consequences. This chapter will focus on the prevalence of multimorbidity among older adults, the epidemiology of polypharmacy in this population, and the negative clinical outcomes associated with the use of multiple medications.

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S. Stegemann (ed.), *Developing Drug Products in an Aging Society*,
AAPS Advances in the Pharmaceutical Sciences Series 24,
DOI 10.1007/978-3-319-43099-7_25

Multimorbidity Among Older Adults

Advances in clinical practice and new medications to treat chronic illness have increased life expectancy for the overall population. Prolonged longevity, however, often results in the development of multiple diseases associated with aging (i.e., multimorbidity) [1]. Multimorbidity is formally defined as the "multiplicity of independent chronic diseases" or the "co-occurrence of two or more chronic conditions" and is quite common among older adults [2, 3]. For example, in the United States (US), 68 % of adults using fee-for-service Medicare have at least two chronic conditions. Of these Medicare beneficiaries, 23 % have 4–5 chronic medical conditions and 14 % have 6 or more [4]. Similar patterns are seen in the United Kingdom, with 6.75 million adults having at least two chronic conditions [5–7]. Unfortunately, clinical practice guidelines often fail to consider multimorbidity and thus recommend treatment for each disease state in isolation without considering the potential to precipitate polypharmacy.

Epidemiology of Polypharmacy

Definitions of Polypharmacy

Polypharmacy may be defined in two ways. The first definition focuses solely on number of drugs. Common thresholds for polypharmacy include five or nine medications, although these cut-points are somewhat arbitrary and may not always be clinically relevant. Alternatively, polypharmacy can be defined in the context of medication necessity, where a medication that lacks an indication, is ineffective, or represents a therapeutic duplication would qualify as polypharmacy [8, 9]. Though more clinically relevant, this approach requires review of all medications and is more difficult to implement in both research and practice [10].

Incidence and Prevalence of Polypharmacy

Regardless of definition, the incidence and prevalence of polypharmacy is increasing. In the US, the median number of medications taken by older adults increased from two to four between 1988 and 2010. Similarly, the proportion of older adults with polypharmacy (defined as five or more medications) tripled during the same period, from 13 to 39 % [11]. The rate of adults over the age of 65 taking at least four medications internationally is similar to the US at approximately 40 % [12].

Interestingly, these trends are found across healthcare settings. Among community-dwelling elders, 37 % of men and 36 % of women between 75 and 85 years old took at least five prescription medications. In those individuals with at

least one prescription medication, 47 % reported using an over-the-counter (OTC) medication and 54 % reported taking a dietary supplement [13]. Using necessity of medications as the measure of polypharmacy, a study within the Veterans Affairs (VA) Health System found approximately 60 % of older male outpatients took at least one unnecessary prescribed drug [9].

Similarly, one study found hospitalized adults aged 85 years or older were taking a median of 10 medications the month before admission [14]. Polypharmacy also seems to persist during hospitalization. For example, at hospital discharge, 40 % of older frail US Veterans were prescribed 5–8 medications, 37 % were prescribed 9 or more medications, and 60 % were prescribed at least one unnecessary drug [8]. An Italian study of older adults supports this finding, as the proportion of patients taking at least 5 medications increased from 52 % on hospital admission to 67 % at hospital discharge [15].

In nursing homes, polypharmacy (i.e., the use of 9 or medications) has been targeted as a quality indicator measure. Of note, the rates of polypharmacy in nursing homes may vary by location. For example, a 2004 US Nursing Home Survey found that approximately 40 % of nursing home patients were taking 9 or more medications, compared to only 15 % of Canadian nursing home patients [16, 17].

Polypharmacy Association with Multimorbidity

Polypharmacy associated with multimorbidity may be a result of guideline-driven management of chronic disease [18]. Charlesworth et al. [11] found individuals with zero medications had an average of 1.3 disease states compared with 4.1 conditions in those taking at least 5 medications. The aforementioned recent increases in medication use may reflect, in part, implementation of new clinical practice guidelines for hypertension, diabetes, cardiovascular health, and bone disease. For example, a patient with type 2 diabetes mellitus, stage II hypertension, dyslipidemia, and coronary artery disease may easily be prescribed six or more medications if the clinical practice guidelines for each disease are consulted independently.

Clinical Consequences of Polypharmacy

Differences in defining polypharmacy have resulted in ambiguity regarding potential clinical consequences associated with the use of multiple medications. Additionally, data is lacking for the application of medications in elderly patients with multimorbidity as most research focuses on the use of one drug per medical indication, and clinical trials generally exclude older adults with many disease states [19]. Among older adults, however, polypharmacy has been consistently identified as a risk factor for adverse drug reactions, potentially inappropriate

prescribing and potentially inappropriate medications, medication nonadherence, declining functional status and mortality, geriatric syndromes, malnutrition, and increased healthcare utilization among older adults [20].

Adverse Drug Reactions

An adverse drug event (ADE) is defined as "an injury due to a medication," and occurs in approximately 35 % of elderly outpatients and 40 % of elderly hospitalized patients [21, 22]. The most common type of ADE is an adverse drug reaction (ADR), which is characterized as a noxious and unintended response that occurs at normal doses of a medication [23]. Cardiovascular drugs, diuretics, nonsteroidal anti-inflammatory drugs, anticoagulants, antibiotics, anticonvulsants, and antidiabetic agents are commonly associated with ADRs in older adults, and are frequently prescribed for chronic conditions [22, 24, 25].

Polypharmacy is the only risk factor that has been consistently associated with the development of ADRs among the elderly. The risk of ADRs increases with the number of medications across practice settings. For example, Onder et al. [26] found that hospitalized older adults taking five or six medications were twice as likely, and those taking seven or more medications were four times as likely, to experience an ADR compared with those taking fewer medications. Similarly, outpatients taking at least five medications had an 88 % increased risk of ADRs [27]. Adverse effects among nursing home patients were twice as high in those individuals taking at least nine medications when compared to those patients taking fewer drugs [28].

The consequences of ADRs may be severe, including unplanned hospitalizations and death. Between 5 and 30 % of all unplanned hospitalizations among community-dwelling elderly have been attributed to ADRs [25, 29–31]. Moreover, taking at least five medications has been identified as a possible risk factor in the 250,000 annual emergency department visits stemming from an ADR [32]. One study of community-dwelling older adults who presented to the emergency department because of an ADR demonstrated that, compared to individuals taking one or two drugs, those taking 3–7 drugs or at least eight drugs were four times or six times more likely to experience an ADR, respectively [33].

Potentially Inappropriate Prescribing and Potentially Inappropriate Medications

Potentially inappropriate prescribing (PIP) occurs when the risk associated with the use of a specific medication outweighs any benefit [34, 35]. Three common types of PIP include drug–drug interactions, drug–disease interactions, and omission of necessary medications [36–38]. Because of pharmacokinetic changes associated with

aging as well as the likelihood of accruing comorbidities, older adults may be more prone to drug interactions and therapeutic omissions than younger adults [39]. Again, polypharmacy has been associated with an increased risk for all three forms of PIP.

Drug–drug interactions are prevalent among older adults, regardless of care setting. In a recent study examining the prevalence of interactions involving cytochrome enzymes, Doan found that 80 % of older adults had a potential drug–drug interaction, and the probability of an interaction increased with the number of drugs prescribed from 50 % with 5–9 medications to 100 % with ≥20 medications [40]. Furthermore, drug–drug interactions are a frequent cause of preventable ADEs and medication-related hospitalizations for the elderly [24]. In a prospective evaluation of medication records for older adults presenting to a Belgian emergency department, older age and number of medications were related to clinically relevant drug interactions [41].

Drug–disease interactions occur when a medication prescribed for one condition may exacerbate another disease. For example, an anticholinergic agent prescribed for urinary incontinence may worsen mental status in a patient with baseline cognitive impairment [34]. The frequency of drug–disease interactions ranges from 10 % in community-dwelling older adults to 40 % among frail hospitalized patients [42, 43]. As may be expected, the risk of a drug–disease interaction increases as both the number of drugs and the number of comorbidities increase [44].

Although perhaps counterintuitive, polypharmacy has also been identified as a risk factor for the omission of recommended therapies (e.g., an angiotensin-converting enzyme inhibitor after a myocardial infarction or warfarin in the presence of chronic atrial fibrillation), a phenomenon known as the treatment risk paradox [2]. Despite the availability of measures to assess underutilization such as the Assessment of Underuse (AOU) index or the Screening Tool to Alert doctors to Right Treatment (START) criteria, approximately 30 % of older adults have at least one prescribing omission [45, 46]. Older adults taking ≥5 drugs are more likely to be undertreated based on treatment guidelines as those receiving four or fewer medications [43, 47]. Additionally, the likelihood of undertreatment increases with the number of medications, with rates up to 80 % in those taking ≥17 medications [47].

In addition to PIP, polypharmacy has been linked with the selection of potentially inappropriate medications (PIM) in which the risk of use may outweigh any derived benefit [48]. Measures such as the Beers criteria, Screening Tool of Older Person's Prescriptions (STOPP), and Medication Appropriateness Index (MAI) are designed to help clinicians to avoid these medications [34, 35, 48]. However, use of PIM persists in older adults despite availability of safer alternatives. In one study of Taiwanese outpatients, the number of chronic medications was associated with a ninefold higher likelihood of having PIM identified by either the 2003 Beers or STOPP criteria [49]. Similarly, a Japanese study of more than 6000 adults older than 65 years found that patients receiving at least one PIM per the Beers criteria were taking significantly more medications compared to controls with no inappropriate medications, at 9.78 medications versus 4.75 medications, respectively [50].

Medication Nonadherence

Polypharmacy may result in complex regimens that make it difficult for patients to adhere to recommended therapies [51–55]. Nonadherence may lead to life-threatening disease progression, treatment failure, hospitalization, and adverse dug events [51, 53, 56]. Overall adherence among the elderly has been estimated to range from 43–100 % [51, 55]. Notably, polypharmacy is a stronger predictor for nonadherence than age [53]. Among patients taking at least four medications, nonadherence has been reported to be 35 % higher compared with those taking fewer than four medications [56].

Functional Status Decline and Mortality

Polypharmacy has also been associated with functional impairment in older patients. Among Finnish patients aged 75 or older, excessive polypharmacy (i.e., taking 10 or more medications) was associated with declining ability to perform instrumental activities of daily living [57]. A cross-sectional analysis of women enrolled in the Women's Health and Aging Study also illustrated that increasing numbers of prescription and over-the-counter medications were associated with increases in the number of domains of disability, including upper extremity function, mobility, self-care, and higher function tasks [58]. After adjusting for demographic characteristics, depression, cognition, and self-reported health, another study of Mexican American older adults taking five or more medications had significantly worse lower extremity function, including a repeated standing measure, balance measures, and gait speed [59]. In addition to functional status declines, polypharmacy has also been associated with an increased risk of mortality. For example, in one study of 5052 older adults in Spain, polypharmacy (≥6 medications) was associated with approximately a 1.8 times increased risk of mortality after controlling for baseline covariates [60].

Geriatric Syndromes

In traditional medical terminology, "syndrome" refers to a cluster of symptoms that frequently occur together and which suggest a particular disease. The term "geriatric syndrome," however, refers instead to a particular disease state (i.e., cognitive impairment/delirium, falls, frailty, dizziness, syncope, and urinary incontinence) that occurs "when the accumulated effects of impairments in multiple systems render [an older] person vulnerable to situational challenges" [61, 62]. Polypharmacy has been consistently identified as a potential risk factor for the development or exacerbation of these geriatric syndromes [10].

Cognitive Impairment and Delirium

Excessive polypharmacy has been associated with declines in cognitive function, as measured by a validated neuropsychological test [57]. Benzodiazepine, histamine type 2 receptor antagonist (H2RA), and anticholinergic medication classes may each exacerbate dementia independently. As such, it is reasonable to surmise that overlap of these classes may cause a dose-dependent worsening of cognitive impairment [34]. Additionally, a recent study has also suggested that cumulative exposure to multiple anticholinergic medications over time may increase the incident risk of dementia [63].

Unlike dementia, delirium is characterized by acute onset and fluctuating course in attention. Drugs are a common risk factor for delirium, and may be the precipitating cause in up to 40 % of cases [64]. Polypharmacy has been cited as an independent risk factor for delirium, and may be especially problematic when certain drug classes (i.e., opioids, benzodiazepines, and anticholinergics) are concomitantly prescribed [65–67]. For example, incident delirium occurred in approximately 18 % of older adults admitted to medical or surgical wards in a community-based hospital in Ontario, Canada. The number of medications received in the hospital was a significant risk factor for delirium, as was administration of opioids, long-acting benzodiazepines, and H2RAs [66]. Similarly, in a prospective cohort study of patients admitted to an acute geriatric ward from the emergency department, patients who were diagnosed with incident delirium within 72 h were more likely to have polypharmacy (>5 chronic medications) compared to those patients who did not develop delirium [68].

Falls and Fractures

Over 30 % of community-dwelling older adults fall each year; of those, nearly half have multiple falls [69]. Falls resulting in hip fractures are especially problematic, increasing morbidity and mortality among the elderly [70]. Polypharmacy has been associated with an increased risk of falls in community-dwelling and hospitalized older adults, as well as those residing in nursing homes [71–73]. In one study of older adults presenting to an Irish emergency department with a fall as the index event, 63 % had at least four medications dispensed per pharmacy claims data [74]. Increasing numbers of medications have been associated with a 19 % increased risk of falls in older adults with at least one fall, and 21 % increased risk of falls in those who were recurrent fallers (i.e., ≥2 falls) [75]. Polypharmacy has also been significantly associated with possible predictor indices of falls, including fall risk index, simple screening tests, and one-leg stand test [71]. Moreover, polypharmacy has a dose-response increased risk of fracture-specific hospitalizations for community-dwelling older adults, from 18 % for individuals with five to nine drugs to 54 % in those 10 or more medications [76].

Polypharmacy and psychotropic medications such as benzodiazepines, antidepressants, and antiepileptic drugs have independently been associated with an increased risk of falls and hip fractures among older adults [70, 73, 77]. Some studies suggest that it is the aggregate impact of multiple CNS medications, however, that may be more problematic. Hanlon and colleagues found that among older adults aged 70–79, both high-dose and concomitant use of multiple CNS medications (defined as antidepressants, antipsychotics, benzodiazepines, and opioid analgesics) increased the risk of recurrent falls compared with no use in a dose-dependent manner [78]. In a recent prospective, population-based cohort study, over 6600 Irish adults over at the age of 50 were asked about any falls, injurious falls, and medications. After adjusting for baseline covariates, polypharmacy (>4 medications) was only associated with injurious falls when an antidepressant or benzodiazepine was included in the medication profile, suggesting that types of medications rather than quantity prescribed may drive the association between polypharmacy and fractures [69].

Malnutrition

Polypharmacy has also been associated with poor nutritional status among older adults [57]. One study demonstrated that greater medication use was associated with decreased intake of fiber, fat-soluble vitamins and minerals, and increased intake of cholesterol, glucose, and sodium. These changes in nutritional components were in turn linked to decrements in self-reported physical health [79].

Increased Healthcare Utilization

In the US, Medicare beneficiaries with multimorbidity represent 90 % of all Medicare spending, due in part to higher medication costs [4, 80–82]. As the number of medications increase, so too does drug expenditure [83]. However, polypharmacy has also been associated with increases in healthcare utilization. One retrospective cohort study conducted among elderly Japanese patients found that patients taking at least five prescription medications were five times more likely to receive a PIM, which in turn was associated with 30 % greater healthcare utilization through increased outpatient visits, hospitalizations, and duration of hospital stays [50]. In another retrospective cohort study of more than 59,000 Taiwanese elders over a 10-year follow-up period, there was a dose-response relationship between number of medications and all-cause hospitalization, with a 34 % increased likelihood among those taking ≥5 medications and a 98 % increased likelihood among those taking ≥10 medications [76].

Current Implications and Future Directions

Due to concomitant disease states, age, or false impressions regarding potential benefit, older adults are often excluded from the clinical trials on which most clinical practice guidelines are based [84, 85]. Although excluding complex older adults may mitigate bias and reduce excessive risk to these patients, this exclusion also limits external validity [84]. For example, clinical benefit or associated risk may differ by age group or clusters of disease states [86, 87]. To extend the generalizability of appropriate recommendations to a "typical" older adult patient, pragmatic clinical trials must include elderly participants with multimorbidity and polypharmacy.

Increasing recognition of the challenges associated with caring for patients with multimorbidity is slowly changing the approach to managing chronic conditions. A 2012 collaboration between the Institute of Medicine and the Department of Health and Human Services has spurred professional societies to increasingly incorporate multimorbidity into recommendations included in clinical practice guidelines [88]. Furthermore, the National Quality Forum has provided guidance to develop quality measures appropriate for clinicians caring for patients with multimorbidity [88]. Future approaches to drug development must consider both polypharmacy and multimorbidity, particularly in older adult patients.

Conclusion

As the population continues to age and develop concomitant medical conditions, complex therapeutic regimens containing multiple medications will be more common. Polypharmacy is often the result of such multimorbidity, and may predispose older adults to geriatric syndromes. Although polypharmacy has been associated with adverse outcomes in the elderly, decreasing the absolute number of medications for patients with multimorbidity is challenging, as concomitant diseases often require pharmacotherapy. Moreover, it is often difficult to avoid drug classes most associated with ADRs as they are essential to the management of older persons. Therefore, careful consideration when prescribing medications to older adults is necessary due to potential for polypharmacy in the presence of multimorbidity.

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Vaccination in Older Adults

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Abstract Older people have an considerably increased risk for viral and bacterial infections. If these infections occur in elderly persons, the risk of severe complications and death is increased too. Ageing of the immune system and therefore risk of infections becomes significant as early as at an age of about 50+. Many infectious diseases endangering older, i.e. >50 years old humans are preventable by vaccinations. The most frequent vaccine-preventable diseases for older adults include seasonal influenza, pneumococcal diseases and herpes zoster. Every adult aged >50 years should therefore be vaccinated against these diseases. Standard vaccinations for younger adults like tetanus and hepatitis A are also mandatory for older adults as are special vaccinations for older persons living in or traveling to endemic areas. The effectiveness of many vaccines decreases with age. This implies that basic vaccinations for older adults should be started and completed as early as possible. Measures to increase vaccine effectiveness in persons with an "aged immune system" include the use of vaccines with adjuvants (e.g. MF 95 for seasonal influenza), high dose vaccines (efficiancy documented for trivalent influence vaccine), intradermal application, and shorter booster intervals (e.g. for tick-borne encephalitis).

Keywords Vaccination · Elderly · Influenza · Pneumococcal disease · Herpes zoster

Introduction

Older adults, especially multimorbid and frail patients, are one of the most vulnerable patient populations, which could benefit from vaccination as a preventive measure for long-term health protection. However, due to various reasons, vaccination of older adults is often insufficient.

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S. Stegemann (ed.), *Developing Drug Products in an Aging Society*,
AAPS Advances in the Pharmaceutical Sciences Series 24,
DOI 10.1007/978-3-319-43099-7_26

Starting at an age of about 50 years, the immune system becomes less efficient. This phenomenon is called “immunosenescence”. It results in an increased risk for infections and for complications from infections including death.

Many infections in older people are preventable by vaccination. However, due to the decrease in the immune function in ageing, vaccinations become less efficient in older age. The administration of more immunogenic vaccines can be beneficial in the elderly. Shorter booster intervals, vaccines with adjuvants and vaccines with higher antigen content may improve effectiveness of vaccination in people with an aged immune system. In live vaccines, there may be an increased risk for severe adverse reactions like Yellow Fever Vaccine Associated visceral disease. This is probably also due to the decrease in immune function.

The good news is that vaccinations can be boostered even in very old age efficiently. Complications from yellow fever vaccinations in old age have only occurred in people who received the vaccine for the first time of their live. There is no documented case of Yellow fever vaccine associated visceral disease from yellow fever booster in older people.

Due to their increased risk for infections and complications, the indication for vaccination of older people should be broad. Vaccination should be planned and conducted as early as possible as the immune system will decrease with increasing age.

Seasonal Influenza/Flu

The influenza virus is a major cause of vaccine-preventable disease mortality with 25–50 million annual cases of influenza estimated to occur in the USA resulting in 30,000–50,000 deaths, mainly in the elderly population [1].

Mortality from flu increases at an age over 50 years and is highest in people aged >65 years [2].

One important complication of influenza in the elderly are secondary bacterial infections. Pneumococcal pneumonia is a frequent complication of influenza in the elderly.

Local influenza outbreaks with fatal outcomes have occured in nursing homes [3, 4], hospitals [5] including geronto-psychiatric wards [6] and on cruise ships [7]. These incidences have demonstrated that especially within the older adult population vaccination against influenza should be considered as an important intervention to prevent transmission of infections across their living communities.

Influenza vaccination is effective in older adults [8] and especially in frail older people in preventing hospitalization and mortality from influenza [9].

In addition, influenza infection is associated with an increased incidence of cardiovascular events and vaccination against influenza has demonstrated to lower the risk of major adverse cardiovascular events. The greatest treatment effect is seen among the highest-risk patients with active coronary disease [10] for which vaccination against influenza should become standard practice.

The MF59-adjuvanted influenza vaccines are more immunogenic in elderly subjects than influenza vaccines without adjuvants and especially so in those with chronic disease. However, post-immunization reactions were more common in the group receiving the vaccine containing the adjuvant MF59. These reactions were predominantly mild and transient, and none were serious [11]

As a result, Flu vaccines containing MF59 are licensed for use in people with an age ≥ 65 years.

Interestingly, in the subgroup of >85 years a high dose trivalent vaccine was more effective in protecting against hospitalization for influenza or pneumonia when compared with the standard dose flu vaccine [12].

Moreover it was reported that vaccination of nursing staff may lower all cause mortality, influenza-like illness (ILI) of residents and lower sick leave from work of staff [13].

This has been recognized by the Center of Disease Control (CDC) by making influenza vaccination mandatory for all old people and staff caring for older people including nursing staff and physicians [14].

Intradermal application of influenza vaccine is an option too. In an RCT with 3707 persons aged 60–97 years, protective antibody titres were higher compared to persons vaccinated with a vaccine without adjuvans. Local side effects were more frequent in the group vaccinated with the intradermal vaccine [15]. Another study compared the intradermal application of an vaccine without adjuvans with an intramuscular application of an adjuvanted vaccine. Haemaggluitinine antibody titres and side effects did not differ significantly [16].

Key points flu/influenza vaccination:

- Every elderly person should be vaccinated against influenza annually
- Flu/influenza vaccination of the elderly reduces hospitalization, mortality from influenza and reduces the incidence of major cardiovascular events
- Due to the decreased response of the immune system in ageing, the elderly should be vaccinated with high dose influenza vaccines or with vaccines augmented with an adjuvants
- Everyone taking care for elderly people should be vaccinated against influenza

Pneumococcal Disease

Pneumococci are gram positive diplococci that can cause pneumonia, sepsis, otitis media, sinusitis and meningitis in humans. There are more than 90 different serotypes causing pneumococcal diseases. One in two people harbour pneumococci in their nasopharynx. Most of them have no symptoms but can spread these bacteria to other people. This is especially important for residents of nursing homes as asymptomatic carriers- staff and other residents can infect susceptible residents. In

contrast to influenza which has a peak incidence during the winter, pneumococcal diseases occur throughout the year with a higher incidence in the spring, autumn and winter ([17, 18, Saunders, Elsevier http://www.health.gov.au/internet/immunise/publishing.nsf/Content/handbook10-4-13).

The incidence of invasive pneumococcal disease is highest in children up to an age of 5 years and in people older than 50 years. Fortunately the mortality from invasive pneumococcal disease has declined during the last decades. However, mortality from pneumococcal disease is still very high (up to 60 %) in the elderly. About 90 % of all patients dying from pneumococcal infection are older than 60 years [19–22].

Streptococcus pneumoniae remains a major cause of morbidity and mortality throughout the world. To date, after the introduction of routine childhood immunization, elderly people (i.e., persons aged 65 years or older) suffer the greatest burden of pneumococcal disease in developed countries.

Risk factors for pneumococcal disease include advanced (>50 years) age, smoking (increases the risk fourfold), chronic alcohol abuse, chronic pulmonary diseases, congestive heart failure (increases the risk twofold), renal insufficiency, splenectomy and other forms of inborn and acquired immunosuppression. People living in nursing homes have an increased risk to acquire the infection [23].

All people over the age of 50 should be vaccinated against pneumococcal infection. Adults under age of 50 should be vaccinated if they have risk factors. However, some guidelines recommend pneumococcal vaccination for patients without risk factors only for those aged ≥ 60 years.

Vaccinating young children in the Veneto region (North of Italy) with the 13 valent conjugated vaccine resulted in a decrease of the rate in pneumonia requiring hospitalisation of children under the age of 4 years. In contrast, the rate of hospitalisation because of pneumonia increased in people with an age of >80 years in the same period in this region [24]. The Invasive Pneumococcal Disease IPD epidemiology in the 65+ is undergoing change due to indirect effects of childhood immunisation. According to a Quasi-Poisson regression model 13 valent pneumococcal conjugate vaccination Invasive Pneumococcal Disease (PCV13-IPD will probably decrease by 71 % from 58 (95 % prediction interval 55–61) cases in 2014/15 to 17 (6–52) in 2018/19 and PPV23-IPD by 32 % from 168 (162–175) to 115 (49–313) cases [25].

The prevalence of non-PCV13 serotypes in Germany has already increased significantly between July 2007 and June 2014, with 15A and 23B being the most strongly increasing serotypes of all. Both serotypes show a high proportion of penicillin non-susceptibility [26].

At present, two anti-pneumococcal vaccines are licensed for adults: the 23-valent pneumococcal polysaccharide vaccine (PPV23, Pneumovax 23®) and the 13-valent pneumococcal conjugate vaccine (PCV13, Prevenar 13®).

13-Valent Pneumococcal Conjugate Vaccine (PCV13, Prevenar 13®)

PCV13 is capable of inducing serotype-specific antibodies in sera of infants, and has been suggested to reduce nasopharyngeal carriage of vaccine-type pneumococci in children [27]. Vaccine-type IPD and carriage in non-targeted populations consistently decreased after PCV introduction, with the magnitude of decrease growing over time [28]. The main advantage of PCV13 is that it may be more effective than PPV23 against community acquired pneumonia (CAP), but a major limitation is that it is directed against strains that are likely to be greatly reduced in the population since its introduction in childhood immunization. [29].

PCV is licensed for all ages. In adults without risk factors, it is licensed for prevention of pneumococcal disease for people aged 50 years and above. The preferred route of application is intramuscular. In case of contraindications (e.g. bleeding disorders or anticoagulation) it may be administered subcutaneously.

23-Valent Pneumococcal Polysaccharide Vaccine (PPV23, Pneumovax 23®)

Clinical studies of 6- and 12-valent pneumococcal capsular polysaccharide vaccines were carried out in controlled studies among young-gold miners in South Africa. The 6-valent vaccine afforded 76 % reduction in cases of laboratory-verified pneumococcal pneumonia caused by the homologous types, and there was 92 % reduction in the cases afforded by the 12-valent vaccine [30]. About 82 % of clinically relevant serotypes are covered by the PPV 23 vaccine.

A Cochrane review analysing 25 studies showed efficacy against IPD with no statistical heterogeneity. Furthermore efficacy against all-cause pneumonia in low-income countries in the general population was shown. Vaccine efficacy against primary outcomes appeared poorer in adults with chronic illness [31].

Vaccine effectiveness of PPV23 is lower in patients aged 80 years and older and those with high risk medical conditions [32].

Compared to PCV13, one disadvantage of PPV23 is that it may be less effective than PCV13 against CAP but a major advantage is that it may provide protection against ten additional serotypes. Repeated vaccination might be less effective, an effect named “hyporesponsiveness”. However, numerous studies have challenged this phenomenon in the context of PPV23 vaccination and hyporesponsiveness has also been seen after vaccination with PCV. As other polysaccharide vaccines, the 23-valent pneumococcal polysaccharide vaccine PPV23 does not lead to mucosal immunity.

No interference was observed with antibody responses to influenza or pneumococcal antigens when an inactivated influenza vaccine and PPV23 were administered concomitantly [33]. If indicated, influenza vaccination should be administered at the same time to improve compliance.

Revaccination with pneumococcal vaccines:

Currently, revaccination with either 23-valent pneumococcal polysaccharide vaccine (PPV23) or 13-valent pneumococcal conjugate vaccine (PCV13) is recommended only for those at highest risk of invasive pneumococcal disease (IPD)-namely immunodeficiency and chronic kidney disease-3 years (for children under 10 years of age) and 5 years (for children over 10 years of age and for adults) after initial vaccination. However, a recent review supports PPV23 revaccination in both adult and pediatric populations [34].

In an open-label study, patients (n = 251) 3–6 months after allogeneic HSCT (hematopoietic stem cell transplant) received 3 doses of 13-valent pneumococcal conjugate vaccine (PCV13) at 1-month intervals, a fourth dose 6 months later, and 1 dose of 23-valent pneumococcal polysaccharide vaccine (PPSV23) 1 month later. Dose 4 was associated with increased local and systemic reactions, but the overall safety profile of a 4-dose regimen was considered acceptable [35].

Immunogenicity trials have shown that PCV13 elicits an equal or greater immune response than PPSV23 for most of the serotypes that both vaccines share [36]. However, clinical relevance of this finding is unclear. Anti-pneumococcal opsonophagocytic activity (OPA) titers in the older adults who received PPV23 after initial PCV13 were significantly higher than those following a first PPV23 for 10 of the 13 serotypes. In adults 50–64 years of age, initial vaccination with PCV13 establishes an immune state that results in recall anti-pneumococcal responses upon subsequent vaccination with either conjugated or free polysaccharide vaccine. In contrast, initial vaccination with PPV23 results in an immune state in which subsequent PPV23 administration yields generally lower responses compared with the initial responses [37].

At present, a strategy for the best protection may be to vaccinate patients with risk factors for pneumococcal disease with PCV13 first and give-for coverage of additional serotypes-a booster with PPV23 at least 2 months apart [38]. Additional boosters may be done at 5 years intervals for those with risk factors.

Research for pneumococcal vaccines should concentrate on the development of conjugated vaccines covering all or as many as possible clinically relevant serotypes.

Key points pneumococcal vaccination:

- All people aged ≥ 50 years should receive pneumococcal vaccination
- Those with risk factors should get a booster
- PCV13 should be administered before PPV23 when possible
- The vaccines currently available do not cover all clinically relevant serotypes

Herpes Zoster (Shingles)

Varicella zoster virus (VZV) is capable to cause two diseases: The primary infection usually takes place during childhood. Nearly all (>99 %) of all adults aged 40 years and over are seropositive for varicella zoster virus. After healing of the primary infection, the virus persists lifelong in the body—the virus concentration is highest in the spinal roots. After many years or decades of persistence the varicella zoster virus may be reactivated causing herpes zoster. Reactivation is caused by decrease of the cell-mediated immunity. The most frequent reason for a decrease of the cell-mediated immunity is advanced age, which already is relevant at 50 years and above. Other reasons for decreased cell- mediated immunity include infection with HIV and treatment with immunosuppressive medications (corticosteroids, agents for treatment of rheumatologic diseases and chemotherapy). Hematologic malignancies may cause reactivation of the varicella zoster virus as do most solid tumors [39–43].

More than two thirds of all herpes zoster cases occur in people aged 50 years and over [40]. Complications of herpes zoster include postherpetic neuralgia (PHN), which is the most frequent complication, Zoster ophthalmicus [44], bacterial superinfection of the skin and visceral complications as a result of varicella zoster viremia like pneumonia and hepatitis [45]. The rate of post zoster neuralgias is increasing with age [46].

Vaccination against herpes zoster boosters the VZV-specific cell-mediated immunity [47]. The herpes zoster vaccine available currently is a life vaccine based on the VZV-line "Oka", the antigen concentration is 14fold compared to the varicella vaccine Varivax®. It is licensed for the prevention of herpes zoster and postherpetic neuralgia (PHN) for persons aged 50 years and over. The dosage is 0.65 ml subcutaneous. As it is a life vaccine, immunosuppressive therapy and AIDS are contraindications for this vaccination.

The shingle prevention study (SPS) [48] showed the safety and efficacy for persons aged 60 years and older: Incidence of herpes zoster, postherpetic neuralgia and burden of illness were reduced significantly over the observation period of 7 years compared to persons without vaccination. Local reactions at the injection side occurred in 48.3 % of persons vaccinated compared to 16, 6 % in the placebo group whereas systemic side effects did not differ between patients vaccinated and the placebo group [48]. The effectiveness was confirmed in a "real life study" for persons ≥ 60 years of age [49]. Herpes zoster vaccination for the elderly has been implemented in England since 2013 [50]. Furthermore, the good safety profile was confirmed in "real life": The Vaccine Safety Datalink (VSD) study [51] including 193 083 adults ≥ 50 years of age showed a slightly increased risk for allergic reactions after vaccination, otherwise the safety profile was good. The Phase 4 Kaiser Permanente Northern California Study (KPNC) showed a good safety profile, too [52].

The ZEST Study [53] showed the safety and efficacy of the vaccine for adults aged 50–59 years. Incidence of herpes zoster was reduced by 70 % by the vaccination in this age group.

A randomized controlled trial with patients aged ≥ 50 years of age who had herpes zoster >5 years ago showed no serious adverse events within 28 days post vaccination as well as a good immune response measured by antibody titers. There is no data on clinical effectiveness in this study. Nevertheless, the National Advisory Committee on Immunization (NACI, Canada) the Advisory Committee on Immunization Practices (ACIP, USA), the Public Health England (PHE) and the Australian Technical Advisory Group on Immunisation (ATAGI) recommend vaccination of persons who have suffered from herpes zoster. The optimal interval for vaccination after an episode of herpes zoster is not generally defined currently. According to ACIP guidelines, symptoms of the disease have to be ceased before vaccination [54]. Australian [55] and Canadian [56] guidelines recommend vaccination at least one year after the herpes zoster episode whereas Cohen [57] recommends an interval of 3 years.

Patients who have had two or more episodes of shingles in one year should have immunological investigation prior to vaccination.

Currently, trials with an inactivated vaccine for herpes zoster are conducted. In a phase 3 trial funded by GlaxoSmithKline Biologicals, the inactivated experimental HZ/su-vaccine containing the VZV-Glykoprotein E, showed a good protection during the first 3 years after vaccination: 7.698 participants were vaccinated. During follow up (3, 2 years) only 6 developed Herpes zoster, whereas in the placebo group (7.713 persons) 210 developed Herpes zoster. Vaccine efficacy in adults who were 70 years of age or older was similar to that in the other two age groups [58].

In contrast to the live vaccine, two doses of the inactivated vaccine were applied 2 months apart. Currently there are no long term data on the protective effect of the HZ/su vaccine beyond 3 years-maybe boosters are necessary to maintain the protective effect. Local side effects -especially pain at the injection site—were significantly increased in the verum group. Furthermore grade 3 symptoms that prevented normal activities and systemic reactions were reported which may decrease compliance for the second dose and boosters.

A phase 1/2a clinical trial with 3 doses of an investigational adjuvanted HZ subunit vaccine (HZ/su) showed a clinically acceptable safety profile in HIV-infected adults [59].

Key points herpes zoster/shingles vaccination:

- Everyone ≥ 50 years should be vaccinated against herpes zoster
- The vaccination reduces the incidence of herpes zoster and postherpetic neuralgia (PHN)
- Zoster vaccine should be given regardless of a history of shingles

Other Vaccinations Relevant for Older Adults

Tetanus Vaccination

More than 80 % of all tetanus cases in developed countries occur in subjects aged >64 years. In Poland, 21 cases of tetanus were reported in 2001. All cases except one occurred among people of age 50 or more. Case fatality rate associated with tetanus was 33.3 % and increased with age [60]. A higher proportion of females with respect to males were reported in this age group. Over two thirds of subjects $\geq$65 years in Italy had tetanus antibody levels <0.01 IU/ml. Tetanus is a continuing problem even in developed countries. Most cases occur in older adults, especially elderly women [61].

Elderly subjects should therefore get regular boosters for tetanus every 10 years. Postexposure prophylaxis for tetanus is mandatory for all elderly subjects without current vaccination and those with unknown vaccination status.

Key point: Nearly all cases of tetanus in developed countries occur in the elderly. Therefore tetanus vaccination and regular boosters are mandatory.

Pertussis, Diphtheria, Poliomyelitis

Pertussis may –seldom- cause persistent cough in adults. Older adults should be vaccinated against pertussis at least once. Revaccinations are probably necessary at least every 10 years. Beside protecting the elderly, this vaccination also protects children who have contact with them. Pertussis vaccination is preferably applied in combination with tetanus, diphtheria and poliomyelitis vaccination. As poliomyelitis cases are increasing at present in Pakistan, Afghanistan and certain african countries, vaccination against this disease is important for the elderly, too due to the risk of polio spread to polio-free countries.

Tick-Borne Encephalitis

Adults 50 years and older often have severe disease, often resulting in permanent/irreversible neuropsychiatric damage. Mortality is increased 15fold compared to younger adults. Due to decreasing immune function, boosters are recommended no later than every 3 years for adults over age 50 in contrast to every 5 years for younger adults [62].

Key point:

Vaccination against tick-borne encephalitis should therefore be offered elderly subjects living in or traveling to endemic areas. Bossters should be given every 3 years for those aged >50 years.

Hepatitis A

Morbidity from Hepatitis A (HAV) is increased in the elderly. The mean age at death among decendents with HAV infection was 76.2 years in 2011 [63].

Middle aged adults show lower antibody titres and seroconversion rates compared to young adults after vaccination against hepatitis A. Data are available on the immunogenicity and efficacy of hepatitis A vaccine in the elderly (>60 years) but data on seroprotection for HAV are limited [64].

Key point:

Elderly patients should have protection for hepatitis A. Those without protecting antibodies should be vaccinated.

Yellow Fever

Severe adverse effects due to yellow fever vaccination, including hospitalization and death, are more frequent in the elderly [65]. Khromava et al. updated the estimates of the age-adjusted reporting rates of serious adverse events, yellow fever vaccine (YEL)-associated viscerotropic disease (YEL-AVD) and Yellow fever-associated neurotropic disease (YEL-AND). They found that the reporting rates of serious adverse events were significantly higher among vaccinees aged 60 years than among those 19–29 years of age [66]. From 1990 to the present, the number of cases (n = 31) and deaths (n = 12) from YEL-AVD in travelers has exceeded the reports of yellow fever (YF; n = 6) acquired by natural infection, raising the question whether the risk of vaccination exceeds the benefit in travelers. For many years, the risk of vaccine-related illness and death was similar to the risk of illness and death from natural infection with YF in South America. Africa posed a substantially higher estimated risk of wild-type YF than vaccine-related injury. Multiple factors should be considered in making decisions about YF vaccination, including specific destination, season of the year, local evidence for YF transmission, likelihood of exposure to vector mosquitoes and individual risk factors for YEL-AVD, with the goal of increasing vaccine coverage for travel to high-risk areas and reducing unnecessary vaccination [67]. A systematic review revealed two out of the five studies showing a significantly higher rate of YEL-AVD among the elderly population [68] Mass yellow fever vaccination should be avoided in areas that present extremely low risk of yellow fever, especially for the elderly [69].

The risk for YEL-AND and YEL-AVD is not increased in persons >60 boostered with the vaccine.

Key point:

Persons over 60 years of age may have an increased risk for serious adverse events (YEL-AVD and YEL-AND) when vaccinated with Yellow Fever live vaccine for

the first time. Even if the absolute risk for these complications is very low, people over 60 years of age should be only vaccinated when living in or traveling to areas with high risk of yellow fever.

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Medication Reviews in Older Adults

Emily P. Peron and Kelechi C. Ogbonna

Abstract Increased scrutiny of medication regimens by healthcare professionals across the continuum of care is to be expected as the worldwide population ages. Similarly, pharmaceutical companies will be expected to develop new drugs that are safe and effective for older adults, including those who are frail, have complex comorbidities, and/or are prescribed multiple medications. Understanding the medication review process from the clinician perspective can help pharmaceutical industry professionals involved in drug development for older adults anticipate potential post-marketing pitfalls.

Keywords Medication reconciliation · Older patients · Polypharmacy · Medication management · Medication review tools

Introduction

On average, older adults (adults 65 years or older) use more medications than people under the age of 65 [1–3]. The prevalence of medication users among those 65 years and older has not changed in recent years; however, the prevalence of polypharmacy (defined as the use of multiple medications or as the use of more medications than are medically necessary) has increased over time [3, 4]. For example, in the United States between 1988 and 2010, the median number of prescription medications used by community-dwelling older adults doubled from two to four [3]. Likewise, the proportion of older adults taking five or more prescription medications nearly tripled over the same time frame, from 12.8 % (3.7 million older Americans) to 39 % (15.1 million older Americans). Increasing use of non-prescription medications and dietary supplements has also been described, further complicating the picture of polypharmacy [1, 5].

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S. Stegemann (ed.), *Developing Drug Products in an Aging Society*,
AAPS Advances in the Pharmaceutical Sciences Series 24,
DOI 10.1007/978-3-319-43099-7_27

The increase in multiple medication-taking among older adults is likely due at least in part to the epidemiologic transition toward death from noncommunicable diseases (rather than from infectious and parasitic infections) [6]. Appropriateness of medication prescribing is of concern, particularly in light of the pharmacokinetic and pharmacodynamic changes that occur with aging [3, 4, 7]. Adding to the complexity of care for older adults is the fact that discrepancies often exist between what medications patients are taking and the medication lists obtained by their healthcare providers [8, 9]. In one study, 27 % of older adults who reported skipping doses or stopping a medication because of adverse drug events or perceived ineffectiveness had not alerted their physician. Similarly, 39 % of those who reported cost-related non-adherence had not talked to their physician about the problem [10]. This gap in communication between older adults and their physicians surrounding prescription medications is noteworthy, as both age and polypharmacy are significantly correlated with the presence of medication discrepancies [8].

While compiling an accurate medication list is a necessary and important component of the medication review process, the presence of an accurate medication list is not sufficient by itself [11]. Expert review by a healthcare professional is essential for identifying medication discrepancies and assessing for medication-related problems. A medication-related problem is classically defined as "an undesirable event experienced by a patient that involves, or is suspected to involve, drug therapy, and actually or potentially interferes with a desired patient outcome." [12]. Medication-related problems can generally be classified into one (or more) of the following categories: untreated indication, medication use without an indication, subtherapeutic dosing, supratherapeutic dosing, improper drug selection/inappropriate prescribing, drug interaction, adverse drug reaction, and medication non-adherence/failure to receive the medication [13–15]. Older adults are at increased risk of experiencing medication-related problems and are four times more likely than those under 65 years of age to be hospitalized as a result of experiencing an adverse drug reaction [16]. Just as medical problems can present atypically in older adults, the symptoms of medication-related problems in older adults are often different than what would be expected for someone under the age of 65. Adding to this complexity, the presenting symptoms of medication-related problems are often nonspecific and resemble geriatric syndromes (e.g., altered mental status, fatigue, falling, constipation, blurred vision, depression, and dizziness) [17]. In many cases, a patient will experience an adverse drug event, which will be misinterpreted as a new medical condition, and they will receive medication for that indication as well. This slippery slope of treating an unidentified medication-related problem with another medication is known as the "prescribing cascade" [18]. Statements from two 1995 publications remain relevant more than 30 years later and highlight the potential for medications to both help and harm, thereby serving as a reminder of the need for ongoing medication reviews for all older adults: "Medications are probably the

single most important health care technology in preventing illness, disability, and death in the geriatric population" [19]; however, "any symptom in an elderly patient should be considered a drug side effect until proven otherwise" [20].

The suspicion or presence of a medication-related problem should prompt healthcare professionals to conduct a thorough medication review. The following list of risk factors may help guide healthcare professionals to target those patients with the greatest potential of experiencing a medication-related problem: presence of six or more current medical diagnoses; presence of polypharmacy (defined in this case as 9 or more medications or 12 or more doses of medications per day); use of high-risk, narrow therapeutic range, or potentially inappropriate medications (PIMs); history of adverse drugs reaction; and presence of certain patient characteristics (i.e., 85 years of age or older, low body weight, body mass index less than 22 kg/m^2, reduced renal function [creatinine clearance less than 50 mL/min]) [21].

At the very least, an annual medication review should be conducted for all older adults, regardless of number of medications, living situation, or functional status [22–24].

The Medication Review

Put simply, the medication review is a thorough discussion about all of a patient's medications in relation to the patient's clinical health conditions [25]. Ideally, therapeutic optimization is achieved by reducing or eliminating inappropriate or unnecessary medications, addressing suboptimal medication adherence, and answering patient and/or caregiver questions. While pharmacists are commonly sought to provide medication reviews, healthcare professionals from other disciplines may be responsible for conducting medication reviews depending on their location, practice model, and interest level.

Differences in practice settings, study designs, interventions tested, and outcomes measured make it difficult to draw conclusions about the large-scale impact of medication reviews on morbidity and mortality; however, systematic reviews suggest that emergency department contacts and 30-day readmission rates can be improved by conducting medication reviews as part of a comprehensive program of care [26–28]. Perhaps some variability in implementation and evaluation strategies is fitting. Just as each patient's medication regimen is unique to them, so too may be their healthcare professional's approach to the medication review. Numerous frameworks have been suggested [18, 23, 24, 29, 30], but there is no internationally agreed upon standard for how to conduct a medication review. Three commonly employed approaches are described below:

Medication Reconciliation

According to The Joint Commission (an accrediting and certifying body organization for healthcare programs in the United States), medication reconciliation is the process by which "a clinician compares the medications a patient should be using (and is actually using) to the new medications that are ordered for the patient and resolves any discrepancies" [31]. Medication reconciliation is intended to be completed at all points of transitions in care, including changes in setting, service, healthcare professional, and level of care. The Joint Commission further highlights a five-step process: Develop a list of current medications, Develop a list of medications to be prescribed, Compare the medications on the two lists, Make clinical decisions based on the comparison, and Communicate the new list to appropriate caregivers and to the patient [32]. Since 2005, medication reconciliation has been included in The Joint Commission's Hospital National Patient Safety Goals, and thus it is most often associated with the hospital setting.

Previous studies on the impact of medication reconciliation have identified unintentional medication discrepancies in 3.4–98.2 % of patients [33]. Omission of a regularly used medication has been shown to be the most common medication error at the time of hospital admission [34]. Medication reconciliation in the hospital setting has consistently been associated with a reduction in medication discrepancies and adverse drug events [35]. As part of a multifactorial intervention, medication reconciliation has also been shown to improve emergency department visits and readmissions within 30 days of discharge [28]. Deficiencies in training and communication across interprofessional healthcare teams can present barriers to implementation of a successful medication reconciliation program [36].

Brown Bag Review

The term Brown Bag Review, first introduced in 1982, was coined by the brown paper bags that were given by pharmacists to patients to encourage them to bring all of their home medications to the pharmacy (or another convenient location) for review [37]. More than 40 years later, this term is still used to describe one method of determining what medications a patient is taking and how those medications are taken.

While an in-home medication review may garner more complete information about a patient's medication list and medication-taking behaviors, this approach is not always feasible [38]. As such, Brown Bag Reviews may be conducted in a variety of settings, such as in a pharmacy or at a community-sponsored event. Increasingly, physicians are asking patients to bring their medications to regularly scheduled office visits. If patients cannot travel to the healthcare professional's location, it is possible to conduct a Brown Bag Review over the phone. Generally though, the presence of the patient's medication vials and the face-to-face nature of

the encounter sets the Brown Bag Review apart from medication reconciliation, which may rely on a patient's medication vials, medication list, or memory [39].

Regardless of the setting, prior to a Brown Bag Review, the patient should be instructed to gather all of their medications (i.e., prescription drugs, over-the-counter drugs, vitamins, dietary supplements, and herbal remedies). The patient should be specifically instructed to bring with them any topical, liquid, injected, or inhaled medications, as these drug formulations may be overlooked. If the patient uses any organizational tools, such as a pillbox, these should be brought to the Brown Bag Review as well. If the patient does not manage his or her own medications, then the patient's caregiver should be present. It is important for the clinician to carefully review each medication, as patients may inadvertently gather discontinued medications, family members' medications, and their current medications in the same bag [36].

During the Brown Bag Review, medications are typically reviewed one-by-one. For example, the healthcare professional may pick up each medication, open the vial, and ask the patient "What do you take this medicine for?" [39] then request that the patient "Tell me how you take this medication" [40]. This approach allows the healthcare professional to identify any variations between how the medication was prescribed or intended to be used and how the patient is actually taking the medication. Understanding a patient's medication-taking behaviors can assist the healthcare professional with appropriately evaluating the medication regimen for therapeutic effectiveness, safety, and cost-effectiveness [40, 41]. If any adverse drug events, knowledge deficits, or access-to-care issues are identified, they can begin to be addressed at that time.

In one study of 45-min pharmacist-run Brown Bag Reviews at senior centers and high-rises, older adult attendees (n = 85 subjects aged 60 years or older taking five or more medications) indicated satisfaction with the experience [42]. 97 % indicated that they trusted the answers of the pharmacists and would attend a Brown Bag Review event again. 95 % indicated that they knew more about their medications after the Brown Bag Review. Within three months after the Brown Bag Review, more than half (51 %) had discussed the drug-related problem recommendations with their doctors, and 25 % more were planning to do so. In this way, pharmacists and other users of the Brown Bag Review method may help close the healthcare communication loop and aid in improving patient satisfaction.

Medication Therapy Management

Appropriate management of the complex older adult does not end at problem identification. It is essential that the healthcare professional and patient work together to resolve each issue. Medication Therapy Management (MTM) exemplifies this process. MTM is a broad range of clinical services provided by a pharmacist aimed at optimizing drug therapy and improving therapeutic outcomes [43, 44].

MTM consists of five core elements: Medication therapy review, Development of a Personal Medication Record, Creation of a Medication-Related Action Plan, Intervention and/or referral, and Documentation and follow-up [43, 44]. The first two elements are focused on gathering accurate information to ensure informed decision-making. The pharmacist and patient must have an open dialogue about all medications the patient is taking in order to create the Personal Medication Record. This careful review then leads to the creation of the Medication-Related Action Plan. The Medication-Related Action Plan is a patient-centered document that details medication-related problems and proposed actions. In the final stages of the MTM process the pharmacist prioritizes medication-related problems, counsels the patient, communicates with the healthcare team, and provides referrals as necessary. A plan for targeted or comprehensive follow-up with the pharmacist conducting the MTM session should also be scheduled. As is the case with any medication review, the exact line of questioning a pharmacist follows may depend on the pharmacist and patient, but the specific documentation requirements of MTM set it apart from other approaches to the medication review. Patients should leave the MTM session with a Personal Medication Record and Medication-Related Action Plan that has been jointly discussed and agreed upon by the pharmacist and patient.

The MTM process ensures that each patient receives the intended benefit of each medication while minimizing potential risk [45]. The clear and defined steps of the MTM process lend it to being effectively implemented across care settings and by pharmacists with differing levels of clinical training. In one large integrated health care system, pharmacist provision of an MTM program was associated with improved clinical outcomes, cost savings, and high patient satisfaction [46]. Further encouraging the growth of MTM as a pharmacist business model is the fact that the American Medical Association has created pharmacist-specific Current Procedural Terminology codes, thus enabling pharmacists to potentially bill for the MTM services they provide [47].

Medication Review Tools

Factors complicating the appropriate use of medications in older adults are the underrepresentation of older adults in clinical trials and a lack of healthcare professionals formally trained in geriatrics. Although not a replacement for formal training in geriatrics, a variety of explicit and implicit tools are available to assist healthcare professionals in evaluating medications prescribed for and used by older adults. Explicit criteria, while useful in evaluating drug trends, are not intended to offer a one-size-fits-all approach for patients; as in any clinical situation, the healthcare professional's judgment and specific needs of the patient should be

prioritized. Moreover, explicit criteria are only updated periodically, while the medical literature is ever-changing, so it is important to consider that some medication-specific recommendations may be out of date within just a few months.

The Beers Criteria [48] (Explicit Criteria)

The Beers Criteria is the oldest and perhaps best known of the geriatric-focused medication review tools available to healthcare professionals. Since the introduction of the Beers Criteria in 1991, four updated iterations have been published (in 1997, 2003, 2012, and 2015). With a focus on improving care for older adults by reducing exposure to PIMs, the 2015 Beers Criteria identified more than 40 medications or medication classes across five categories: PIMs for older adults outside the palliative care and hospice setting, including medications to avoid in many or most older adults; medications for older adults with specific diseases or syndromes to avoid; medications to be used with caution; clinically important non-anti-infective drug–drug interactions; and non-anti-infective medications to avoid or the dosage of which should be adjusted based on an individual's kidney function. Consistent with the 2012 criteria, the 2015 Beers Criteria provides quality and strength of evidence designations in addition to a rationale and recommendation for each medication. All updated Beers Criteria resources, including a separate document listing the references each recommendation, are available at GeriatricsCareOnline.org. A list of alternative drug and nondrug therapies has also been released [49].

The Screening Tool of Older Persons' Prescriptions and Screening Tool to Alert Doctors to Right Treatment [50] Criteria (Explicit Criteria)

The Screening Tool of Older Persons' Prescriptions (STOPP) and the Screening Tool to Alert doctors to Right Treatment (START) criteria were based on Delphi consensus of experts from Europe. STOPP is similar to the Beers Criteria in that it identifies PIMs for older adults. START is aimed at addressing potential prescribing omissions and offers suggestions for commonly undertreated conditions, thereby filling a gap left unaddressed by the Beers Criteria and the STOPP. The final list of 114 criteria—80 STOPP criteria and 34 START criteria—and supporting references are available online in Supplementary data through *Age and Ageing*.

Assessing Care of Vulnerable Elders [51] (Explicit Criteria)

RAND Health's Assessing Care of Vulnerable Elders (ACOVE) project has been ongoing since 2000, with the latest edition (ACOVE-3) released in 2007. ACOVE-3 identifies quality-of-care process indicators to evaluate the care provided to older adults who are at highest risk for serious declines in health and function. Among the 392 quality indicators addressing 26 medical conditions are 19 quality indicators specifically related to medication use in older adults. The quality indicators are unique in that they offer process-based and medication-specific recommendations and even address drug monitoring and patient education. Supporting evidence for each quality indicator is provided within the guidance document.

Medication Appropriateness Index [52] (Implicit Criteria)

The Medication Appropriateness Index (MAI), originally developed in 1992, is a list of 10 questions aimed at assessing the appropriateness of a single medication for an individual patient. When used as directed, the MAI is time-consuming to conduct and score, thereby limiting its utility in the clinical setting; however, the questions (e.g., "Is there an indication for the drug?" and "Is this drug the least expensive alternative compared to others of equal utility?") can be used to guide the medication review process. The MAI also asks directed questions to evaluate the correctness and practicality of medication directions, which may provide a gentle reminder to the healthcare professional to address health literacy. The MAI poses questions related to drug–drug and drug–disease interactions, but without explicit recommendations regarding overuse or underuse, significant geriatric medication therapy knowledge is required on the part of the healthcare professional.

Implications for Drug Development

The emphasis on evidence-based medicine in the most recent Beers and STOPP/START criteria is consistent with a shift in geriatric clinical practice away from reliance on anecdotal data or expert opinion. Supplementary lists of peer-reviewed references and alternative drug and non-drug therapies further enable clinicians to practice evidence-based medicine as their patients age beyond 65 years. Systematic exclusion of older adults from randomized controlled trials [53] increases the risk for older adults to experience medication-related problems once a drug reaches the market; for this reason, prescribers or healthcare professionals conducting medication reviews often suggest older drug entities about which they feel more is known in the geriatric population. New drug treatment

options are sometimes even limited for older adults when the disease or syndrome is most commonly seen in the geriatric population (e.g., Parkinson disease, Alzheimer disease). Indeed, pharmaceutical companies must consider the unique needs of an aging population in order to improve success in drug development.

Dosage form design and product packaging are of particular importance when developing drugs for older adults. For example, limitations in dexterity may make it difficult for a patient to access an over-the-counter product intended to help treat their osteoarthritis pain. A tablet that is too big may lead a patient to chew an extended-release dosage formulation, while a tablet too small may be dropped on the floor when the patient is putting it into or taking it out of their pillbox. A medication with a short half-life may not be taken multiple times a day as recommended, putting the patient at risk of an adverse drug withdrawal event. Finally, a drug not tested in older adults during the development phase may be found to have an increased risk of morbidity or mortality in the geriatric population only after it has been released to the general public. Medication reviews exists to help ensure the ongoing safety and efficacy of medication regimens and to identify opportunities to improve care. Situations like the ones just described often come to light during the medication review process and may lead healthcare professionals to suggest alternate therapies. Another consideration that commonly arises during medication reviews is cost. Concerns over medication costs are expressed in the inpatient and outpatient settings by patients, providers, and health systems alike, and indeed they account for a considerable proportion of overall healthcare costs [54]. By considering the needs of older adults—those who may stand to benefit most from drug treatment—during the drug development process, pharmaceutical companies have the opportunity to help clinicians and health systems ultimately meet the triple aim of providing better care for individuals, improving the patient experience of care, and reducing the per capita cost of healthcare [55].

Conclusion

The medication review provides an opportunity to strengthen trust and enhance communication between the healthcare professional and patient. Moreover, the clinician can better understand the patient's unique medication needs and potentially resolve medication-related problems to improve health outcomes. As chronic disease burden increases and medication-taking behaviors among older adults change, the need for specially trained healthcare professionals will continue to rise [56]. Increased scrutiny of medication regimens by healthcare professionals across the continuum of care is to be expected as the worldwide population ages. Similarly, pharmaceutical companies will be expected to develop drugs that are safe and effective for older adults, including those who are frail, have complex comorbidities, and/or are prescribed multiple medications.

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The Personalization of Drug Therapy for Elderly Patients

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Abstract Personalized drug therapy, described as tailoring the selection of drug and drug dosing to a given patient in order to optimize efficacy and minimize toxicity, has been a longstanding goal in medicine. This goal has been met at various levels of success for different patients and patient populations. While specific dosing regimens and labeling recommendations based on clinical trial data are available for adults, they are frequently lacking for pediatrics and geriatrics. These special patient populations are clinically understudied resulting in a lack of data to be used for establishing respective optimal drug and dosing regimen. While regulators around the globe have responded to this unmet medical need by establishing or updating pediatric guidance documents, the situation is much less evolved for geriatrics. However, there is a plethora of ongoing research, which ranges from reaching expert consensus to genotyping frailty that is geared towards improving the situation. The objective of this book chapter is to introduce and discuss personalized medicine approaches for the elderly patient.

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S. Stegemann (ed.), *Developing Drug Products in an Aging Society*,
AAPS Advances in the Pharmaceutical Sciences Series 24,
DOI 10.1007/978-3-319-43099-7_28

Keywords Biomarkers · Metabolism · Personalized medicine · Pharmacogenetics · CYP complexes · Glomerular filtration rate (GFR) · Beers criteria · Physiologically based pharmacokinetic (PBPK) models

Introduction

The purpose of personalizing drug therapy is to optimize the benefit and minimize the harm of medication interventions on a patient-by-patient basis [1]. This objective has been pursued by physicians and other health care providers for decades at various levels of sophistication, with varying degrees of success. There are many approaches to personalization, such as therapeutic drug monitoring (TDM) or, more recently, the assessment of pharmacogenomic (genetic) and non-genetic biomarkers [2]. The terms pharmacogenetics, and pharmacogenomics have been used interchangeably in recent years to describe the study of genetic variations and their impact on how patients respond to medications.

Translating the information obtained from these approaches into appropriate doses and dosing regimens for a specific drug label frequently requires the use of quantitative decision support tools. These quantitative decision support tools contain a wide variety of mathematical and statistical approaches, of which population pharmacokinetic/pharmacodynamic (PK/PD) or physiologically based (PB) PK/PD modeling and simulation approaches, have proven particularly valuable for drug development and regulatory decision-making as they allow for the integration of data from both preclinical and clinical settings into a single, unifying approach [3]. However, "one size fits all" dosing, also referred to as flat dosing, is still the most widely used dosing approach in clinical practice for many therapeutic indications. In addition, flat dosing approaches are frequently associated with high interindividual variability in treatment response, which can have serious consequences for the patient, especially for drugs with a narrow therapeutic index. Some patients may receive a subtherapeutic dose, whereas others may experience drug-mediated adverse events (ADEs). Interindividual variability is particularly problematic for heterogeneous populations receiving multiple medications, such as the older adults, due to highly variable organ function, comorbid illnesses, multiple medications (and thus, a high drug-drug interaction (DDI) potential), compliance [4] as well as genetic factors.

The International Conference on Harmonization (ICH) Efficacy Guideline E7 defines the elderly patient as a person of the standard retirement age 65 years or older [5]. A further split of the elderly population into "young old" (65–74 years), the "old" (75–84 years), and the "oldest old" (≥85 years) has been suggested in order to account for interindividual variability in this large age group. However, due to multiple comorbidities, age-related organ impairment, as well as physical and cognitive impairments, the use of "chronological age" (years since birth) may or may not accurately reflect the patient's actual "biological age". There are many approaches of defining biological age. In general, biological age is often referred to

as "a quantity expressing the true global state of an aging organism or its true life expectancy". As a consequence, flat dosing regimens that fail to take the biological age into account and are unlikely to appropriately meet the medication needs of each elderly patient.

According to the fourth version of the ICH E7 Guideline, clinical trials should: (i) be reflective of the demographics of the target patient population and (ii) be comparable to trials of other drugs for the same indication. In fact, the ICH E7 guideline recommends that at least 100 geriatric patients should be included in phase 2 or 3 clinical trials in order to appropriately account for comorbidities and poly-medications in the elderly patient. However, these recommendations are frequently not fully implemented as, for example, shown by phase II and III type 2 diabetes mellitus trials, where only 1 % of the studied patient population was older than 75 years [6]. In addition, the outcome of a typical trial may not be accurately reflective of clinical reality because elderly subjects included in clinical trials are typically young, healthy old, who are using few medications [7]. As a consequence, FDA recommends that the marketing applications for new drugs should also include data for elderly patients of all subgroups [8]. In addition, these subgroups should be considerable in size and comparable in patient numbers, if possible, in order to appropriately evaluate the impact of aging on the drug's efficacy and safety [9].

Despite these efforts, there continues to be a strong bias in the patients enrolled in clinical trials. The young old and "healthy" elderly patients are more likely to enroll in clinical drug trials than, for example, the oldest old. Clinical trials also continue to exclude patients that are at high risk for ADEs. Efforts to enroll a diverse sample of older adult patients is hampered by the fact that frail oldest-old patients are less likely to drive and are in-effect more likely to be geographically isolated from studies conducted at large medical centers. Other older adults that are generally underrepresented in clinical trial settings include patients with dementia, nonnative speakers, functionally dependent (nursing home or homebound) and those who are unable to consent to participate in a research study [10]. Similarly, patients with advanced comorbid illnesses are also often excluded. It is not surprising that 61 % of new cancers are diagnosed in the elderly, whereas only 25 % of oncology trial participants can be assigned to this age group [11]. In addition, insufficient data is often collected in geriatric clinical trials intended to develop geriatric-specific dosing information [12]. This shortcoming becomes particularly apparent when comparing specific dosing recommendations for other special patient populations, such as children and hepatically or renally impaired patients, to those for the elderly, where "start low, go slow" recommendations are common. This is in part due to the fact that the dynamic interplay between age, lifestyle, comorbidity and resulting poly-medication are to date insufficiently understood as indicated by recent studies, where an increase in mortality was observed in older adults as the result of over-treating hypertension and diabetes mellitus [13]. Furthermore, the development and application of drug treatments in the elderly is limited by the lack of reliable biomarkers in this special patient population.

The objective of this book chapter is to provide a comprehensive overview of potential personalized medicine approaches in the elderly. Following a brief

summary of the physiology in the elderly, we will discuss the different personalized medicine approaches currently employed in this special patient population with focus on respective quantitative approaches and how they relate to biomarkers of aging before concluding with a brief description of the current challenges and opportunities for geriatric personalized medicine.

Physiology in the Elderly

Although aging is a continuous process, patients are assigned to different age groups in order to distinguish between physiological differences between segments of the patient population [14]. A chronological age classification, as feasible in children as an indicator of physiological maturation, is not applicable at the other end of the age scale. Age-related changes in cellular, tissue, and organ function are highly heterogeneous. Moreover, the probability of suffering from multiple illnesses arises in elderly patients leading to unrecoverable physiological capacity loss, such as a continuous decrease in the metabolic capacity of the liver over time. Biological aging is consequently a dynamic process with a large degree of variability among older adult patients.

The rate of decline in organ function is not uniform and is affected by environmental factors (i.e., smoking, alcohol, diet) as well as comorbid illnesses (i.e., diabetes, hypertension, chronic obstructive lung disease, and atherosclerosis). Acute medical illness and hospitalization can dramatically accelerate the biological aging process, while patients may also partially recover following therapeutic and lifestyle interventions [15].

In certain patient populations, such as pediatrics and obstetrics, there is much physiologic homogeneity allowing for nomograms that can be used to estimate proper drug dosing. Developing respective dose–exposure–response relationships is typically more problematic in elderly patients due to highly variable organ function (s) and, thus, altered pharmacokinetics resulting from interindividual differences in the drug(s) absorption, distribution, metabolism, and elimination.

Clinical case:

Mrs. Fields is a 76-year-old nursing home resident with longstanding diabetes (with neuropathy and nephropathy), hypertension, chronic kidney disease (baseline serum creatinine = 2.1 mg/dL) peripheral vascular disease, and a stroke history that has left her bedbound with severe atrophy and contractures in all four extremities. She has been on clopidogrel for the last 2 years and has had her metformin recently discontinued due to concern about her renal impairment. A percutaneous endoscopic gastrostomy (PEG) tube was placed due to the patient's dysphagia and severe weight loss. One evening the nursing home staff noted that she was delirious. She was transferred to the emergency department at a local hospital. On physical exam in the emergency department she had an infected ischemic ulcer of her left great toe. The wound is extremely painful. The staff had concerns regarding the dosing of antibiotics and narcotic pain medication.

Absorption

While passive intestinal permeability seems to be unaffected by aging [16], the bioavailability of high permeable drugs may be affected by reduced gastrointestinal blood flow. The altered gastrointestinal (GI) tract physiology, including prolonged colonic transit time may impair the oral absorption of low permeable and low soluble compounds [17]. The impact of age-related changes in gut wall metabolism and transporter is still not fully understood. In addition, absorption may be hindered by common factors, such as the use of enteral nutritional support (tube feeding), mineral supplements, and antiulcer drugs, as well as disease states, such as diabetic gastroparesis.

Distribution

Drug distribution is impacted by changes in body composition and quantified by the apparent volume of distribution (V_d), a hypothetical reference volume that relates the amount of drug in the body to drug concentrations measured in blood or plasma. There is an age-related decrease in fat-free (e.g., hydrophilic muscle) mass and an increase in body fat [18], which leads to a shift in the body's fluid distribution [19]. For many drugs this age effect is well studied and it is generally accepted that lipophilic drugs, such as diazepam, show a higher V_d [20], while hydrophilic drugs, such as Levodopa, tend to have a smaller V_d [21–23]. Furthermore, reduced albumin concentrations [24, 25] and hematocrit values [26, 27] in elderly patients may lead to an increase level of the drug's unbound fraction in blood or plasma [28]. In contrast, α_1-acid glycoprotein levels are assumed to be unchanged in healthy elderly [25]. These physiological differences in the elderly might lead to changes in the drug's V_d, which does not necessarily change its clearance, but will have to be considered for loading dose selection.

Metabolism

In general, hepatically eliminated drugs can be classified according to the extent to which drug is cleared from blood or plasma upon first pass through the liver. This classification system can also be used for evaluating the impact of aging on a drug's hepatic clearance. The clearance of drugs which are eliminated to more than 70 % from blood or plasma upon passage through the liver (i.e., high-extraction drugs) is mainly restricted by the liver blood flow, whereas the clearance of low extraction drugs (cleared to less than 30 %) is dependent on the metabolic capacity of the eliminating organ, in this case, the liver. While the majority of studies do not report a significant impact of age on enzyme-mediated processes, Cytochrome P450

(CYP)-mediated processes seem to be affected by aging [29]. One of the major CYP complexes, the 2C subfamily, is involved in the metabolism of frequently used drugs in the elderly age group, such as anticonvulsants and nonsteroidal anti-inflammatory drugs [30]. CYP2C19 is also needed for the enzymatic activation of clopidogrel, a widely used anticoagulant, into its pharmacologically active metabolite [31]. While the expression of CYP2C9 and CYP2C19 appears to be unaffected by age, respective clearance rates of drugs eliminated via these pathways seem to be decreasing. The CYP2D subfamily, on the other hand, seems to maintain its metabolic capacity with increasing age [30, 32, 33]. The situation seems less clear-cut for the CYP3A4 subfamily since contradicting reports exist in the literature [30]. In addition, conjugation, acetylation, and sulfation are generally not influenced by age [34], while glucuronidation may be impaired in the elderly [35]. It should also be noted that compared to children, where metabolites that are different from those in adults can be formed, no such difference seems to exist in the elderly [30].

Elimination

Hepatic clearance is generally decreased for high-extraction drugs due to the reduced blood flow and liver mass with increasing age [36]. Due to this physiological impairment, clearance rates of verapamil, [37] and β-adrenoceptor antagonist [38] are reduced. This has a clinical implication on the maintenance dose, which needs to be adjusted by a prolonged dosing interval.

Changes in renal clearance with aging, on the other hand, are associated with a loss of glomeruli and a decline in the number of functional nephrons, particularly in the renal cortex [39, 40]. These changes result in a reduced number of functional tubular and glomerular cells and, thus, a reduced glomerular filtration rate (GFR) [41, 42]. Long-standing diabetes and hypertension may further impair kidney function. Most antibiotic drugs and morphine are cleared primarily via the kidneys and are consequently strongly affected by altered renal function in the elderly patient [43].

Although, exogenous markers like the gold standard inulin [44] as well as ^{125}Iothalamate [45], ^{99m}Tc-diethylenetriaminepentaacetic acid (Tc-DTPA) [46], ^{51}Cr-ethylenediaminetetraacetic acid (Cr-EDTA) [46, 47] and iohexol [48], represent the most precise estimation of human GFR, their clinical applicability is limited. Results of studies using unlabeled markers should be interpreted with care as they may underestimate the GFR [45].

GFR is most frequently estimated in the clinic through the use of the Cockcroft-Gault equation using the patient's serum creatinine concentrations [49]. This equation may yield unreliable GFR estimates in the elderly patient as renal clearance and its approximations are also dependent on food intake [50], lipid levels [51], blood pressure [52], muscle mass, and race [53]. Even small changes in serum creatinine can result in under- or over-prediction of GFR since the relationship between serum

creatinine and GFR is not linear. In order to avoid these pitfalls and to support clinicians with more reliable GFR estimates in elderly individuals, several groups developed equations based on larger cohort assessments [44, 54, 55]. Most of the newer equations use cystatin C, a second endogenous marker. It too can be influenced by age, especially in males, smoking, obesity, height, or by elevated levels of C-reactive protein [56]. The application of these newer equations is still limited by the fact that most of the dosing recommendations for renally cleared drugs are still based on GFR measures that were approximated using the Cockcroft-Gault equation.

Personalized Medicine Approaches in the Elderly

There is a clear need for personalized medicine approaches to improve the quality of medication treatment for older adult patients. We will use the following sections of this book chapter to introduce and discuss some of the most commonly employed personalized medicine approaches in the elderly at increasing levels of complexity. We will start with a description of clinical guidelines for healthcare professionals that are derived from expert consensus before elaborating on the use of quantitative clinical pharmacology applications and genome-based approaches for single and multiple drug therapies.

Expert Consensus-Based Personalized Medicine Approaches

Clinical Case:

Mr. Smith is an 86-year-old man with a diagnosis of severe depression who was brought to the physician's office with complaints of poor appetite, poor concentration, depressed mood, and insomnia. Mr. Smith was on no medications for his depression and both he and his family are reluctant to try a medication. Upon further questioning, their concerns stem from his experience taking amitriptyline which made him confused, lethargic, and unable to urinate. He then tried fluoxetine which lead to severe diarrhea and abdominal pain. After much reassurance from his doctor, Mr. Smith is ready to try a new medication for his depression.

Beers Criteria

The Beers' Criteria for inappropriate medications were developed by expert consensus in 1991 and have subsequently been updated in 1997, 2003, 2012, and 2015 [57–61]. The criteria were developed to "guide" health care professionals with prescribing for older adult patients. Although they have been used as a quality of care measure by many health care systems, these criteria were not intended to imply that these medications are absolutely "contraindicated." In addition, many newer

medications are not included in the criteria and issues of inappropriate drug interactions and drug class duplications are not included [62]. Studies to date have had trouble demonstrating a correlation between compliance with the Beers Criteria and improved clinical outcomes.

STOPP/START Criteria

The Screening Tool of Older People's Prescriptions (STOPP) and the Screening Tool to Alert to Right Treatment (START) were originated in 2008 [63] and updated in 2015 [64]. Like the Beers Criteria, STOPP Criteria were developed through expert review using Delphi consensus methodology to identify medications to be avoided in older adults. The START Criteria were through a similar methodology to identify medication prescribing omissions. Direct comparisons between the most recent versions of the STOPP and the Beers criteria to predict adverse drug events do not exist.

One of the major concerns about using a "hit list" approach includes lack of allowance for exceptions (e.g., palliative care). Another concern is the potential misuse of a "beneficial" drug in medically complex frail older adult patients. Budnitz et al. [65] investigated hospital admissions due to ADEs and pointed out that only a few drugs cause the majority of hospitalizations. These drugs are mainly the anticoagulant warfarin and the insulins. However, the retrospective review of emergency room and hospital claims data may underestimate the true risk of adverse events in older adults as many medication side effects (i.e., dry mouth, incontinence, anorexia, confusion) are not captured [66].

Quantitative Personalized Medicine Approaches

Mathematical and statistical approaches that integrate information on drugs, diseases, and clinical trials at both the population and the individual patient level have been increasingly used in drug development and regulatory decision-making since the 1990s. Compared to the expert consensus-based approaches, quantitative personalized medicine approaches, also referred to as *pharmacometrics*, use information on the dynamic interplay between drug(s), pharmacology, disease pathogenesis, and intrinsic as well as extrinsic patient factors to characterize and predict age-dependent physiologic changes in the elderly. The majority of the currently employed pharmacometric approaches are descriptive (nonmechanistic or empirical) in nature and use statistically robust criteria to characterize the data. While these approaches have proven valuable for drug development and regulatory decision-making, they have found limited application at the bedside. This is primarily due to a lack of practitioner friendly decision support tool interfaces, which is needed to facilitate the translation of biomarker data and other patient-specific

information into actionable treatment recommendations, without burdening practitioners with the underlying technical details [67].

Pharmacometric Scaling Approaches

Pharmacometric scaling approaches are intended to extrapolate dose—and concentration ranges from populations that have been extensively studied to special patient populations, such as pediatrics or geriatrics, where respective information is missing. While exposure matching using allometric scaling is most commonly employed in pediatrics [68], age- or organ function-based (e.g., creatinine clearance) scaling approaches are frequently employed in geriatrics [69]. For example, the FDA label for apixaban [70], a novel anticoagulant, recommends age-, weight-, and serum creatinine-based dosing. The normal dose is 5 mg twice daily except for patients with two of the three factors: age ≥80 years, bodyweight ≤60 kg and serum creatinine ≥1.5 mg/dL. Under these circumstances the dose is reduced to half of the normal dosing. Similarly for edoxaban, the recommended dose is 60 mg daily with a normal renal function (50–95 mL/min) which is reduced to 30 mg daily for reduced kidney function with a creatinine clearance of 15–50 mL/min. "Scaling by size only" approaches typically face limitations in the absence of dose proportionality. For pediatrics, this nonlinearity is typically the result of enzyme ontogeny, whereas other factors, such as changes in body composition, play a bigger role in the elderly. Ideal body weights based on age do not exist for geriatric patients and hypervolemic states from congestive heart failure, cirrhosis, and nephrotic syndrome are common. Even accurate height and weight measures may be unattainable in patients who are bedridden or have amputations, contractures, or kyphosis.

Although pharmacometric scaling approaches are typically empirical and drug-centric in nature, they are routinely employed for dose selection. They may further allow for evaluation of covariates, both genetic and nongenetic, in order to account for interindividual differences in patients' dose–concentration–response relationships [71]. Once established and qualified, drug-disease models could be used to address specific questions, either during drug development or clinical practice, using clinical trial simulations [72]. Clinical trial simulations are an innovative pharmacostatistical analysis technique that allows for the simulation of the dose–concentration–response (PK/PD) relationship of a drug or combination of drugs in a given patient population, which can then be prospectively qualified in a clinical trial setting. If linked to epidemiological, biological, clinical or real world patient data, these trial simulations can be used to generate a virtual elderly patient population (cf. Fig. 1) [73], which could estimate the benefit-risk relationship of a given treatment in a given patient population [74].

This approach consequently can help to decrease the number of studies to be conducted, which is essential for special patient populations, such as the older adults, given the practical limitations outlined earlier in this chapter. Combining these innovative simulation approaches with prospective clinical trials may

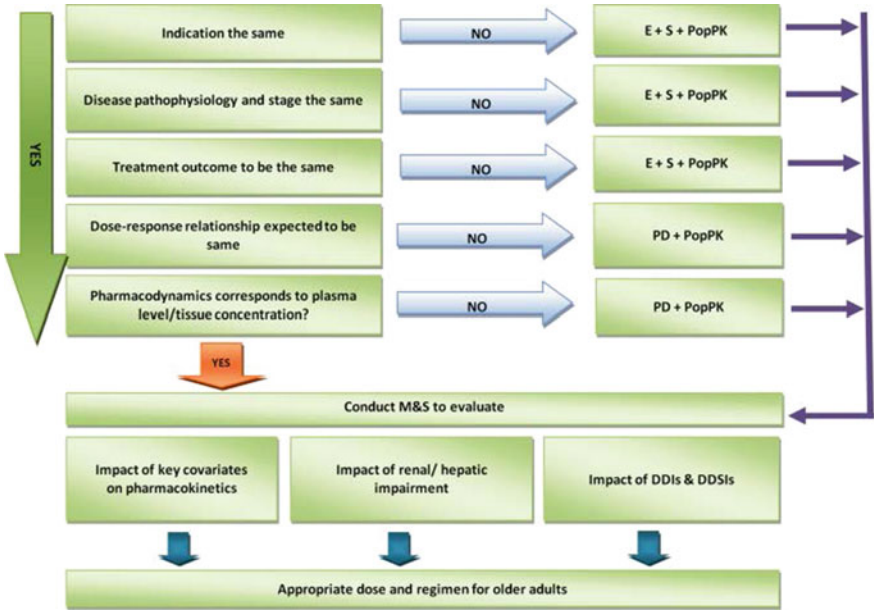

Fig. 1 Proposed decision tree for generating/synthesizing evidence of safety and efficacy of a medicine in the older adult population. *PD* pharmacodynamics; *E* efficacy; *S* safety; *PopPK* population pharmacokinetics; *DDI* drug–drug interactions; *DDSI* drug/disease interactions; *M&S* modelling and simulation. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

therefore help to establish respective geriatric dosing recommendations, while reducing cost, and burden to the elderly patient.

Figure 2 shows an example of how a combination of quantitative clinical pharmacology approaches, such as population pharmacokinetic (PopPK) analysis, and clinical trials can serve as a tool for establishing safe and effective dosing regimen for older adults. It also outlines the impact of critical assumptions on the selection of a drug and dosing regimen. For example, if it is reasonable to assume that: (i) the indication, (ii) disease pathophysiology and disease state, and (iii) treatment outcome are the same in adults and older adults, full-blown efficacy and safety trials may not be necessary as an abbreviated development program may provide equally informative data. If, in addition, the dose-response relationship is expected to be the same in adults and older adults and changes in pharmacodynamics endpoints correlate to changes in blood or plasma concentrations, modeling and simulation (M&S) approaches may be used to evaluate the impact of key covariates, organ impairments such as renal or hepatic function, and drug-drug interactions (DDIs) on the dose–concentration–response relationship in older adults based on respective clinical information in adults. This approach has been extensively used in clinical drug development for children [75] and could also be used for extrapolation of adult dosing regimens to older adults.

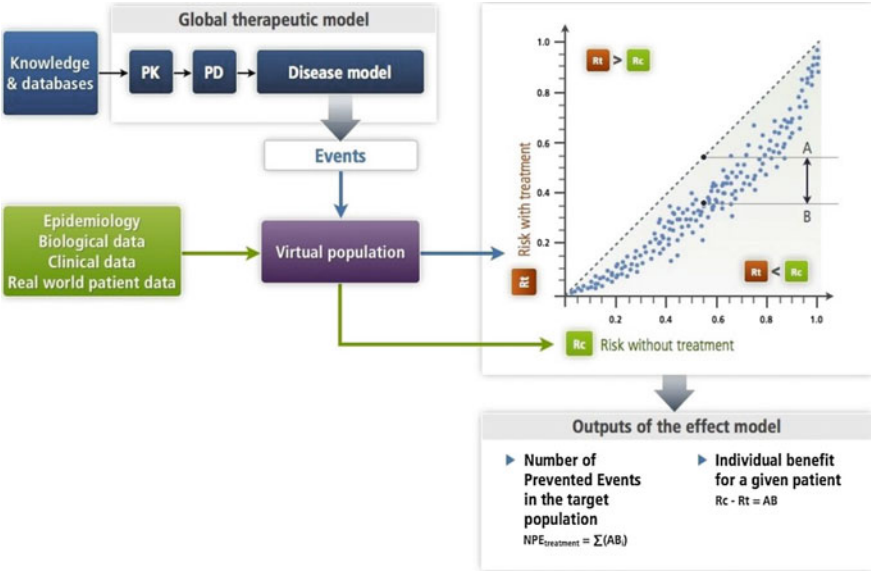

Fig. 2 Workflow of a clinical trial simulation for comparing benefit and risk in the presence (Rt) and absence of treatment (Rc). Legend was modified from reference [73]

Physiologically Based Approaches

Physiologically based pharmacokinetic (PBPK) models are set up to characterize and predict drug exposure at different target sites by dividing the biological system into a number of compartments, each representing a different organ or tissue. These organs or tissues are connected through arterial and venous blood flow. PBPK models consist of three distinct parts: (1) drug-specific parameters: characterize the physicochemical properties of the drug (e.g., pKa, molecular weight, logP) and can be predicted on the basis of in vitro assays. (2) system-specific parameters: describe the functioning of the underlying physiological system and can differ between and within species, e.g., between adult and elderly patients. (3) trial design parameters (also referred to as intrinsic and extrinsic factors): determine the impact of intrinsic (e.g., demographics, disease state, genetic constitution) and extrinsic (e.g., diet, smoking, drug-drug interactions) factors on the drug's pharmacokinetics [68]. PBPK models have been primarily used to characterize and predict the impact of drug-drug-interactions (DDIs) but have also gained popularity for pediatrics, pharmacogenomics, organ impairment, drug absorption, and combinations thereof [76].

As such, PBPK approaches are uniquely positioned for evaluating the dose–exposure relationship in clinically understudied populations. While the strengths of this approach have been increasingly leveraged for dose selection in pediatrics [77, 78], it has found little application for the elderly thus far. However, there are multiple ongoing initiatives that are attempting to expand PBPK modeling and

simulation platforms to geriatrics by accounting for changes in the underlying pathophysiology with age. Once established and qualified, these expanded PBPK models may also serve as a platform for evaluating the impact of age as well as the impact of clinically relevant factors, such as DDIs, in elderly patients in the absence of actual clinical trial data. They may also serve as screening tools during early stages of drug development to facilitate decision-making with respect to selecting the best compound and formulation [79].

It should be noted, however, that in isolation, information on PK is of limited clinical utility and needs to be linked to the corresponding PD response. While the impact of age on a drug's PK is typically easier to assess, respective PD changes remain understudied. Drug effects are most often based on a complex molecular cascade [80]. For example, the density of receptors with increased age can be reduced as shown for α-adrenergic [81] or μ receptors [82]. There may be increased sensitivity to various central nervous system drugs, including benzodiazepines, halothane, metoclopramide, and narcotic analgesics, as patients become older [40]. While some of these effects can be studied directly in the elderly patient, our understanding of others relies on extrapolated animal data.

The use of integrated PBPK&PD models allow for the integration of information on relevant PK (e.g., changes in metabolic capacity, or transporter expression) and PD (e.g., changes in receptor expression and activity) processes into a unifying approach [83, 84]. Once established and qualified, these PBPK&PD models can be used for individualization of drug and dosing regimen in elderly patients by accounting for differences in, e.g., organ function or genetic make-up [85]. However, the implementation and predictive performance of these approaches, will rely on the use of clinically relevant biomarkers.

Biomarkers for the Elderly

Clinical Case:

Mr. Marx is a 66-year-old man with diabetes, hypertension, and a history of cirrhosis secondary to alcohol abuse who was admitted to the hospital with sepsis. On exam he was noted to have a fever of 102 degrees Fahrenheit, abdominal pain, abdominal ascites, and extensive lower extremity edema. Initial laboratory analysis showed a white blood cell count of 22,100, a serum creatinine of 2.1 mg/dL, a serum albumin of 1.7 g/dL, and a serum C-reactive protein (CRP) of 54 mg/L. Peritoneal fluid analysis revealed 530 polymorphonuclear neutrophils/mm^3, a total protein of 1.5 g/dL and a glucose level of 38 mg/dL. He was started on cefotaxime for empiric treatment for spontaneous bacterial peritonitis. He was started on a benzodiazepine for the prevention of delirium tremors. Two days later his right leg became more swollen and painful. A lower extremity ultrasound revealed a deep vein thrombosis. Anticoagulation will need to be started at a safe and effective dose.

In general, a *biomarker* is defined by the Biomarkers Definitions Working Group (BDWG) as "a characteristic that is objectively measured and evaluated as an

indicator of normal biologic processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention" [86]. Given that many bodily functions either change or lose physiologic capacity as subjects become older, it is currently unclear which biomarkers identified in healthy adults are equally applicable for the elderly patient.

Different authors have proposed different biomarker classification systems [87]. For example, Danhof et al. proposed seven types of biomarkers:

type 0: genotype/phenotype determining drug response
type 1: concentration of drug or drug metabolite
type 2: molecular target occupancy
type 3: molecular target activation
type 4: physiological measure
type 5: pathophysiological measures
type 6: clinical rating scales

Others have proposed a more technical classification of biomarkers [88]: laboratory-based biomarkers (e.g., serum creatinine), functional biomarkers (e.g., PET imaging) and genetic biomarkers (e.g., cytochrome genotype). Both of these classification systems show some overlap and allow to assess the functionality of biological systems as well as changes therein. Features of the ideal biomarker are listed in Table 1 [88].

The development of biomarkers for aging remains problematic. For example, proinflammatory cytokines, such as interleukin-6 (IL-6) or Tumor Necrosis Factor-α (TNF-α), are routinely used as biomarkers for characterizing morbidity and mortality [89, 90]. Despite the fact that there is increased morbidity and mortality in the elderly, these biomarkers may also be elevated in other age groups. As a consequence, they cannot be used in isolation to accurately predict outcomes in the elderly patient.

Some disease-specific biomarkers, such as the Framingham Risk score for cardiovascular disease, typically combine a number of factors (e.g., ECG, blood pressure), which increases its specificity. In the case of the Framingham Risk Score, its applicability to the "old" and "oldest old" is limited due to the fact that scoring it

Table 1 Features of the ideal biomarker [29]

• Patient acceptability
• In vivo and in vitro stability
• Adequate analytical (functional) sensitivity
• Reproducibility and accuracy
• Feasibility
• Complete assay automation
• International standardization
• Low cost
• Low biological variation
• Reference range and cut-off values tested for gender, age, and ethnicity dependence
• Good diagnostic and prognostic accuracy
• Cost-effectiveness

has been established and qualified for subjects under the age of 75 years. There are attempts of overcoming this limitation with the study of other biomarkers. N-terminal pro-brain natriuretic peptide (NT-pro-BNP) [88] and homocysteine are examples of emerging biomarkers for cardiovascular disease, including individuals above the age of 85 years [91, 92]. Research into the development of frailty indices are examples of such individual risk scores that are typically composed of disease, physical activity, and lifestyle related factors and how they relate to an elderly patients prospects of health and disease [93].

The example of disease-specific biomarkers indicates that a combination of markers and scores may be more specific and, thus, more relevant for characterizing organ functionality and mortality in elderly patients. A combination of low albumin, high C-reactive protein (CRP), low cholesterol, and high IL-6 to an inflammatory summary score has been shown to be more predictive of the risk of hospitalization and mortality compared to each single marker alone [94, 95]. Ultimately, however, we are interested in optimizing drug therapy in individual elderly patients [93].

One of the main challenges with biomarkers that are accurately reflective of the patient's health status is that, they not always easy to measure, particularly since individuals do not age at the same rate [96]. Biomarkers intended for the use in medically complex geriatric patients consequently need to be qualified, ideally in a prospective fashion, in order to avoid unspecific bias.

Genome-Based Personalization Approaches

During the past two decades, the quest for identifying the genetic basis for aging has sparked an entire field of research with focus on cellular aging processes. The study of nutrient signaling pathways, reactive oxygen species (i.e., "free radicals"), telomere length, DNA repair mechanisms, and mitochondrial dysfunction have been of particular interest here as they represent cellular mechanisms for senescence and apoptosis [97]. Studies in centenarians (age ≥100 years) have gained prominence in evaluating the genetic basis for extreme longevity and the delay of frailty [98]. Several genes, such as APOE and FOXO3A, have been associated with aging [99] during Genome Wide Association Studies (GWAS). GWAS studies determine statistical correlations the genomic variability among individuals and the phenotypic variability among the same individuals [100]. It should be noted though that other factors, such as environment and/or comorbidities, also play a significant role for aging. The dynamic interplay between these factors and the patient's genome will ultimately determine the aging process within certain physiological limits.

Genotype Guided Dosing

Genotype guided dosing regimens are available for many drugs [101–103]. They are intended to enable safer and more effective drug treatment by identifying genetic sources of interindividual variability in response to drug treatment. For example, warfarin, a substrate of polymorphic CYP2C9, shows an impact of age and weight on its PK/PD relationship. Although, age was not identified as the most significant covariate, dose reduction of 0.2 mg per decade, independent of CYP2C9 phenotype and weight, is recommended [104]. The development of comprehensive dosing strategies that consider all possible covariates including age and genotype are time consuming and expensive [105, 106]. It may be important to consider an elderly patient's genotype when attempting to personalize drug therapy if a genetic component to the dose-response has been identified in the general adult population. On the other hand, it is not necessary to study the impact of genetic polymorphism again if respective information is already available in adults as their impact does not change over time.

Genome-Based Disease Risk Assessment

Clinical Case:

Mrs. Jones is a 62-year-old woman who just retired after 35 years of teaching elementary school. Her mother died of complications related to end-stage Alzheimer's disease two years ago. As her mother's primary caregiver, Mrs. Jones is well aware of the clinical, psychological, and financial impact that this disease has on patients and families. She read in a magazine that there is a genetic test APOE that identify people who are at increased risk for developing the disease.

Certain diseases are associated with age or have an increased prevalence in the elderly. Based on genomic testing, decisions can be made with respect to risk assessment for the occurrence and/or prognosis of a particular disease. However, the genetic basis for most diseases remain poorly understood. Efforts, for example, to develop clinically useful genomic tests that can predict a higher risk for Alzheimer's disease in individual patients remains elusive. Similarly, efforts to develop effective medications for the prevention and treatment of Alzheimer's disease are hampered by the lack of established biomarkers for preclinical detection and for monitoring treatment response [107].

Pharmacogenomics will continue to play a more dominant part in drug development and medical care. While pharmacogenomics considerations for drug usage might not vary with increasing age, the value for a timely diagnosis will become more important for the elderly population. Similarly, understanding a patient's genetic variation is needed in order to optimize dosing strategies to reduce toxicity and increase efficacy of a particular drug treatment.

Despite the limitations in our knowledge, several companies offer a direct-to-consumer (DTC) genetic testing. Samples can be obtained by saliva/buccal swabs

and are used to estimate the relative disease risk in comparison to a reference population. Currently, there are major pitfalls to the adaption of DTC testing (e.g., lack of infrastructure for genetic testing, timely availability of results to the physician, insurance coverage). Of even greater concern are the implications for future life insurance coverage and patient anxiety.

Challenge and Opportunities of Personalization of Medicine in the Elderly

What Are the Current Challenges?

The inclusion of older patients in the testing of new medications as outlined in the ICH7 guidelines is not mandatory for pharmaceutical industry as long as reasonable justification for not doing so is provided. In addition, a comprehensive representation of the elderly in clinical trials remains hindered by the complex nature of this patient group including heterogeneous comorbidities, poly-medication socioeconomic backgrounds, and physiological state. It also disqualifies a direct comparison of the elderly population in its entirety to healthy adults. The situation is particularly challenging for narrow therapeutic index drugs and warrants close assessment in older adults. In addition, adherence to medication and off-label use due to poly-medication, complex dosing regimen, cognitive, and functional disabilities are major challenges in geriatric pharmacotherapy in general and individualization in particular and have been discussed in greater detail in the previous sections of this book chapter.

What Are The Opportunities?

Personalization of drug therapy holds tremendous potential to change the way drug therapies could be used in elderly patients. Over the past decade, FDA and other regulatory authorities are on the forefront of establishing approaches that increase the benefit of drug therapies while minimizing their risk in this vulnerable patient population. While pediatric guidances have been frequently updated over the past decade [108, 109], respective regulatory documents are not yet available for the elderly. However, the concepts outlined for pediatrics may be used as reference point for geriatrics as well.

Whenever possible, clinical trials should include elderly subjects as well in order to establish appropriate dosing regimen for this special patient population. The conduct of these trials can be supported through the use of modeling and simulation approaches that account for the dynamic interplay between genetic and nongenetic factors in older adults as well as their impact on the drug's PK/PD as a function of

age. The success and failure of these approaches is closely linked to the identification of reliable biomarkers of aging. While the identification of aging biomarkers is currently primarily subject to academic research [69], an increase in research efforts can be expected over the next decade given the importance of this growing patient population. In addition, to these "hard" endpoints, the impact of socioeconomic factors and patient behavior on drug therapy needs to be better understood when attempting to optimize treatment on a patient-by-patient basis.

To that end, a promising approach was recently used in Novartis's Signature Program, where multiple single agent protocols enrolled multiple tumor types in a tissue-agnostic manner with the key inclusion criterium being the presence of an actionable mutation or pathway activation [110]. Based on a hierarchical Bayesian approach, information gained in one subgroup can verify the potency of a compound in another subgroup [111]. This approach can be used in elderly cancer patients who are highly variable in their tumor set of mutations. This approach is already feasible with small study groups and, thus, could facilitate and personalize geriatric clinical development.

The development of large databases and big data management that integrate prescription payment and medical claims information provide an opportunity for postmarketing geriatric pharmacovigilance. Database analysis allows for pharmacovigilance of older generic mediations that may no longer be under active investigation. The data mining of these large health care databases does not prove a medication-related side effect but shows association that provides the hypotheses generation for future studies.

Summary of chapter:

- Personalization of drug therapy is required to maximize benefit and minimize side effects in the elderly.
- Current inclusion criteria often do not represent the entire age spectrum of the elderly for a particular geriatric clinical trial.
- The International Conference on Harmonization (ICH) Efficacy Guideline E7 defines various groups for the elderly patients in order to enable the sponsors to conduct geriatric clinical research effectively.
- Highly variable ADME processes in the elderly which if not considered accurately will impact informed decision-making for guiding dose recommendations.
- Quantitative tools such as pharmacometric and physiologically based approaches can be used for dose personalization in the elderly.
- Genotype guided and genome-based risk assessment techniques can be employed for advanced screening and pharmacotherapy.
- Key challenges include adherence to medication, poly-medication, complex dosing regimen, cognitive, and functional disabilities in geriatric pharmacotherapy.
- Key opportunities rely on determination and validation of reliable biomarkers of aging, accurate determination dynamic interplay between genetic and non-genetic factors along with PK/PD consideration in the elderly.

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Importance of Clinical Nutrition in Therapy to Older Adults

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Abstract This book chapter approaches the importance of clinical nutrition of older adults in therapy. The field of geriatric nutrition is expanding and it is not possible to give a full review of the whole scientific scope due to its extraordinary width. Restricted to the year 2015 there were 16201 papers listed in the PUBMED (PubMed Health. Bethesda (MD): National Library of Medicine (US); access 14.07.2015) database concerning "*Nutrition*" as a subject heading and 1241 systematic reviews. This chapter will NOT give an overview of nutrition "*as a therapy*". This is covered elsewhere in this book and in external sources [1–5] same with the "*Nutrition*"—aspect of elderly people living in the community [6, 7]. Instead, the chapter focuses on the role of the nutrition process as a part of procedures connected with the framework of "*developing drugs for the older patient*". This discussion is composed from two different perspectives: a hospital geriatrician and a social gerontologist. The key question for this chapter is: "*What details of nutrition have to be considered on the way to developing drugs for elder patients*?"

Keywords Gastrointestinal changes on ageing · Dosage control in ageing physiology · Access to drug and managing containers

Introduction

Abstaining from food is connected with disease, sarcopenia [8, 9], frailty [10] and dying. The latter—with and without intent—was reported by Marcus Tullius Cicero in 44 B.C. in two cases (p. 52/53) of man at the end of life [11]. In ancient medical

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S. Stegemann (ed.), *Developing Drug Products in an Aging Society*,
AAPS Advances in the Pharmaceutical Sciences Series 24,
DOI 10.1007/978-3-319-43099-7_29

book publications, "*Nutrition*" was part of the hygienic discussion of Lorand at the beginning of the twentieth century. He published his book [12] nearly a decade[1] before Nascher edited the first geriatric textbook [13]. Geriatric "*Nutrition*" has been a modern scientific topic for more than 60 years and was earlier more related to nursing than to medical publications [14–19].

Clinical nutrition has intervening dependencies to and from following functional dimensions: biological, psychological, social, medical, occupational, physiotherapeutical, communicational, ethical, historical and cultural.

Getting Access to Drugs

Drug access depends on the economic power of states and nations [20] and their abilities to provide food and drug deliverance [21]. Geriatric patients (in developed countries) have access to drugs through physicians' and assistant nurse's prescriptions [22–25] and over-the-counter-drugs (OTC) [26–28]. The process of prescription depends on the different education-levels of physicians, their knowledge about guidelines, their experienced skills level and the caregivers. Drug studies usually neglect the cohort of multimorbid geriatric patients [29] due to methodological challenges [30–35]. Guidelines are rare in the field of geriatric medicine and some authors are concerned they "may have undesirable effects" [36, 37]. Multimorbidity itself is correlated with social inequalities [38], which complicate food security, leading into a *circulus vitiosus* of nutrition.

Handling Medication Containers

Many elderly patients have difficulties in managing medication containers [39–41]. Therefore it is necessary (a) to decrease errors in handling [42] and (b) to develop nutrition-related drugs and ingredients which are elder-sensitive in opening, handling, intake, and restoring at household.

Dosage Control

Drug usage is changing on the timeline between hospital admission/demission and ambulatory evaluation [43]. It has to be considered that dosage is regularly changed after leaving the hospital due to the restrictions imposed on general practitioners in

[1]The German 1st edition.

the field of medication prescriptions. Dosage controls are required for renal and hepatic deficiency and protein loss.

Many drugs cause constipation (i.e. opiods, antidepressants) or nausea (i.e. antibiotics, analgetics). The overall rate of adverse drug events is approximately 50.1 per 1000 person-years in the study of Gurwitz and colleagues [44], with a rate of 13.8 preventable adverse drug events per 1000 person-years. Twenty-one percent of all adverse drug events occur with gastro-intestinal problems.

Getting Access to Food

Worldwide, 795 million people are suffering from chronic hunger and undernutrition. More than half of them are children [45], the others are adults and older adults. Special data no the hunger of the oldest-old are difficult to find. One assumption for this is that undernutrition has no "geriatric data monitoring" e.g. in the 7 countries that cover about 60 % of all hunger-victims of the world (Ethiopia, Tanzania, China, Bangladesh, India, Pakistan and Indonesia). The overlying catastrophe of 2.9 million dying children per year (up to 5 years of age) from hunger appears as the problem in front.

In Northern America, undernutrition in gerontology is prevalent in 5–12 % of the community-dwelling older adults, 5–10 % of the nursing home population, 32–50 % of the hospital patients and 70–92 % of the homebound persons [46, 47].

In Europe approximately 8 million persons are underweight (categorized by BMI) and 17 millions suffer from diabetes mellitus.[2] For the latter topic, further readings can be found at [48–50].

Older adults which have (theoretically) access to enough food-markets may have other reasons for acquiring frail [51–53]. If we look at the ingredients we see a complex situation: Protein intake of healthy elderly subjects is recommended with 0.8 g/kg body weight/day, the same as for younger adults [54] due to the new "geriatric giant" sarcopenia [8, 9]. Despite this recommendation, undernutrition is apparent [47]. The role of dietary recommendations by physicians is unclear [55].

Actually ter Borg and colleagues described in a systematic review that "*the percentage of the population at risk for inadequate intakes of vitamins from food alone was greater than 30 % for both men and women for three of the ten analysed vitamins: thiamin, riboflavin and vitamin D, […] the percentage of the population at risk for inadequate dietary intakes of minerals from food alone was equal to or greater than 30 % for both men and women for three of the analysed minerals: Ca, Mg and S.*" [56]. *This affects other body compartments of elderly people*" [57].

[2] http://appsso.eurostat.ec.europa.eu/nui/show.do?dataset=hlth_ehis_de2&lang=de; Abruf am 04.08.2015.

Vegetables and fruits are rarely examined in the field of clinical surroundings. Kim and colleagues found that a dietary intake of vegetables or fruits and both vegetables and fruits was associated with a significantly reduced risk of sarcopenia [58].

Physiologic Aspects of Ageing and Eating

Smelling and tasting can be altered in ageing humans [59]. Drugs cause adverse side effects in elderly patients, (see above) enhancing problems in the gastrointestinal tract.

The Gastrointestinal Tract

Mouth and teeth problems affect the oral intake of nutrition [60–63]. Swallowing disorders and esophageal diseases reduce the amount of food that is ingested [64, 65]. The esophagus and the stomach have specific changes: e.g. delayed emptying and reduced elasticity in the wall and reduced gastric mucosal protection [66]. Lipid absorption is reduced and pancreatic enzymes are lowered [67, 68]. The eating-surroundings impact the nutrition of older adults [69, 70] especially in nursing homes [71–76]. Eating in nursing homes also depends on the quality of the nursing staff [77].

The large intestine has decreased transit time for the bolus/stool which hast to be transported. This leads frequently to constipation.

Eating is dependent on multiple conditions and modified by 'aversions'—the interventions in this field are somewhat complex. Some researcher reports suggest that nutritional interventions should be aimed at bolstering hunger and curbing aversion.

Culture of Eating

Intake of food is a highly cultural ritus which differs across the world—even in the nutrition sciences [78–81]. In the process of drug development, the ingredients should be appropriate for the cultural landscape. For example, there should be an absence of amino acids from pork when developing drugs for Islamic countries, or "Xi"[3] should be considered when altering ingredients (based on the background of traditional Chinese medicine).

[3]"Life-energy".

How Malnutrition Affects Drug Administration from the Clinical Viewpoint

Malnutrition can be associated with an altered state of hydration [82]. Dehydration affects the visual function of the eyes [83, 84] which are needed to see and recognize drug containers, pills, fluids, suppositoria, and other applications of drugs. Malnutrition and dehydration can worsen ocular diseases [85, 86] and the capability to see, as mentioned above.

An elder person must have enough fine motor skills on the upper extremities to pick up a spoon, a fork, and/or knife to prepare meals or fluids in order to take these in. The same level of motor function is needed to grab a mug to drink some water for pill intake and other drugs. The trunk must be in an upright position. The upper extremities, especially the finger, hand and elbow flexion is dependent on adequate muscle power. Muscle power [87] and fine motor skills are associated with nutrition [77]. If the lacking these skills, then drug administration has to be controlled by the caregiver viewing the whole meal process. Pill counting is not equivalent because pills regularly get "lost" (intended and unintended)—under the bed, the waste paper basket, the floor, the furniture, and the toilet. The aim is not to count but to better the method of drug administration

Malnutrition and sarcopenia can decrease [88–90] the muscle power of the smooth muscle tissue in the gastrointestinal tract which can lead to swallowing disturbances [91–94].

Therapeutic approaches must be interdisciplinary [95]:

Visual function	Leading professionals in therapeutic approaches
Clear and patient-fitted light concept in the room where meals take place	Architects, leaders of the nursing home
Glasses and other viewing aids—must be clean without refraction barriers	Patients, families and nursing staff
Nutrition plan	Patients, families and Nursing staff, physician and dietary assistant, cook, meal delivery service
Hydration plan	Nursing staff, physician
Upright position of the trunk	Nursing staff and physiotherapists
Muscle weakness of the arms	Nursing staff and physiotherapists
Fine motor skills of finger and hands	Nursing staff, physiotherapists, occupational therapists
Drug application controlling	Physician, pharmacists, nursing staff
Swallowing disorders	Physician, nursing staff, speech and swallow therapist

Adverse Drug Reaction (ADR) Impacts Food Intake of Elderly Patients

Potential of New Drugs to Have ADR'S in the Gastro-Intestinal Tracts/Function and Aspects with Eating

We will take a look at the ten FDA-proved new oncology drugs of the year 2014[4] which are developed for a cohort of cancer patients which is ageing in an extent that special geriatric curricula are recommended [96].

Nine of ten drugs have ADR's related to bowel, appetite and eating functionalities:

Drug no. ADR	1	2	3	4	5	6	7	8	9	10
Dyspepsia	+									
Constipation	+		+		+	+				
Nausea		+	+		+		+			
Vomiting		+					+			
Hyperkaliaemia			+							
Diarrhea				+	+	+			+	
Stomatitis					+					
Appetite decreased					+	+				
Dysgeusia							+			
Dyspepsia							+			
Abdominal pain/discomfort							+			+

Gastro-intestinal tracts/function ADR's will have a much more critical effect in older than younger adults due to their diminishing physiological reserve functions.

Nutritional Related Adverse Drug Reaction in the Elderly Are Common in Conventional Drugs

Examples of ADR's [97]:

[4]Data access via http://www.centerwatch.com/drug-information/fda-approved-drugs/oncology: 31.08.2015 13:41–14:00.

Anorexia is reported with:

Amantadine, amphetamine, benzodiazepines, digoxin, gold, levodopa, metformin, nicotine, opioids, selective serotonin reuptake inhibitors (SSRI), theophylline.

Altered smell or taste is reported with:

ACE inhibitors, calcium channel blockers, spironolactone, iron, levodopa, pergolide, selegiline, opioids, gold, allopurinol.

Dry mouth is reported with:

Antihistamines, anticholinergics, diuretics.

Nausea and vomiting is reported with:

Antibiotics, bisphosphonates, digoxin, levodopa, opioids, tricyclic antidepressants, SSRI.

Conclusions

Drug developers are recommended

- to develop new drugs that causes no nausea and vomiting or to combine with antiemetics, or if not possible, at least minimize the risk of the adverse symptoms
- to have a look at newer 'nutrition developments' [8, 98] especially evidence-based nutrition nursing [99]
- to provide improved drug/nutrition/applications which can be handled, opened and taken even when a senior is vision-impaired and has arthritic hands and joints
- to reconsider the physiological changes of the elderly patient, which influence transportation or absorption of drugs and their metabolic impact
- to reconsider the central nervous changes which influence cognitive management capabilities for application handling in the elderly
- to reconsider that caregivers are central in the therapy of octa—nonagenarians and older people
- to reconsider the number and availability of other ("concurring") prescriptions
- to reconsider the lack of knowledge of nutrition in aspects of health care professions and of popular health care publications [100]
- to contact other nutrition-related health care professionals.

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Part VI
Management of Drug Therapy in Older Adults

Managing Drug Therapy of Older Patients in Primary and Secondary Care

Gabriel Ariza, Marta Martínez-Reig and Pedro Abizanda

Abstract The progressive aging of the European population faces us with a new challenge for healthcare, secondary to the increasing prevalence of chronic diseases and subsequent drugs use. In Europe, population aged 65 and older consume 2–3 times more health resources than younger ones. Onder et al. described that in Italy, prescription drug costs represent approximately 17 % of total public health expenditures. In this country, in 2012, public expenditure for pharmaceuticals in primary care exceeded 11 billion Euros, and adults aged 65 or older accounted for more than 60 % of these costs [1]. Furthermore, it is well known that older people are at higher risk of adverse events than younger ones, mainly related to pharmacokinetic and pharmacodynamic changes associated with aging, high comorbidity rates, and subsequent polypharmacy. Surprisingly, there are not targeted Clinical Practice Guidelines for managing older people with multimorbidity, leading to a great amount of different prescription recommendations from several guidelines of specific diseases. Consequently, treatment of chronic conditions in older adults is frequently associated with polypharmacy, and an increased risk of interactions and adverse events. The risk–benefit ratio of each medication individually, and in association with other drugs, should be considered to optimize drug prescription in older people with multimorbidities, to achieve realistic therapeutic objectives. Limited evidence is available to perform this drug selection, but giving thought to patient preferences, prognostic of the diseases, and life expectancy will be necessary to achieve appropriate prescription. Moreover, regular reassessment of drug indication is often forgotten, and should be included as a routine to warrant that the medication is used uniquely while there are relevant benefits, hence avoiding "for life" prescriptions.

Keywords Polypharmacy · Older adults · Adverse drug reactions · Frailty · Inappropriate prescription

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S. Stegemann (ed.), *Developing Drug Products in an Aging Society*,
AAPS Advances in the Pharmaceutical Sciences Series 24,
DOI 10.1007/978-3-319-43099-7_30

Adverse Drug Reaction Risk Factors in Older Adults

Adverse Drug Reactions (ADR) are more frequent in old ages. Patients admitted to the emergency room or hospitalized with an ADR are on average 10 years older than those without an ADR, and a prevalence of ADR at hospital admission of 14.2 % has been described in this population [2]. Added to older age, multimorbidity, frailty, and polypharmacy are also among the main risk factors for ADR.

The majority of ADR in older people are Type A reactions, those that are attributable to a predictable known pharmacological effect of a drug. These ADR are potentially avoidable and usually involve commonly prescribed medications. In a prospective Italian study of 1,756 consecutively admitted patients aged over 65 years, 45.1 % of ADR were classified as definitely avoidable and 31.4 % as potentially avoidable [3].

It should be noted that ADR in older people often appear with atypical presentations, the so-called *Geriatric Syndromes*, including functional loss, frailty, immobility, cognitive impairment, delirium, balance impairment, falls, urinary incontinence, dizziness, or depression. In a North American study of 1,247 long-term care residents, the most common manifestations of an ADR were delirium, oversedation, and falls [4]. The presence of new symptoms in older patients should always be considered as possible ADR, mainly when prescribed in the last month, in order to prevent the spiral of polypharmacy.

Frailty

Frailty is a medical syndrome with multiple causes and contributors that is characterized by diminished strength, endurance, and reduced physiologic function that increases an individual's vulnerability for developing increased dependency and/or death [5]. Many tools are available to determine frailty, although the Fried's frailty phenotype (Table 1) [6] is the most commonly used, followed by the Frailty index and the FRAIL instrument. Frailty is a common syndrome in community-dwelling older adults, with a pooled prevalence of 10.7 % in more than 60,000 individuals [7]. In institutionalized older adults, the prevalence ranges between 34.9 and 68.8 % [8]. Frailty has been associated with health-related adverse events like mortality, disability in basic activities of daily living [BADL] and mobility disability, hospitalization, institutionalization and falls in community-dwelling older adults [9]. Recently, the association between frailty and incident mortality or disability in BADL in institutionalized older adults has been demonstrated [10]. Although closely related, frailty, comorbidity, and disability are different entities, and frailty is actually considered a pre-disability state of vulnerability to adverse events [11]. For this reason, frail older adults are a special population in which preventive measures are of outstanding relevance, including medication control.

Table 1 Fried's frailty phenotype

Unintentional weight loss in last year greater than 4.5 kg or 5 %			
Weakness: grip strength (kg) lower quintile			
Men		*Women*	
• BMI ≤ 24	≤29	• BMI ≤ 23	≤17
• BMI 24.1–26	≤30	• BMI 23.1–26	≤17.3
• BMI 26.1–28	≤30	• BMI 26.1–29	≤18
• BMI > 28	≤32	• BMI > 29	≤21
Low energy and exhaustion: CES-D			
Gait speed: lower quintile (gait 4 m)			
Men		*Women*	
• Height ≤ 173 cm	≥7 s (0.65 m/s)	• Height ≤ 159 cm	≥7 s (0.65 m/s)
• Height > 173 cm	≥6 s (0.75 m/s)	• Height > 159 cm	≥6 s (0.75 m/s)
Low physical activity: Minnessota leisure activity questionnaire			
Men: Weekly kcal physical activity < 383			
Women: Weekly kcal physical activity < 270			

Since frail older adults seldom participate in clinical drug trials, clear information is not available for this patient group on the balance between the chance of efficacy and the risk of harm of drug therapy, and few studies have analyzed the association between frailty and appropriateness of prescription or ADR. Discussion with the patient about his or her preferences and options with respect to drug therapy is the basis for all subsequent steps and must form part of the periodic reviews of medication.

Recently, the British Geriatrics Society published a document called "*Fit for Frailty: Consensus Best Practice Guidance for the care of older people living with frailty in community and outpatient settings*" [12]. In this document, one of the recommendations is to conduct evidence-based medication reviews for older people with frailty. Furthermore, polypharmacy control has been described as one of the cornerstones of frailty prevention and treatment, added to physical exercise and nutritional intervention.

Many drugs are particularly associated with adverse outcomes in frailty such as antimuscarinics in cognitive impairment, long-acting benzodiazepines, and some sulphonylureas. Other sedatives and hypnotics increase falls risk, some opiate-based analgesics increase risk of confusion or delirium, and NSAID can cause severe symptomatic renal impairment in frailty. Conversely, some drugs which would offer symptomatic benefit are omitted because of concerns about frailty, when with careful monitoring they would be safe to use (such as angiotensin converting enzyme [ACE] inhibitors in systolic heart failure). Actually, prescribing guidelines for frail older adults are available for diabetes and chronic pain [13, 14].

Polypharmacy

The term polypharmacy refers to the use of multiple medications, and/or the administration of more medications that are clinically indicated. Polypharmacy is also often used in the context of unnecessary medication use. However, for many years, there has been no agreement regarding the number of concomitant medications that could be defined as "polypharmacy." Actually, the most used cut-off point in medical publications is five or more medications. A recent study concluded that five or more drugs were an optimal discriminating number for polypharmacy because this number, even though not causal, was associated with frailty, disability, falls, and mortality, supporting credibility to this figure as the best definition for polypharmacy.

There are great differences in the prevalence of polypharmacy between studies, which may range from 5 to 78 %, due to differences in cut-off points, age groups, study settings, data sources, and type of medications in each publication, but in developed countries, approximately 30 % of patients aged 65 years or older are prescribed five or more drugs. Average drug use ranged from 2 to 8 medications per person. Even though older people represent about 17 % of the population, they are responsible for 70 % of pharmaceutical expenditures and more than 85 % of those aged 65 and more use at least one medication prescribed by a physician. These percentages are even higher in nursing homes where more than 50 % of residents use at least six drugs per day [15], or in hospitalized older adults who receive an average of 6.5 drugs per person and day. Beside the clinical conditions, polypharmacy in these patients increased the risk of ADR. Some studies show that up to 81 % of patients in Acute Units receive five or more drugs chronically [16]. In spite of a great number of attempts to optimize pharmacological management in older patients, medication use in developed countries has increased dramatically during the last two decades. The most polymedicated population group (up to 57 % of the total prescriptions) is the one including patients older than 75 years, and the mean age of polymedicated subjects is 74.5 ± 10.9 years [17]. An Italian analysis of several databases showed that polypharmacy is extremely common in this population, with more than 1.3 million individuals (11.3 %) receiving prescriptions for ten or more drugs at the same time. Interestingly, the group aged 75–84 years was exposed to the highest pharmaceutical burden, with 14.1 % of individuals in this age group receiving ten or more drugs. Only 8.6 % of individuals in the group aged 65–74 years and 13.8 % in the group aged 85 years or older received the same number of prescriptions. Another population-based study was developed by the same group, analyzing the 2011 database from the *Osservatorio dei Medicinali*. They collected data on drugs dispensed to 11,593,989 subjects aged 65 years or older, representing 94.2 % of the Italian residents of this age group, as reported by the Italian National Institute of Statistics (n = 12,301,537). In this study, more than 1.3 million of older adults (11.3 %) received a simultaneous prescription of ten or more drugs, and more than six million (49 %) received five to nine medications. In particular, the group aged 75–84 years was exposed to the highest pharmacological

burden, with 55.0 and 14.1 % of subjects receiving five to nine drugs and ten or more drugs, respectively [18].

In terms of costs, the average number of prescriptions billed monthly per polymedicated patient was 32 ± 2 in a recent study, with an average cost of 452.7 ± 27.5 €. The total cost of those prescriptions corresponded to 2 % of the drug expenditure in Catalonia (Spain). The groups N (nervous), C (cardiovascular), A (alimentary tract and metabolism), R (respiratory), and M (musculoskeletal) represented 71.4 % of the total number of drug package units dispensed to polymedicated patients, making these groups especially relevant [17].

The literature describes the following risk factors as commonly associated with increased medication use: age (although for others to be older than 85 years is a protective factor); presence of comorbidity; education level; frequent use of health services; female gender; mental problems (anxiety or depression); low self-perceived health status, and involvement of multiple prescriptors which sometimes result in treatments duplicity. Probably, the main reasons for polypharmacy are a longer life expectancy, the accumulation of multimorbidities, and the implementation of evidence-based clinical practice guidelines.

At any event, polymedication is associated with greater complexity in clinical management, and a potential higher rate of adverse events. A higher risk of ADR, drug interactions, non-adherence, diminished functional status, and geriatric syndromes (cognitive impairment, falls, urinary incontinence, and poor nutritional status), are among such negative health outcomes of inappropriate polypharmacy. Another fact to consider is the high economic cost associated with inappropriate polypharmacy and their complications, both related to direct and indirect costs.

Polypharmacy is one of the main risk factors for ADR presentation, increasing from 13 % in a person taking two medicines to 58 % when taking five, and 82 % when taking seven or more [19]. The risk of presenting an ADR increases with the number of regular prescribed medications, from an *Odds ratio* (OR) of 2.0 in those taking five to six medicines to an OR of 2.8 in those taking seven to eight medicines, and to an OR of 3.3 in those taking nine or more medicines [20]. Despite the fact that polypharmacy is often considered to be among the most important risk factors for ADR, and medication-related hospital admissions in older people, a high usage of drugs should not necessarily be taken as inappropriate. In fact, it may become necessary to add on new medications in patients with various comorbidities, based on an appropriate risk/benefit evaluation.

Interventions to Improve Polypharmacy

It is known that the identification and prevention of polypharmacy results in a lower incidence of adverse events, drug–drug interactions, drug-related hospitalizations, duplicity of medications, unnecessary medication costs, and better understanding of medication use by both the patient and the caregiver. Many proposals oriented to aid in pharmacologic therapy management have been described, including

Table 2 NO TEARS tool

Need an indication
Open questions
Tests and monitoring
Evidence and guidelines
Adverse events
Risk reduction or prevention
Simplification and switches

systematic review of treatments, multidisciplinary teams, computer systems, etc. Some of them, like the *Prescribing Optimization Method* (POM), have demonstrated an improvement in prescription. This tool is easy to perform, suitable, and is composed of six simple questions addressed to Primary Care physicians. Another useful instrument is the NO TEARS tool for medication review (Table 2) [21]. Other instruments, like the ACADEMIA eight steps list, are more elaborated and academic, and thus complex to use in ordinary clinical practice (Table 3).

Other proposals for improving polypharmacy are computerized alerts. Electronic prescriptions and Computerized Decisions Support Systems (CDSS) are among the most used ones. Although these technical supports have proved to diminish and improve prescriptions, there is a general lack of acceptance among practitioners, so more than a half of these alerts end up being canceled or ignored by the prescriber. There are two further mnemonic instruments to aid prescribers in reducing polypharmacy: SAIL (Simplify, Adverse effects, Indication, List) and TIDE (Time, Individualize, Drug interactions, Educate), but they have not been accepted or implemented in daily clinical practice.

The instrument that has probably increased its relevance in the development of deprescribing recommendations in the last years is the *Good Palliative-Geriatric Practice algorithm* for drugs withdrawal. It has been validated, and its utility has been demonstrated in reducing polypharmacy and improving mortality and morbidity in institutionalized subjects. Furthermore, its usefulness in community-dwelling subjects has been demonstrated with comparable degrees of comorbidities and functionality.

Table 3 The ACADEMIA eight steps list

Asses (to evaluate current drugs use)
Comprehensive (comprehensive geriatric assessment)
Adherence
Development (to develop a well-reasoned treatment plan based on patient preferences)
Emergence (of the optimized medication record)
Minimization (of drugs list, discontinuation)
Interdisciplinarity (chemist role)
Alertness (monitoring and reevaluation of eventual rebound effects and adverse effects)

Suboptimal Prescribing

Suboptimal prescribing has been defined as overuse (polypharmacy), misuse (inappropriate prescribing), and underuse (potential prescription omissions). *Overprescribing* refers to prescribing more drugs than are clinically needed, *misprescribing* refers to incorrectly prescribing needed drugs or presence of potentially inappropriate medications (drugs whose risks are greater than the benefits in older adults), and *underprescribing* refers to omissions of prescribing drugs that are potentially indicated for the treatment or prevention of a disease. Approximately, 80 % of community-dwelling adults older than 65 years experience any sort of suboptimal prescribing, making it a frequent problem [22].

Potentially Inappropriate Prescribing

Potentially inappropriate drug prescription in older adults cause major consequences, both in individual's health (increased risk of adverse events, geriatric syndromes, and even mortality), and in healthcare systems (higher costs or longer length of hospital stays). It has been calculated that total cost related to potentially inappropriate prescriptions accounts for more than 5 % of total pharmaceutical expenditure in subjects older than 69 [23].

A prescription is considered to be potentially inappropriate when risks related to its use outweigh potential benefits, as well as when the prescription is ineffective, particularly if safer and/or more effective therapeutic options are available. Furthermore, it should be considered inappropriate prescribing when an unnecessary high-dose of certain drug is used, or drugs are prescribed during a too long period of time, as well as the use of medications with high risk of drug-drug interactions or drug-disease interactions, and the use of duplicated drugs or drugs belonging to the same therapeutic class. Nowadays, inappropriate prescriptions should also include the lack of use of beneficial medications with a clinical indication.

A recent systematic review of the literature found that approximately one in five prescriptions to older adults in primary care is inappropriate despite the attention that has been directed to prescription quality. Diphenhydramine and amitriptyline were the most common inappropriately prescribed medications with high-risk adverse events, while propoxyphene and doxazosin were the most commonly prescribed medications with low risk adverse events [24].

Criteria to Determine Inappropriate Prescribing

There are two main groups of criteria to detect potentially inappropriate prescriptions: implicit and explicit criteria. Implicit criteria are based on the indication of each medication through patient features, being the *Medication Appropriateness*

Index (MAI) the most widely used. Implicit criteria are reliable instruments, but may be not practical in clinical practice as they require too much time and depend on physician knowledge. Other implicit criteria are the *Screening Medications in the Older Drug User* (SMOG), a six-question instrument developed specifically for community pharmacists, the *Assess, Review, Minimize, Optimize, Reassess* (ARMOR) tool, the *Tool to Improve Medications in the Elderly* via *Review* (TIMER), the *Assessing Care of Vulnerable Elders-3* (ACOVE-3), and the *Good Palliative-Geriatric Practice Algorithm* (GPGPA).

On the other hand, explicit criteria are predetermined criteria groups according to experts consensus based on best scientific evidence available, which probably makes them easier to use. The most used explicit criteria include potentially inappropriate medicines (PIMs) that should be avoided in any circumstances, and drugs that should be avoided in patients with specific disorders.

Different screening tools have been developed to detect potentially inappropriate prescribing. The Beers criteria, published in 1991, and later reviewed and updated in 1997 and 2003, was the first and most widely known of these tools and has been used in most of the research published on PIMs [25, 26]. However, in Europe, these criteria have several weaknesses, being the main one that many drugs on the list are rarely used or unavailable in most European countries. Furthermore, the Beers criteria give no consideration to drug–drug interactions, duration of treatment, different indications for certain drugs, and underuse of indicated drugs. In view of these limitations, the *Screening Tool of Older Person's Potentially Inappropriate Prescriptions* (STOPP) (Table 4) and *Screening Tool to Alert doctors to the Right Treatment* (START) (Table 5) criteria have been developed and validated in Europe [27]. More recently, with the support of the American Geriatrics Society (AGS), a new update of the Beers criteria has been published, the 2012 AGS Beers criteria (Tables 6, 7, and 8), providing a more dynamic list, in line with clinical practice [28]. The inclusion of an evidence-based approach has improved the quality of these criteria. Each criterion now includes a clear strength recommendation with a given quality of evidence. The addition of several recently marketed medications, together with the exclusion of drugs no longer available are further positive points, and another new feature is a third list of drugs to be used with caution in older adults. Likewise, at the end of 2014 the latest update of STOPP-START criteria have been published [29].

STOPP-START criteria have been validated in many countries and healthcare levels (outpatient level, acute hospital care, nursing homes, and even intensive care units). These criteria are more sensitive to detect potentially inappropriate prescriptions as well as to prevent adverse events and ADR. The limited studies that compare STOPP-START criteria with Beers 2012 criteria show higher PIMs rates in Beers 2012 criteria, both in hospitalized older adults and in community-dwelling ones [30]. Therefore, authors suggest using both criteria as complementary instruments.

It should be noted that in the last years, alternative criteria groups to detect potentially inappropriate prescriptions have appeared not only in Europe (French Consensus, PRISCUS, NORGEP, Austrian consensus, etc.), but also in Canada (McLeod's list, IPET), Asia (Winit-Watjana) or Australia. Yet, most of them have

Table 4 Screening tool of older people's potentially inappropriate prescriptions (STOPP) version 2

Section A: indication of medication
1. Any drug prescribed without an evidence-based clinical indication
2. Any drug prescribed beyond the recommended duration, where treatment duration is well defined
3. Any duplicate drug class prescription, e.g., two concurrent NSAIDs, SSRIs, loop diuretics, ACE inhibitors, anticoagulants (optimisation of monotherapy within a single drug class should be observed prior to considering a new agent)
Section B: cardiovascular system
1. Digoxin for heart failure with normal systolic ventricular function (no clear evidence of benefit)
2. Verapamil or diltiazem with NYHA Class III or IV heart failure (may worsen heart failure)
3. Beta blocker in combination with verapamil or diltiazem (risk of heart block)
4. Beta blocker with bradycardia (<50/min), type II heart block or complete heart block (risk of complete heart block, asystole)
5. Amiodarone as first-line antiarrhythmic therapy in supraventricular tachyarrhythmias (higher risk of side effects than beta blockers, digoxin, verapamil or diltiazem)
6. Loop diuretic as first-line treatment for hypertension (safer, more effective alternatives available)
7. Loop diuretic for dependent ankle oedema without clinical, biochemical evidence or radiological evidence of heart failure, liver failure, nephrotic syndrome, or renal failure (leg elevation and/or compression hosiery usually more appropriate)
8. Thiazide diuretic with current significant hypokalaemia (i.e. serum K+ <3.0 mmol/l), hyponatraemia (i.e., serum Na+ <130 mmol/l) hypercalcaemia (i.e., corrected serum calcium >2.65 mmol/l) or with a history of gout (hypokalaemia, hyponatraemia, hypercalcaemia and gout can be precipitated by thiazide diuretic)
9. Loop diuretic for treatment of hypertension with concurrent urinary incontinence (may exacerbate incontinence)
10. Centrally acting antihypertensives (e.g., methyldopa, clonidine, moxonidine, rilmenidine, guanfacine), unless clear intolerance of, or lack of efficacy with, other classes of antihypertensives (centrally active antihypertensives are generally less well tolerated by older people than younger people)
11. ACE inhibitors or angiotensin receptor blockers in patients with hyperkalaemia

(continued)

Table 4 (continued)

12. Aldosterone antagonists (e.g., spironolactone, eplerenone) with concurrent potassium-conserving drugs (e.g., ACEI's, ARB's, amiloride, triamterene) without monitoring of serum potassium (risk of dangerous hyperkalaemia i.e. >6.0 mmol/l – serum K should be monitored regularly, i.e., at least every 6 months)
13. Phosphodiesterase type-5 inhibitors (e.g., sildenafil, tadalafil, vardenafil) in severe heart failure characterized by hypotension, i.e., systolic BP <90 mmHg, or concurrent nitrate therapy for angina (risk of cardiovascular collapse)
Section C: antiplatelet/anticoagulant drugs
1. Long-term aspirin at doses greater than 160 mg per day (increased risk of bleeding, no evidence for increased efficacy)
2. Aspirin with a past history of peptic ulcer disease without concomitant PPI (risk of recurrent peptic ulcer)
3. Aspirin, clopidogrel, dipyridamole, vitamin K antagonists, direct thrombin inhibitors, or factor Xa inhibitors with concurrent significant bleeding risk, i.e., uncontrolled severe hypertension, bleeding diathesis, recent nontrivial spontaneous bleeding) (high risk of bleeding)
4. Aspirin plus clopidogrel as secondary stroke prevention, unless the patient has a coronary stent(s) inserted in the previous 12 months or concurrent acute coronary syndrome or has a high grade symptomatic carotid arterial stenosis (no evidence of added benefit over clopidogrel monotherapy)
5. Aspirin in combination with vitamin K antagonist, direct thrombin inhibitor or factor Xa inhibitors in patients with chronic atrial fibrillation (no added benefit from aspirin)
6. Antiplatelet agents with vitamin K antagonist, direct thrombin inhibitor, or factor Xa inhibitors in patients with stable coronary, cerebrovascular or peripheral arterial disease (No added benefit from dual therapy)
7. Ticlopidine in any circumstances (clopidogrel and prasugrel have similar efficacy, stronger evidence and fewer side effects)
8. Vitamin K antagonist, direct thrombin inhibitor, or factor Xa inhibitors for first deep venous thrombosis without continuing provoking risk factors (e.g., thrombophilia) for >6 months, (no proven added benefit)
9. Vitamin K antagonist, direct thrombin inhibitor or factor Xa inhibitors for first pulmonary embolus without continuing provoking risk factors (e.g., thrombophilia) for >12 months (no proven added benefit)
10. NSAID and vitamin K antagonist, direct thrombin inhibitor or factor Xa inhibitors in combination (risk of major gastrointestinal bleeding)
11. NSAID with concurrent antiplatelet agent(s) without PPI prophylaxis (increased risk of peptic ulcer disease)

(continued)

Table 4 (continued)

Section D: central nervous system and psychotropic drugs
1. TriCyclic Antidepressants (TCAs) with dementia, narrow angle glaucoma, cardiac conduction abnormalities, prostatism, or prior history of urinary retention (risk of worsening these conditions)
2. Initiation of TriCyclic Antidepressants (TCAs) as first-line antidepressant treatment (higher risk of adverse drug reactions with TCAs than with SSRIs or SNRIs)
3. Neuroleptics with moderate-marked antimuscarinic/anticholinergic effects (chlorpromazine, clozapine, flupenthixol, fluphenzine, pipothiazine, promazine, zuclopenthixol) with a history of prostatism or previous urinary retention (high risk of urinary retention)
4. Selective serotonin reuptake inhibitors (SSRI's) with current or recent significant hyponatraemia, i.e., serum Na + <130 mmol/l (risk of exacerbating or precipitating hyponatraemia)
5. Benzodiazepines for ≥4 weeks (no indication for longer treatment; risk of prolonged sedation, confusion, impaired balance, falls, road traffic accidents; all benzodiazepines should be withdrawn gradually if taken for more than 4 weeks as there is a risk of causing a benzodiazepine withdrawal syndrome if stopped abruptly)
6. Antipsychotics (i.e., other than quetiapine or clozapine) in those with parkinsonism or Lewy Body Disease (risk of severe extrapyramidal symptoms)
7. Anticholinergics/antimuscarinics to treat extrapyramidal side effects of neuroleptic medications (risk of anticholinergic toxicity)
8. Anticholinergics/antimuscarinics in patients with delirium or dementia (risk of exacerbation of cognitive impairment)
9. Neuroleptic antipsychotic in patients with behavioral and psychological symptoms of dementia (BPSD) unless symptoms are severe and other non-pharmacological treatments have failed (increased risk of stroke)
10. Neuroleptics as hypnotics, unless sleep disorder is due to psychosis or dementia (risk of confusion, hypotension, extrapyramidal side effects, falls)
11. Acetylcholinesterase inhibitors with a known history of persistent bradycardia (<60 beats/min), heart block or recurrent unexplained syncope or concurrent treatment with drugs that reduce heart rate such as beta blockers, digoxin, diltiazem, verapamil (risk of cardiac conduction failure, syncope and injury)
12. Phenothiazines as first-line treatment, since safer and more efficacious alternatives exist (phenothiazines are sedative, have significant antimuscarinic toxicity in older people, with the exception of prochlorperazine for nausea/vomiting/vertigo, chlorpromazine for relief of persistent hiccoughs and levomepromazine as an anti-emetic in palliative care)

(continued)

Table 4 (continued)

13. Levodopa or dopamine agonists for benign essential tremor (no evidence of efficacy)
14. First-generation antihistamines (safer, less toxic antihistamines now widely available)
Section E: renal system. The following drugs are potentially inappropriate in older people with acute or chronic kidney disease with renal function below particular levels of eGFR (refer to summary of product characteristics datasheets and local formulary guidelines)
1. Digoxin at a long-term dose greater than 125 μg/day if eGFR <30 ml/min/1.73 m^2 (risk of digoxin toxicity if plasma levels not measured)
2. Direct thrombin inhibitors (e.g. dabigatran) if eGFR <30 ml/min/1.73 m^2 (risk of bleeding)
3. Factor Xa inhibitors (e.g., rivaroxaban, apixaban) if eGFR <15 ml/min/1.73 m^2 (risk of bleeding)
4. NSAID's if eGFR <50 ml/min/1.73 m^2 (risk of deterioration in renal function)
5. Colchicine if eGFR <10 ml/min/1.73 m^2 (risk of colchicine toxicity)
6. Metformin if eGFR <30 ml/min/1.73 m^2 (risk of lactic acidosis)
Section F: gastrointestinal system
1. Prochlorperazine or metoclopramide with Parkinsonism (risk of exacerbating Parkinsonian symptoms)
2. PPI for uncomplicated peptic ulcer disease or erosive peptic oesophagitis at full therapeutic dosage for >8 weeks (dose reduction or earlier discontinuation indicated)
3. Drugs likely to cause constipation (e.g., antimuscarinic/anticholinergic drugs, oral iron, opioids, verapamil, aluminum antacids) in patients with chronic constipation where non-constipating alternatives are available (risk of exacerbation of constipation)
4. Oral elemental iron doses greater than 200 mg daily (e.g., ferrous fumarate >600 mg/day, ferrous sulfate >600 mg/day, ferrous gluconate >1800 mg/day; no evidence of enhanced iron absorption above these doses)
Section G: respiratory system
1. Theophylline as monotherapy for COPD (safer, more effective alternative; risk of adverse effects due to narrow therapeutic index)
2. Systemic corticosteroids instead of inhaled corticosteroids for maintenance therapy in moderate-severe COPD (unnecessary exposure to long-term side effects of systemic corticosteroids and effective inhaled therapies are available)
3. Antimuscarinic bronchodilators (e.g., ipratropium, tiotropium) with a history of narrow angle glaucoma (may exacerbate glaucoma) or bladder outflow obstruction (may cause urinary retention)

(continued)

Table 4 (continued)

4. Non-selective beta blocker (whether oral or topical for glaucoma) with a history of asthma requiring treatment (risk of increased bronchospasm)
5. Benzodiazepines with acute or chronic respiratory failure, i.e., $pO_2 < 8.0$ kPa $\pm$ $pCO_2 > 6.5$ kPa (risk of exacerbation of respiratory failure)
Section H: musculoskeletal system
1. Nonsteroidal anti-inflammatory drug (NSAID) other than COX-2 selective agents with history of peptic ulcer disease or gastrointestinal bleeding, unless with concurrent PPI or H_2 antagonist (risk of peptic ulcer relapse)
2. NSAID with severe hypertension (risk of exacerbation of hypertension) or severe heart failure (risk of exacerbation of heart failure)
3. Long-term use of NSAID (>3 months) for symptom relief of osteoarthritis pain where paracetamol has not been tried (simple analgesics preferable and usually as effective for pain relief)
4. Long-term corticosteroids (>3 months) as monotherapy for rheumatoid arthrtitis (risk of systemic corticosteroid side effects)
5. Corticosteroids (other than periodic intra-articular injections for monoarticular pain) for osteoarthritis (risk of systemic corticosteroid side effects)
6. Long-term NSAID or colchicine (>3 months) for chronic treatment of gout where there is no contraindication to a xanthine-oxidase inhibitor (e.g., allopurinol, febuxostat) (xanthine-oxidase inhibitors are first choice prophylactic drugs in gout)
7. COX-2 selective NSAIDs with concurrent cardiovascular disease (increased risk of myocardial infarction and stroke)
8. NSAID with concurrent corticosteroids without PPI prophylaxis (increased risk of peptic ulcer disease)
9. Oral bisphosphonates in patients with a current or recent history of upper gastrointestinal disease, i.e., dysphagia, oesophagitis, gastritis, duodenitis, or peptic ulcer disease, or upper gastrointestinal bleeding (risk of relapse/exacerbation of oesophagitis, oesophageal ulcer, oesophageal stricture)
Section I: urogenital system
1. Antimuscarinic drugs with dementia, or chronic cognitive impairment (risk of increased confusion, agitation) or narrow
2. Selective alpha-1 selective alpha blockers in those with symptomatic orthostatic hypotension or micturition syncope (risk of precipitating recurrent syncope)
Section J: endocrine system
1. Sulphonylureas with a long duration of action (e.g., glibenclamide, chlorpropamide, glimepiride) with type 2 diabetes mellitus (risk of prolonged hypoglycaemia)

(continued)

Table 4 (continued)

2. Thiazolidenediones (e.g., rosiglitazone, pioglitazone) in patients with heart failure (risk of exacerbation of heart failure)
3. Beta blockers in diabetes mellitus with frequent hypoglycaemic episodes (risk of suppressing hypoglycaemic symptoms)
4. Oestrogens with a history of breast cancer or venous thromboembolism (increased risk of recurrence)
5. Oral oestrogens without progestogen in patients with intact uterus (risk of endometrial cancer)
6. Androgens (male sex hormones) in the absence of primary or secondary hypogonadism (risk of androgen toxicity
Section K: drugs that predictably increase the risk of falls in older people
1. Benzodiazepines (sedative, may cause reduced sensorium, impair balance)
2. Neuroleptic drugs (may cause gait dyspraxia, Parkinsonism)
3. Vasodilator drugs (e.g., alpha-1 receptor blockers, calcium channel blockers, long-acting nitrates, ACE inhibitors, angiotensin I receptor blockers,) with persistent postural hypotension, i.e., recurrent drop in systolic blood pressure ≥20 mmHg (risk of syncope, falls)
4. Hypnotic Z-drugs, e.g., zopiclone, zolpidem, zaleplon (may cause protracted daytime sedation, ataxia)
Section L: analgesic drugs
1. Use of oral or transdermal strong opioids (morphine, oxycodone, fentanyl, buprenorphine, diamorphine, methadone, tramadol, pethidine, pentazocine) as first-line therapy for mild pain (WHO analgesic ladder not observed)
2. Use of regular (as distinct from PRN) opioids without concomitant laxative (risk of severe constipation)
3. Long-acting opioids without short-acting opioids for break through pain (risk of persistence of severe pain)
Section N: antimuscarinic/anticholinergic drug burden
Concomitant use of two or more drugs with antimuscarinic/anticholinergic properties (e.g., bladder antispasmodics, intestinal antispasmodics, tricyclic antidepressants, first-generation antihistamines) (risk of increased antimuscarinic/anticholinergic toxicity)

Taken from O'Mahony et al. [29]

Table 5 Screening tool to alert to right treatment (START) version 2

Section A: cardiovascular system
1. Vitamin K antagonists or direct thrombin inhibitors or factor Xa inhibitors in the presence of chronic atrial fibrillation
2. Aspirin (75–160 mg once daily) in the presence of chronic atrial fibrillation, where Vitamin K antagonists or direct thrombin inhibitors or factor Xa inhibitors are contraindicated
3. Antiplatelet therapy (aspirin or clopidogrel or prasugrel or ticagrelor) with a documented history of coronary, cerebral or peripheral vascular disease
4. Antihypertensive therapy where systolic blood pressure consistently >160 mmHg and/or diastolic blood pressure consistently >90 mmHg; if systolic blood pressure >140 mmHg and/or diastolic blood pressure >90 mmHg, if diabetic
5. Statin therapy with a documented history of coronary, cerebral, or peripheral vascular disease, unless the patient's status is end-of-life or age is >85 years
6. Angiotensin Converting Enzyme (ACE) inhibitor with systolic heart failure and/or documented coronary artery disease
7. Beta blocker with ischaemic heart disease
8. Appropriate beta blocker (bisoprolol, nebivolol, metoprolol, or carvedilol) with stable systolic heart failure
Section B: respiratory system
1. Regular inhaled β2 agonist or antimuscarinic bronchodilator (e.g., ipratropium, tiotropium) for mild to moderate asthma or COPD
2. Regular inhaled corticosteroid for moderate-severe asthma or COPD, where FEV1 <50 % of predicted value and repeated exacerbations requiring treatment with oral corticosteroids
3. Home continuous oxygen with documented chronic hypoxaemia (i.e., pO_2 <8.0 kPa or 60 mmHg or SaO_2 <89 %)
Section C: central nervous system and eyes
1. L-DOPA or a dopamine agonist in idiopathic Parkinson's disease with functional impairment and resultant disability
2. Non-TCA antidepressant drug in the presence of persistent major depressive symptoms
3. Acetylcholinesterase inhibitor (e.g., donepezil, rivastigmine, galantamine) for mild-moderate Alzheimer's dementia or Lewy Body dementia (rivastigmine)
4. Topical prostaglandin, prostamide, or beta blocker for primary open-angle glaucoma
5. Selective serotonin reuptake inhibitor (or SNRI or pregabalin if SSRI contraindicated) for persistent severe anxiety that interferes with independent functioning
6. Dopamine agonist (ropinirole or pramipexole or rotigotine) for Restless Legs Syndrome, once iron deficiency and severe renal failure have been excluded

(continued)

Table 5 (continued)

Section D: gastrointestinal system
1. Proton Pump Inhibitor with severe gastro-oesophageal reflux disease or peptic stricture requiring dilatation
2. Fiber supplements (e.g., bran, ispaghula, methylcellulose, sterculia) for diverticulosis with a history of constipation
Section E: musculoskeletal system
1. Disease-modifying antirheumatic drug (DMARD) with active, disabling rheumatoid disease
2. Bisphosphonates and vitamin D and calcium in patients taking long-term systemic corticosteroid therapy
3. Vitamin D and calcium supplement in patients with known osteoporosis and/or previous fragility fracture(s) and/or (bone mineral density T-scores more than −2.5 in multiple sites)
4. Bone antiresorptive or anabolic therapy (e.g., bisphosphonate, strontium ranelate, teriparatide, denosumab) in patients with documented osteoporosis, where no pharmacological or clinical status contraindication exists (bone mineral density T-scores ≥2.5 in multiple sites) and/or previous history of fragility fracture(s)
5. Vitamin D supplement in older people who are housebound or experiencing falls or with osteopenia (bone mineral density T-score is ≥1.0 but ≤2.5 in multiple sites)
6. Xanthine-oxidase inhibitors (e.g., allopurinol, febuxostat) with a history of recurrent episodes of gout
7. Folic acid supplement in patients taking methotexate
Section F: endocrine system
1. ACE inhibitor or angiotensin receptor blocker (if intolerant of ACE inhibitor) in diabetes with evidence of renal disease, i.e., dipstick proteinuria or microalbuminuria (>30 mg/24 h) with or without serum biochemical renal impairment
Section G: urogenital system
1. Alpha-1 receptor blocker with symptomatic prostatism, where prostatectomy is not considered necessary
2. 5-alpha reductase inhibitor with symptomatic prostatism, where prostatectomy is not considered necessary
3. Topical vaginal estrogen or vaginal estrogen pessary for symptomatic atrophic vaginitis
Section H: analgesics
1. High-potency opioids in moderate-severe pain, where paracetamol, NSAIDs or low-potency opioids are not appropriate to the pain severity or have been ineffective
2. Laxatives in patients receiving opioids regularly
Section I: vaccines
1. Seasonal trivalent influenza vaccine annually
2. Pneumococcal vaccine at least once after age 65 according to national guidelines

Taken from O'Mahony et al. [29]

Table 6 AGS 2012 Beers criteria: potentially inappropriate medications and classes to avoid

Anticholinergics (excludes TCAs)			
First-generation antihistamines (as single agent or as part of combination products)	Antiparkinson agents: Benztropine (oral), Trihexyphenidyl		Antispasmodics
Antithrombotics			
Dipyridamole, oral short acting[a]	Ticlopidine		
Anti-infective			
Nitrofurantoin			
Cardiovascular			
Alpha1 blockers	Antiarrhythmic drugs (Class Ia, Ic, III)	Dronedarone	Nifedipine, immediate release[a]
Alpha agonists, central	Disopyramide[a]	Digoxin >0.125 mg/d	Spironolactone >25 mg/d
Central nervous system			
Tertiary TCAs, alone or in combination	Thioridazine, Mesoridazine	Benzodiazepines	Ergot mesylates[a] Isoxsuprine[a]
Antipsychotics, first (conventional) and second (atypical) generation	Barbiturates	Chloral hydrate; Meprobamate	Nonbenzodiazepine hypnotics
Endocrine			
Androgens: Methyltestosterone[a], Testosterone	Desiccated thyroid	Estrogens with or without progestins	Growth hormone
Insulin, sliding scale	Megestrol	Sulfonylureas, long duration: Chlorpropamide, Glyburide	
Gastrointestinal			
Metoclopramide	Mineral oil, oral	Trimethobenzamide	
Pain			
Meperidine	Non-COX-selective NSAIDs, oral (Aspirin >325 mg/d)		Pentazocine[a]
Skeletal muscle relaxants	Indomethacin; Ketorolac, includes parenteral		

[a]**Infrequently used drugs.** *COX* cyclooxygenase; *NSAID* nonsteroidal anti-inflammatory drug; *TCA* tricyclic antidepressant. Adapted from the AGS 2012 Beers Criteria Update Expert Panel

lacked international spreading and validation compared to the Beers and STOPP-START criteria.

The AGS recently commented that despite having substantial overlapping with Beers 2012 criteria (comprising considerable common medications), STOPP-START criteria include some aspects that Beers criteria do not include. For this reason, AGS suggests employing both instruments as complementary to assist physicians in the decision-making about safe prescribing in older adults [28].

Table 7 AGS 2012 Beers criteria: potentially inappropriate medications and classes to avoid in older adults with certain diseases and syndromes

Cardiovascular	
Heart failure	NSAIDs and COX-2 inhibitors; Nondihydropyridine CCBs (avoid only for systolic heart failure); Pioglitazone, rosiglitazone; Cilostazol; Dronedarone
Syncope	AChEIs; Peripheral alpha blockers; Tertiary TCAs; Chlorpromazine, thioridazine, and olanzapine
Central nervous system	
Chronic seizures or epilepsy	Bupropion; Chlorpromazine; Clozapine; Maprotiline; Olanzapine; Thioridazine; Thiothixene; Tramadol
Delirium	TCAs; Anticholinergics; Benzodiazepines; Chlorpromazine; Corticosteroids; H_2-antagonist; Meperidine; Sedative hypnotics; Thioridazine
Dementia and cognitive impairment	Anticholinergics; Benzodiazepines; H_2-receptor antagonists; Zolpidem; Antipsychotics, chronic and as-needed use
History of falls or fractures	Anticonvulsants; Antipsychotics; Benzodiazepines; Nonbenzodiazepine hypnotics; TCAs and selective; SRIS
Insomnia	Oral decongestants; Stimulants; Theobromines
Parkinson's disease	All antipsychotics (except for quetiapine and clozapine); Antiemetics
Gastrointestinal	
Chronic constipation	Oral antimuscarinics for urinary incontinence; Nondihydropyridine CCB; First-generation antihistamines as single agent or part of combination products; Anticholinergics and antispasmodics
History of gastric or duodenal ulcers	Aspirin (>325 mg/d); Non-COX-2 selective NSAIDs
Kidney and urinary tract	
Chronic kidney disease Stages IV and V	NSAIDs; Triamterene (alone or in combination)
Urinary incontinence (all types) in women	Estrogen oral and transdermal (excludes intravaginal estrogen)
Lower urinary tract symptoms, BPH	Inhaled anticholinergic agents; Strongly anticholinergic drugs, except antimuscarinics for urinary incontinence
Stress or mixed urinary incontinence	Alpha blockers

CCB calcium channel blocker; *AChEI* acetylcholinesterase inhibitor; *BPH* benign prostatic hyperplasia; *CNS* central nervous system; *COX* cyclooxygenase; *NSAID* nonsteroidal anti-inflammatory drug; *SRIS* serotonin reuptake inhibitors; *TCA* tricyclic antidepressant. Adaptado de The AGS 2012 Beers Criteria Update Expert Panel

In spite of its limitations, it seems that these standardized tools are necessary and valuable for medication prescription in older adults. The use of these instruments to support and reinforce therapeutic guidelines, together with the implementation of systematic reevaluation of drug prescription in daily practice, may help to reduce adverse drugs events in this population and, obviously, to optimize clinical practice.

Table 8 AGS 2012 Beers criteria: medications to be used with caution in older adults

Drug	Rationale	Recommendation
Aspirin for primary prevention of cardiac events	Lack of evidence of benefit versus risk in individuals aged >80	Use with caution in adults aged ≥80
Dabigatran	Greater risk of bleeding than with warfarin in adults aged >75; lack of evidence for efficacy and safety in individuals with CrCl <30 mL/min	Use with caution in adults aged ≥75 or if CrCl <30 mL/min
Prasugrel	Greater risk of bleeding in older adults; risk may be offset by benefit in highest-risk older adults (e.g., with prior myocardial infarction or diabetes mellitus)	Use with caution in adults aged ≥75
Antipsychotics; Carbamazepine; Carboplatin; Cisplatin; Mirtazapine; SNRI; SSRI; TCA; Vincristine	May exacerbate or cause SIADH or hyponatremia; need to monitor sodium level closely when starting or changing dosages in older adults due to increased risk	Use with caution
Vasodilators	May exacerbate episodes of syncope in individuals with history of syncope	Use with caution

CrCl Creatinine clearance; *SIADH* syndrome of inappropriate antidiuretic hormone secretion; *SNRI* serotonin–norepinephrine reuptake inhibitor; *SSRI* selective serotonin reuptake inhibitor; *TCA* tricyclic antidepressant. Adapted from the AGS 2012 Beers Criteria Update Expert Panel

Furthermore, it is important to note that although these tools try to make medical practice easier, they should not replace either the comprehensive geriatric assessment (considering risk–benefit ratio), or the comorbidities and functional assessment, among other conditions necessary for a good prescription in older adults.

Prevalence

It is difficult to estimate the real prevalence of PIMs due to the heterogeneity of the studies, which depends not only on the used criteria but also on the level of care, the different prescription practices, or even the country, or region where the study is developed, leading to a great variability of results. Thus, in community-dwelling older adults, prevalence of PIMs range from 20 to 70 % according to STOPP criteria, with higher features in hospitalized subjects (16–77 %), and almost reaching 100 % in institutionalized ones [31].

In Spanish studies, both in hospitalized older adults and in community-dwelling ones, the most prevalent STOPP single criterion was the use of long-acting

benzodiazepines, and at hospital level, the use of neuroleptic drugs as hypnotic ones, the prescription of nonsteroidal anti-inflammatory drugs (NSAIDs) in patients with hypertension, and the duplicity of drugs belonging to the same therapeutic class have also been identified as highly prevalent [31]. On the other hand, in Primary Care level, besides the aforementioned benzodiazepines, acetylsalicylic acid without clinical indication and the use of NSAIDs for longer than 3 months to treat chronic osteoarticular pain were identified as the main STOPP criteria.

Literature review concludes that the use of explicit criteria contributes to detect medication-related problems, but it would be important to demonstrate that their use improve older adult's health outcomes. In this sense, the ambitious European multicentric project "Senator" is being conducted to try to determine if the use of STOPP-START criteria in hospitalized older adults is useful for reducing the incidence of adverse drugs reactions. At the moment, the use of STOPP criteria has demonstrated to detect adverse events and ADR both in hospitalized subjects and in community-dwelling ones. Moreover, they have also demonstrated their utility in predicting the risk of readmission through the first year after hospital discharge, and in reducing the incidence of ADR during the hospital stay if used at admission. Likewise, in economic terms, net cost of potentially inappropriate prescriptions in Ireland in 2007 using STOPP criteria was about 38,664,640 €, which means 318 € per patient and year [23].

Medications Frequently Associated to Adverse Drug Reactions

Half of the drug-related hospitalizations in adults older than 80 years are related to the use of warfarin, antiplatelet agents, insulins, and oral hypoglycemic agents. For that reason, adequate management of these drugs is important to reduce hospitalization risk due to ADR. Furthermore, the addition of digoxin to warfarin and insulin, explains up to a third of emergency department visits due to drug-related problems. In fact, adverse drug events associated with the use of any of these three agents suppose a 35-fold increased risk of needing emergency department assistance, compared with the remainder drugs included in Beers criteria [32]. NSAIDs, the group with more easily avoidable prolonged prescriptions, should also be included in a hypothetical medication list to detect increased risk of hospital assistance.

Obviously, the association between antiplatelet agents, hypoglycemic agents, and digoxin with an increased rate of healthcare demand should be appropriately interpreted. First, all of them are widely used in clinical practice and therefore the risk of causing drug-related problems increases proportionally. Second, nobody question their utility in certain well-known situations. For that reason, the aforementioned data should only be an attention call to encourage an appropriate

prescription, and suitable information for the patient and caregivers in order to be able to know and recognize eventual medication-related problems. We should also take into account that anticipating problems is not always the same than avoiding them. Clinicians should take care when prescribing a new drug to choose the most appropriate one in the context of the medication schedule, and later on to early detect drug-related problems, and specially survey those drugs with a narrow therapeutic range.

Underprescribing

In the past, physician efforts have focused on avoiding polypharmacy and its undesirable consequences. Even though, when comparing with other forms of potentially inappropriate prescribing (misuse, overuse), medication underuse is also frequent but still poorly understood in its nature. Explicit screening instruments for assessing prescriptions such as the START and *Assessing Care of Vulnerable Elderly* (ACOVE) are commonly used for this issue, while implicit criteria such as the *Assessment of Underutilization index* (AOU) are less often applied. In any case, these tools are a promising and easy to apply strategy against underprescribing, and have demonstrated their utility in detecting underprescribing prevalence.

Most of the studies related to underprescription focus on specific symptoms or disorders: antiplatelet agents in patients with cardiovascular risk factors, statins in secondary prevention, calcium in osteoporosis, or use of diverse analgesics to manage chronic or oncologic pain. In a population-based study, underprescribing was observed in 64 % of outpatients aged 65 years and older, who were using five or more medications, regardless of polypharmacy. The results of the studies using START criteria estimate underprescription in around 25 % of community-dwelling older adults, and 60 % of the hospitalized ones. Spanish studies in community-dwelling older participants described higher prevalence of underprescribing of up to 40 %, ranging from 20 to 54 % [33].

The most common underused drugs in community-dwelling older adults according to START criteria are ACE inhibitors in heart failure patients, anticoagulants in atrial fibrillation, statins in diabetes when at least another cardiovascular risk factor is present, metformin in diabetes, and calcium and vitamin D in older adults with osteoporosis [33]. Some studies in Spanish hospitalized older adults have shown a similar pattern of underprescription. However, in the case of intensive care units, the accuracy of these data should be reviewed, since there is a frequent underuse of drugs that can be considered secondary in hospitalized elders with severe disease. It should be outlined, nevertheless, that most common underused drugs in hospitalized older adults in international studies are those related to the cardiovascular system.

There are numerous causes for underprescribing. The first one is the lack of evidence of some drugs in older adults with comorbidities, related to inclusion omission and biases in randomized clinical trials of this population. The second is

the absence of Clinical Practice Guidelines for older adults, or disagreement on them. The third one is the reluctance of physicians to add new drugs in older adults with polypharmacy, due to concerns about lack of adherence or increased risk of drug-drug interactions and adverse drug events. Ageism should never be a reason for underprescription, and economic burden neither. However, they represent a relevant problem, particularly in countries where the out-of-pocket contribution to drug expenditure is high.

There are obvious consequences of underprescribing in certain diseases: deficient pain control (underuse of painkillers), increased incidence of embolic events (underuse of antithrombotic agents in atrial fibrillation), or poorer control of arterial blood pressure (underuse of antihypertensive drugs in patients with hypertension), among others. Overall, the consequences of underprescribing are increased morbidity, disability, healthcare utilization and costs, as well as mortality. Thus, underprescribing cost according to START criteria has been estimated in 112,745 € per 600 patients per year [34].

Some interventions may help to improve the quality of prescriptions and reduce the burden of underprescribing, like the use of comprehensive geriatric assessment, or treatment chart reviews by pharmacists or other trained experts [35]. Besides that, educational interventions supported often by implicit and explicit criteria, have demonstrated improving drug prescription quality by reducing underuse [36]. Since START criteria are easier to apply in clinical practice than other instruments, it is conceivable that their systematic use may contribute to reduce underprescribing and to improve health outcomes in older patients.

However, underprescription might be a legitimate medical decision. In older patients with a limited life expectancy, the prescription of a new drug to treat a specific comorbidity which has an expected time-until-benefit longer than the expected survival time, could not be appropriate. In fact, underprescribing (defined as the omission of drug therapy that is indicated for the treatment or prevention of a disease or condition according to the current clinical practice guidelines) can be divided into inappropriate and rational underprescribing. In rational underprescribing, the physician or individual makes a well-considered deliberate decision not to prescribe or take a recommended drug. Therefore, it is important to distinguish between rational and inappropriate underprescribing, because only the last one should be avoided.

Polypharmacy Versus Potential Prescription Omissions

Some studies show the possible association between polypharmacy and underprescription of indicated medicines, two apparently opposing concepts, since the probability of potential prescribing omissions increased significantly with polypharmacy. In a study of community-dwelling subjects older than 65 from Lanzarote, a Spanish Canarias island, the proportion of patients with at least one omission was 59 % in polymedicated ones [33].

However, it is also reasonable to think that physicians may be discouraged from adding more medications to an already long prescription list. Faced with a clinical case of comorbidity and polypharmacy, it is likely that priorities for therapy are set and, as a result, other therapies intended for prevention are sacrificed. Thereafter, we must be cautious when interpreting these markers of prescribing quality. We think they may not always be inappropriate and should be evaluated together with other major issues such as life expectancy, time-to-benefit, goals of care, and patient preferences. It would also be reasonable not only to include standard efficacy variables within the therapeutic goals but also to give consideration to the possible improvement in functional status and the quality of life for the patients.

Appropriate Prescription

When facing a new prescription for an older adult in primary or secondary care, 15 factors should be taken into consideration in order to improve the quality of life of that person, minimizing risks of ADR.

1. Clear clinical indication for the drug, revising diagnosis, and clinical guidelines specially designed for older adults if available. Consider non-pharmacological actions if possible before medicine prescription. Evaluate benefits and harms of the drug in this patient.
2. Identify patient goals, preferences, and barriers to prescription.
3. Use the most adequate or preferred pharmaceutical formulation for drug administration.
4. Be aware of pharmacokinetic and pharmacodynamic changes with aging. Revise renal function and changes in body composition.
5. Assess patient's characteristics through a geriatric assessment including age, sex, frailty, function, cognition, geriatric syndromes, nutritional status, comorbidity, and social support.
6. Consider therapeutic goals, mainly when dealing with frail, disabled, demented, or palliative-care older adults. In these population, frailty control, function preservation, quality of life, symptoms relief, and lag-time-to-benefit, should prevail over survival time.
7. Drug chart review, both including usually prescribed medication, and "over the counter" medication. Furthermore, patients over 75 years should have their medicines reviewed annually, and those on four or more twice yearly, promoting communication between the Primary Care physician, the specialist, and the pharmacist.
8. Consider drug-drug, drug-food, and drug-disease interactions.
9. Consider deprescribing low utility or preventive drugs when time-to-benefit exceeds survival time, before prescribing new agents.
10. Include new medications one by one, beginning with low doses, and regularly increase until efficacy or maximal dose.

11. Consider potential for patient-related errors (poor vision, cognitive impairment, lack of caregiver, polypharmacy, non clear instructions, medication difficult to administer like inhalators or subcutaneous).
12. Consider use of prescribing indicators in order to reduce PIMs. The most recommended ones are the STOPP/START and the Beers criteria. Use of Computer-Based Systems could be of value.
13. Be aware of patient transitions between emergency departments, hospitalization, nursing home, and own house, to avoid discrepancies in prescriptions. Medication reconciliation is mandatory in every patient transition.
14. Empower patients and caregivers about medication control, including adherence, possible benefits, and possible adverse effects. Use calendars, reminders, multi-compartment medication distribution aids, or information and communication technologies (ICTs) when necessary and available.
15. Monitor adherence in a near scheduled visit, and be aware of new symptoms appearance in order to early detect ADR.

Deprescribing

Many elements are actually available to optimize drug prescription in older adults, in other words, to detect avoidable drugs, or drugs to be worried about, as they are usually related to complications needing hospital care. We define deprescribing as the systematic process of identifying and discontinuing drugs in instances in which existing or potential harms outweigh existing or potential benefits within the context of an individual patient's care goals, current level of functioning, life expectancy, values, and preferences. We should deprescribe unnecessary drugs, potentially harmful ones, or even those with longer time-until-benefit compared with the expected survival time. Medications without real benefit just lead to unneeded costs and risks [37].

For this reason, the objective of a Geriatrician who deprescribes should neither be reducing the number of drugs just in a quantitative or qualitative manner, nor only optimizing the prescription profile. The main objective should be to improve the functionality and quality of life of the older adult by the application of the aforementioned attitudes. Evidence of efficacy for deprescribing is emerging from randomized trials and observational studies, and frequently takes as a targeted population those polymedicated older adults fulfilling Fried's frailty criteria.

Deprescribing should be considered as a continuous and dynamic process in which both the physician and the patient should be involved and, if necessary, the caregivers or relatives. However, it does not consist in removing drugs randomly, but in optimizing the medication on the basis of good clinical practice principles, in the same way on which drug prescription is based upon. Deprescription in frail and disabled older adults should be done with a close monitoring of eventual

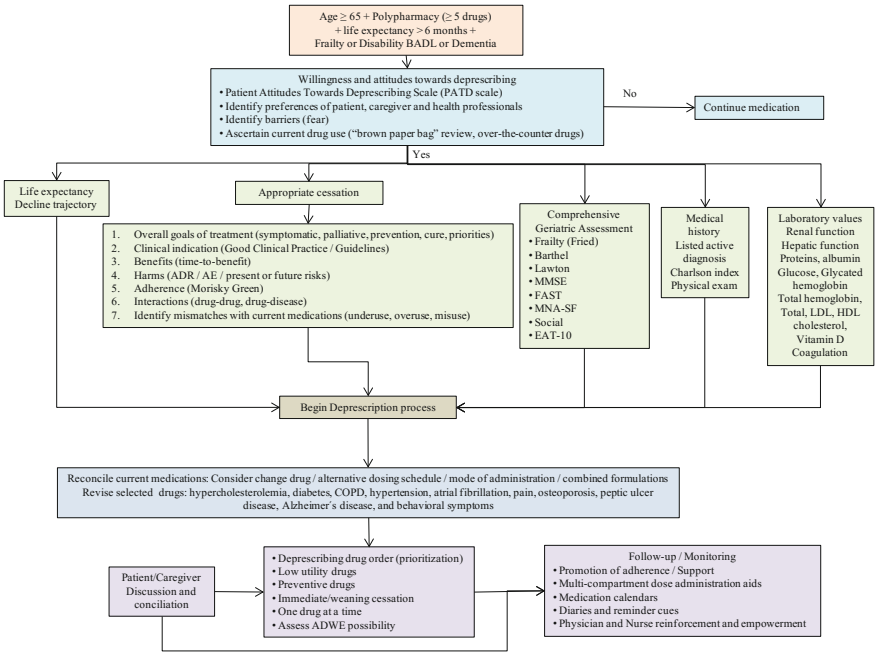

Fig. 1 Deprescribing process in frail and disabled older adults. *ADR* Adverse drug reaction. *AE* Adverse event. *MMSE* Minimental state examination. *FAST* Functional assessment staging. *MNA-SF* Mininutritional assessment short form. *EAT-10* Eating assessment tool 10. *ADWE* Adverse drug withdrawal event

withdrawal consequences, and should be oriented to improve treatment adherence, taken into account patient preferences and characteristics (Fig. 1) [38].

It has been reported that between 20 and 100 % of antihypertensive drugs, neuroleptics used to dementia-related behavioral symptoms, and benzodiazepines, could be discontinued safely if the next recommendations are followed: make an adequate patient selection, agree with the patient about decisions made, train the patient in risks and benefits of deprescription, and take a close follow-up of the process. Furthermore, more than three of them had normal blood pressure values after a year with an additional decrease of falls and an improvement of cognition. Other therapeutic groups as lipid lowering drugs or biphosphonates, in which time-to-benefit often exceeds life expectancy, should be looked after. Nowadays, enough evidence exists in the literature about long-term benefit of this kind of interventions, even despite the heterogeneity of the studies or the questionable methodological quality in some cases.

Deprescribing should be done anyway step by step, discontinuing only one or at most two drugs each time in order to minimize adverse withdrawal events, and

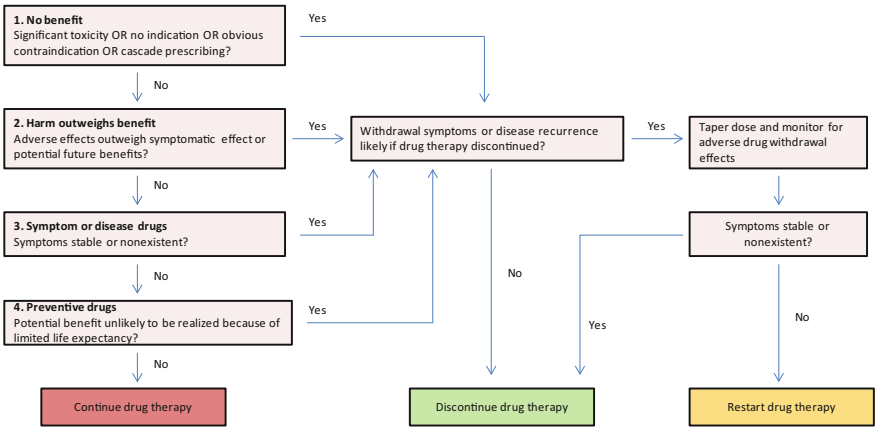

Fig. 2 Decision algorithm for order and mode drug discontinuation (modified from Scott et al. [38])

identify them easily. In that sense, it should be accepted that sometimes it would not be possible to deprescribe all the drugs identified as inadequate, and that deprescribing is not necessarily an unchangeable decision and can be reverted based on the clinical outcomes.

When deprescribing, the first step should always be to identify every drug the patient is taking, even those taken by request or without medical prescription, and the indication of each one. After that, it should be decided which drugs are suitable to be removed. For this purpose, we should pay attention to drugs without clear indication or prescribed to treat a problem for which its utility has not been demonstrated. We also should check those drugs prescribed by knock-on effect (prescribed to reverse or mitigate adverse effects of another drug included in the patient's medication list), those potentially inappropriate drugs according to PIMs criteria, and high-risk drugs (those in which its potential or real risks exceed the expected benefit). Finally, we should identify the drugs that have not been effective for the purpose they were prescribed for, the cases in which the problem is already resolved, and those preventive drugs in which time-to-benefit exceeds life expectancy (Fig. 2).

Lag-Time-to-Benefit

The benefit of a medication could be more difficult to achieve in the presence of one or more comorbidities, associated to changes in pharmacokinetics, drug interactions, the patients' function, or life expectancy. In patients with multimorbidity taking multiple medications, there are less certain benefits and greater susceptibility

to harms. Individualization of decisions in this group of patients is mandatory because it is possible that time-to-benefit exceeds patient's life expectancy. Likewise, in patients with multimorbidity, life expectancy may be reduced as a consequence of multiple chronic diseases, eliminating the clear benefit of treating any specific condition. We define time-to-benefit as the time until a statistically significant benefit is observed in trials of people taking a therapy compared to a control group not taking the therapy.

Most of the parameters used in clinical trials (relative risk, odds ratio, or absolute risk reduction) analyze the amount of benefit of a treatment or intervention versus not implementing this treatment/intervention. It is unusual to determine, or at least publish and inform, about time required until benefit begins. However, time-to-benefit in older populations is at least as important as the benefit of the treatment, or even more. Consequently, when time-to-benefit of a preventive action exceeds individual's life expectancy, the risk–benefit ratio might shift and the risk becomes dominant. Furthermore, it should not be forgotten that same factors that reduce life expectancy as advanced age, functional decline or comorbidities, are also risk factors for complications and adverse drug events [39].

It is quite frequent to see how treatments for chronic diseases as hypertension or diabetes are associated to adverse events in older adults like orthostatic hypotension, hypoglycemia, falls, depression, or cognitive impairment, leading to impaired quality of life and increasing the risk of immediate complications (fractures, fear to fall syndrome, dizziness, functional decline, immobility syndrome, etc.), while benefits take years to appear. Spanish scientific societies have developed consensus documents on primary and secondary prevention of cardiovascular disease for persons aged 80 and older, on which recommendations about lifestyle modifications and the treatment of cardiovascular risk factors in this specific population are made. Furthermore, there are European guidelines specifically focused on diabetes mellitus in frail older adults. Anyway, given immediate risks and delayed benefits, treatments for asymptomatic conditions should also be targeted to older patients whose life expectancy is greater than the lag-time-to-benefit. The process for calculating lag-time-to-benefit in a determined patient could be as follows [40]:

1. Estimate life expectancy by using estimation indexes. Mortality indexes which include comorbidity and functionality together with age are more accurate in predicting life expectancy than those that include only age, and should be preferred. There are calculators available as, for example: http://eprognosis.ucsf.edu.
2. Estimate the preventive intervention's lag-time-to-benefit.

3.a If life expectancy is much greater than lag-time-to-benefit, the intervention may help and should generally be recommended.

3.b If life expectancy is much less than lag-time-to-benefit, the intervention is more likely to harm and generally should not be recommended.

3.c If life expectancy and lag-time-to-benefit are roughly equivalent, patient preferences should play the dominant role in decision-making.

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Medication Adherence and Monitoring

Hubert Ebner and Günter Schreier

I often say that when you can measure what you are speaking about, and express it in numbers, you know something about it;
(Lord Kelvin)

Abstract Non-adherence to a drug therapy is often the reason for not achieving the therapeutic goals in patients. Thus, measuring and monitoring drug adherence is an important aspect to understand patients' adherence patterns and behavior as well as to provide supportive measures to enhance or reestablish adherence to a prescribed regimen. A variety of different Adherence Measurement and Monitoring Systems (AMS) exist although there is no single AMS or method considered to be the gold standard today. These range from simple Apps that issue alerts and reminders to patients up to AMS that facilitate automated, telemedical interactions between the physician and the patient to initiate corrective interventions by making use of a variety of data sources. When applied to patients with several morbidities, co-morbidities, and disabilities appropriate AMS still remain a challenge.

Keywords Mobile health (mHealth) · Adherence quantification · Telehealth · Adherence management systems · Drug identification

This chapter builds on a previous article [1] which comprehensively elucidated the pivotal role of adherence for health care today and expands the technical aspects of the underlying concepts, in particular the relationship of Adherence Measurement and Monitoring Systems (AMS) and telehealth. It strives to give an overview on algorithm-based definitions of adherence and summarizes the current state-of-the-art of AMS. The chapter tries to sort the huge variety of AMS into different

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S. Stegemann (ed.), *Developing Drug Products in an Aging Society*,
AAPS Advances in the Pharmaceutical Sciences Series 24,
DOI 10.1007/978-3-319-43099-7_31

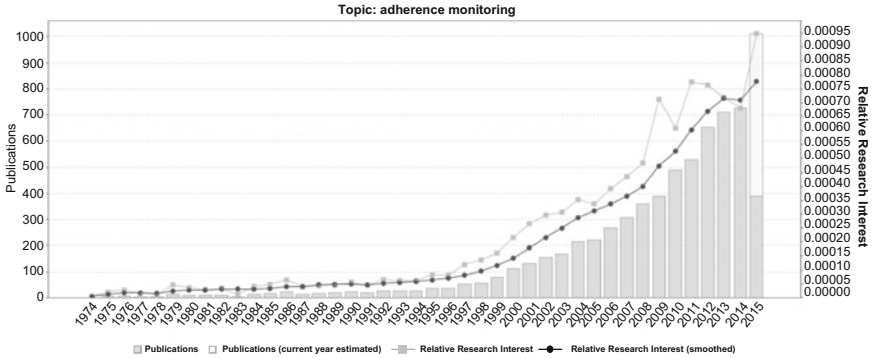

Fig. 1 Evolution of the number of publications listed in PubMed in the topic 'adherence monitoring' over the years

classes based on aspects like the point of its action in the medication therapy process chain, the underlying technology or the type of communication involved and gives an outlook on what AMS could look like in the future based on current technological developments like the Internet of Things (IoT), all from the perspectives and often related to the activities of the authors.

General Importance of the Topic

Figure 1 displays the evolution of the number of articles retrieved from PubMed by using the search term 'adherence monitoring.'[1] Although the numbers somewhat change depending on the query terms, it clearly indicates both that the absolute number ('Publications') of articles rapidly increase as does the 'Relative Research Interest,' i.e., the percentage of articles dealing with this topic as compared to all articles indexed in PubMed over time. This reflects that the topic is of increasing importance today and in the foreseeable future.

What Is Adherence?

In medicine, adherence is defined as the degree of consistency to which the patient's behavior (e.g., taking medication, modifying lifestyle, etc.) corresponds to the recommendations of the healthcare provider, e.g., the treating physician. There is an important difference to the concept of 'compliance,' in that adherence focuses

[1] www.gopubmed.org, last accessed 7.7.2015.

on a jointly responsible agreement of the healthcare provider AND the patient [2]. The ultimate goal is to increase patients' self-competence in dealing with their illnesses and to integrate it into their lives [3].

What Is Non-adherence?

Unintended and Intended Non-adherence

Basically, adherence to a drug therapy requires that a patient has the intention to be adherent to the medication regimen in the first place. Patients may have difficulties to manage the medication schedule on their own, i.e., taking the right drug in the right dose at the right time, which may lead to unintended non-adherence. This type of non-adherence can potentially be corrected with AMS. Intended non-adherence, however, is a self-determined decision of a patient deliberately not to follow the therapy regimen. These two types of non-adherence, obviously, need to be tackled by different approaches. Whereas the first type needs to address the patients' difficulties, e.g., sending proper reminders to ameliorate forgetfulness, intended non-adherence needs to address the issue of motivation and, e.g., try to communicate the benefits of adhering or the hazards of not adhering to the patient.

Alert systems with acoustic and visual signaling or any other signaling that is detectable by the patient can be sufficient to improve the adherence in older patients with forgetfulness or cognitive impairments, which might not work in patients with poor believes in the usefulness of the therapy as such. Because of the high prevalence of frailty and cognitive decline in a geriatric patient population, the percentage of unintended non-adherence is likely to be higher and the primary concern in those patients.

Since the concepts of adherence and non-adherence are strongly related to psychological issues, any attempt to improve or manage adherence benefits from an interdisciplinary approach where clinicians, pharmacologist, psychologists, engineers and—last but not least—patients, collaborate to find tailored solutions for specific settings.

Qualitative Adherence Measures

Non-adherence has been described as six distinct types of behavior, according to the following list [4]:

1. Nearly adherent
2. Mainly adherent with some irregular timing
3. Occasionally missing dose and irregular timing
4. Some drug holiday periods

5. More often drug holidays and dose omissions
6. Take the drug only very few times or never

These six stages of adherence represent a quantitative scale (ordinal value set). For further processing by computerized methods in an AMS context, this and other quantitative scales need to be mapped to a numerical scale.

Quantitative Adherence Measures

Beyond the qualitative adherence definitions, some more stringent definitions based on algorithms that can be used to quantify adherence are needed. Only with quantitative measures adherence can be compared in various contexts, for example within a given individual:

> the adherence of the patient increased by 10 % as compared to the previous month

or across a patient cohort:

> as compared to the control group, adherence increased significantly by 15 %" in the group of patients who were supplied with an AMS.

The following table lists the most commonly used quantitative adherence measures which have been described in the literature so far.

The adherence measures as provided in Table 1 share some common concepts but differ in the details of how they are computed. The most frequently used definition in the literature is the A_{pilltime} [5, 6]. A_{pilltime} is calculated as the number of pills gone, assuming that the patient has taken them in a specified period of time X divided by the number of pills prescribed for the same period of time X, multiplied by 100. As a rule of thumb, patients who exhibit an A_{pilltime} value above 80 % are considered to be adherent. Similar to the A_{pilltime}, A_{pilldays} defines adherence as the dosing days ratio calculated with the number of days doses were taken, divided by the number of days where doses were prescribed, multiplied by 100 [7]. Therefore, in contrast to A_{pilltime}, which focusses on the number of pills, A_{pilldays} is based on the count of days the prescribed dosage was taken.

A_{MEMS} designate medication event monitoring system (MEMS) adherence rates [8]. They can be considered as an approximation of A_{pilltime}, in which MEMS are used to monitor the opening of pill bottles to capture the patient's medication intake. The authors of [8] define adherence measured by MEMS as the mean number of bottle openings not exceeding the number of doses prescribed per day divided by daily prescribed doses over a month. This accounts for excess bottle openings which would otherwise lead to A_{MEMS} values higher than 1. Another MEMS related definition [9] is to count the number of days on which at least one bottle opening occurred and divide this by the number of monitoring days, which is the MEMS equivalent of A_{pilldays}.

Table 1 Adherence measure and different definitions of adherence and related terms as found in the literature

Adherence measure[a]	Definition	References
A_{pilltime} [%]	Number of pills gone (assuming they have been taken) in time period *X*/number of pills prescribed for time period *X*	[5, 6]
A_{pilldays} [%]	Number of days dose taken/number of days of dosing	[7]
A_{MEMS} [%]	The mean of the number of bottle openings not exceeding the number of doses prescribed for the day divided by the number of doses prescribed per day, over a month	[8]
A_{MEMSdays}[%]	Number of days on which at least one bottle opening was registered divided by the total number of monitored days	[9]
$A_{\text{therapeuticcoverage}}$ [%]	Time spent with efficacious drug concentrations/time on therapy	[10–13]
$A_{\text{frequencyholiday}}$	Frequency of drug holidays: Frequency of episodes with ≥3 days without drug intake	[14]
A_{MMAS} [score from 1 to 8]	Questionnaires consisting of four items/8 items scored with 'Yes' = 0 and 'No' = 1. The adherence is finally calculated by the sum of the scores	[15, 16]
A_{VAS} [%]	The patients points on a visual analog scale from 0 to 100 % to indicate to which extent he/she was adherent to the prescribed medication	[17, 18]

[a]The notations of the adherence measures were defined by the authors of this chapter

One further metric for adherence found in the literature [10–12], is the therapeutic coverage ratio $A_{\text{therapeuticcoverage}}$. It is defined as the sum of intervals between the doses where the drug acts divided by the total duration of the treatment. Very similar to this definition, [13] defined adherence based on monitoring of therapeutic drug levels. Patients are considered adherent if their measured drug level is in the therapeutic range of the specified drug intake. A drop in the medication level of a certain predetermined percentage is interpreted as non-adherent.

$A_{\text{frequencyholiday}}$, defined in [14], does not care about details of the number of pills taken, drug doses or drug concentrations. It assesses the occurrence of drug holiday events. Drug holidays, also known as drug vacations, are defined as periods of time when the patient completely stops taking a particular or all prescribed medication. The authors defined one drug holiday event as the lack of medication intake for at least 3 days in a row. Therefore, the drug holiday event frequency $A_{\text{frequencyholiday}}$ is inversely related to the degree of adherence.

Adherence definitions based on questionnaires use scales for the determination of the adherence. One example is the Morisky Medication Adherence Scale (MMAS) [15]. The original MMAS consists of four items: (1) Do you ever forget to take your medicine? (2) Do you ever have problems remembering to take your medication? (3) When you feel better, do you sometimes stop taking your medicine? (4) Sometimes if you feel worse when you take the medicine, do you stop taking it?

The latest scale, called MMAS-8, consists of eight items. The first seven follow the yes/no regime of the MMAS-4, the eighth item consists of a 5-point Likert response [16]. A_{MMAS} is classified into the following adherence scores: high (score: 0), medium (score: 1–2) and low (score ≥3) for both, MMAS-4 and MMAS-8.

Another example for questionnaire based adherence is the use of a visual analog scale (VAS) [17] which is used to measure subjective perceptions (e.g., pain). Often, the scale is a simple line with endpoints representing the start- and end-conditions of the measurement value. In [19] the scale was used by patients to guess their medication adherence A_{VAS}. It started from point 0 %, meaning that the patient did not take any prescribed medication to the endpoint 100 %, and meaning that the patients exactly took their medication as prescribed. Additionally, the scale was divided into 10 % intervals.

Adherence to What and by Whom?

The primary topic of this article deals with the adherence of patients to drug therapies. However, the same term has also been used to assess whether doctors prescribe medicines according to related guidelines and that this type of adherence may also significantly affect the outcome [20].

In advanced therapeutic settings, for example, where patients perform frequent blood glucose self-measurements and doctors are supposed to provide telemedical feedback in regular intervals, the very same definition of adherence may be directly applied to both, the doctor's and the patient's behavior.

AMS Information Sources in the Medication Pathway

The medication process consists of a number of distinct steps, each of which can be used as a source of data for adherence monitoring. In Fig. 2, eight such steps are depicted, starting with the prescription and ending with the drug causing the therapeutic effect.

Table 2 lists eight steps of the medication process, starting with prescribing to finally causing the therapeutic effect.

Table 2 gives brief explanations how data in each of these eight steps can be utilized for AMS as well as references to AMS approaches found in the literature.

In the first task of the process chain, i.e., prescribing, the doctor should assess the prescription data periodically together with the medical record data and look for hints related to adherence [21]. Distributing adherence monitoring primarily deals with adverse drug events (ADE) [22] and their detection. As an example of how to explore ADEs Sauters et al. [22] developed a tool that searches through the Austrian health claims data.

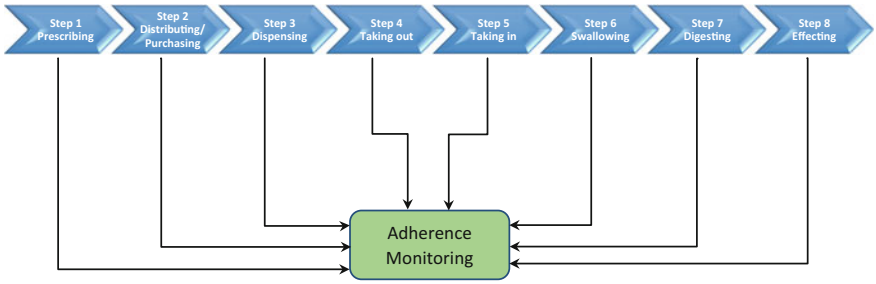

Fig. 2 The medication process chain—each step can potentially provide data for AMS

Table 2 The medication process chain broken down into eight distinct steps as the basis for AMS

Step	Source and relevance for adherence monitoring	References
1	Prescribing Assessment of prescription pattern in the electronic health record (EHR) for adherence signs	[21]
2	Distributing/purchasing Assessment of data for consistency with adherence pattern	[22]
3	Dispensing Monitoring the dispensation of drugs via eDispensors	[23, 24]
4	Taking out Monitoring when pills are taken out of their packaging using medication event monitoring systems (MEMS) or eBlisters	[25–27]
5	Taking in Monitoring when pills are taken with the hand and moved to the mouth (recognition of characteristic movements)	[28, 29]
6	Swallowing Monitoring the swallowing process	[30–32]
7	Digesting Monitoring the process of digesting	[31, 32]
8	Effecting Monitoring the proximal effects of just-in-time treatments	[33]

Adherence in the process of dispensing can be monitored automatically or manually. In automatically dispensation systems like they were used in [23], patients got equipped with a prefilled eDispenser for each cycle of their drug regime. An alarm sounded to remind the patients to take their medication. The eDispenser, which had to be filled periodically and individually by caregivers, allowed to monitor whether the patients took their daily dose during the programmed time slot.

'Taking out' adherence monitoring focusses on the opening of pill bottles or blisters. Therefore, these devices need to be equipped with electronic sensors that recognize the process of opening [25–27]. The sensors are either active or passive.

Active sensors send the event of opening directly to the AMS. Passive sensors need to be read by a receiver device, e.g., a smartphone and subsequently need to be sent to the AMS.

The next step following 'taking out' step is the process of orally taking in the drugs. There is an approach where patients are videotaped during these process steps, starting with opening the pill bottle until putting the pills into their mouth. To ensure a correct monitoring of the intake process the patients have to do this in a prepared environment, e.g., while sitting at a table with the pill bottles on it. The camera is positioned some meters in front of the table. Adherence monitoring is done by successfully detecting each part of the intake process (grabbing the pill bottle, opening the bottle, taking the pill out, movement of the hand to the mouth) in the correct order [28, 29].

Adherence monitoring based on swallowing measurements applies to special modified pills. These pills contain an extra piece of technology in addition to their drug substance. In [30] this piece of technology is a tiny magnet attached to the pill. To monitor the swallowing process, patients wear a necklace with an integrated magnetic sensor module. This module powered by a battery is able to detect the magnetic field that is produced by the pill when the pill is swallowed by the patients.

A further development of so-called smart pills is to attach the pills with an ingestible sensor [31, 32]. This sensor allows measuring the adherence and other important metrics in real time after their ingestion. It consists of an integrated circuit (IC) and special layers that act as a battery when they get in contact with the gastric acid. To receive the signals processed by the IC the patients have to wear a receiver patch directly on the skin. Additionally, care needs to be taken that the patch is attached close to the stomach of the patient.

Finally, the last link of the adherence monitoring process chain is called 'effecting' [33]. It deals with the idea of just-in-time interventions. That means, these interventions intend to provide treatments in the moment they are needed (e.g., medication intake on time). These treatments are supposed to have a proximal measurable effect to the patients for example blood pressure reduction. The detection of this proximal effect allows determining the adherence to the just-in-time treatment of the patient. This last step somehow links back to the first one since it is the treating physician who is actually in the best position to assess whether his/her prescriptions do cause the intended pharmacological or therapeutic effect. If this is the case, the patient can be assumed to be adherent with some probability. The challenge remains that—if not—the cause cannot directly be attributed to non-adherence but may be as well be caused by non-effectiveness of the drug in this particular patient.

Some of these process links are not suitable for adherence monitoring in real time since the lag between the observation of the initial event and the availability of the data are simply too long. For example, it may take many days or even months until the reimbursement claim for a drug that has been purchased by a patient becomes available to a healthcare fund. Most of these principles, however, are well suited to become part of AMS approaches where the crucial data are captured and

immediately relayed to computerized analysis so as to inform all parties about adherence issues in quasi real time. Such concepts are designated 'Telehealth-based AMS' in the following.

Telehealth-Based AMS—Overview

Figure 3 depicts the three major elements of a telehealth system to overcome barriers and facilitate advanced communication between patients and their caregivers, i.e.,

1. The patient—he/she is provided with a way to collect and communicate health-related data to.
2. The Telehealth service—which receives, stores, and processes the received data and presents it to.
3. The caregiver—who has access to the data, interprets the data and derives decisions with the aim to optimize the care for the patient.

These three elements are the basis of so-called closed-loop telehealth systems that allow to overcome the following three major barriers which stand in the way of optimizing adherence and thus, the therapy, in particular of chronically ill patients:

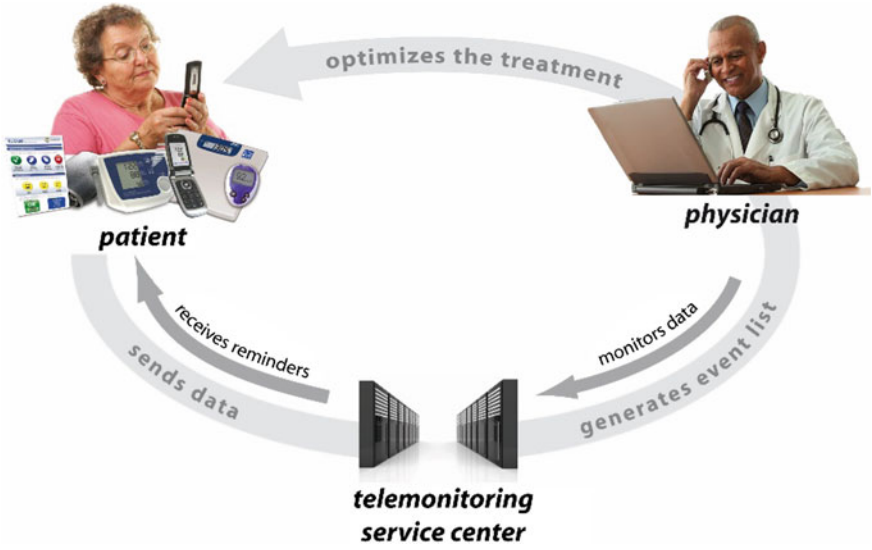

Fig. 3 Telehealth system to overcome barriers and facilitate advanced communication between patients and their caregivers across space, time, and knowledge

1. Space—patients and their caregivers no longer need to meet in the same place and at the same time to communicate. By virtue of Information and Communications Technology (ICT), patients can collect their health-related data in their natural environment, in their homes or on the move. The same applies for the capability of the doctors to make sense out of these data. Both parties can organize their lives unconstrained by the needs to make regular face to face appointments and yet the can keep in touch.
2. Time—instead of meeting at predefined dates which have been scheduled in advance or in cases of unforeseen emergencies ('just in case'), patients and caregivers communicate, when needed ('just in time') or when it is convenient and useful to them ('on demand'). Also, both partners can be notified or even alerted within a short period of time in case of major changes in health status,' as, for example, indicated by the patient ('wellbeing downgraded') or the system based on basic ('threshold exceeded') or advanced analytics ('predictive models'). Measurements can be done more frequently and timely in a telehealth setting.
3. Knowledge—the context of the patient can be observed and assessed on a much broader basis by a variety of sensors and the resulting data can be processed automatically to provide the caregivers with a compressed and tailored view on the health progression over time and the actual health situation. As a consequence, more specific, 'actionable information' can be derived which enables the caregiver to conclude on the necessary next steps. In this process, context specific and relevant clinical decision support and external knowledge sources can be included so as to support the caregiver in arriving at a suitable conclusion what needs to be done next.

After proper processing of data from both parties, the system can be set-up to automatically send reminders and alerts to correct for non-adherence, ideally in real time. The mode of sending reminders and alerts via appropriate channels or corrective interventions can be context specific and tailored to the reasons for the event in the first place.

This general concept is fully applicable to the establishment of an AMS. The sensors need to provide data about medication utilization and the therapeutic outcome targeted by the therapy. The physician needs to be provided with proper visualized adherence indicators in a timely and intelligible way as well as an integrated method to communicate back to the patient or other system partners to initiate or guide measures for adherence improvements.

Adherence and Telehealth

Telehealth and adherence are related to each other in both directions. On the one hand, telehealth approaches are needed to monitor adherence across the distance and in 'real time'. On the other hand, adherence is crucial for most telehealth

settings, since they are often designed to allow for remote medication adjustments as the primary, telemedical intervention. Therefore, up to date and comprehensive knowledge about the current medication regimen and adherence situation is crucial as a basis for adjustments, e.g., to change the dosage or to add or remove 'on demand' medication. AMS in such situations is highly relevant as a basis for remote drug therapy adjustments by healthcare providers, e.g., in heart failure patients [21]. AMS, thus, need to be an essential part of most telehealth approaches. However, a recent systematic review indicated, that the impact of adherence on costs and benefits in telehealth settings have not yet comprehensively been investigated [34].

Major challenges in the design of telehealth systems as well as AMS today are still

1. to provide patients with an easy-to-use and easy-to-learn user interface and
2. to integrate caregivers' access to such systems into their existing working infrastructure.

mHealth, pHealth, and 'The Internet of Things' for AMS

Mobile and smart phones have evolved as very flexible and convenient devices to provide access to such systems by both, patients and physicians. Today, systems are often addressed as mobile Health (mHealth) or personalized Health (pHealth) systems [35]. Due to their ubiquitous availability, mHealth-based AMS are increasingly the method of choice since they provide communication capabilities anywhere and anytime. Additionally, many smartphones today offer ways to link the physical world, i.e., dispensing devices, smart medication bottles, boxes or blisters, and even individual pills, to the virtual world to establish so-called cyber-physical systems (CPS) which is a term quite similar to the 'Internet of Things' (IoT) [36].

Near Field Communication (NFC) is a wireless interface increasingly available in current mobile phones and smartphones. It is a short range (<10 cm) wireless technology evolving from radio frequency identification (RFID). NFC is well positioned to support any activity of users that can be mapped to a 'tap and go' paradigm, e.g., where users need to 'touch' items in their environment to initiate and perform a brief communication with this item, for example, to read out sensor data. NFC is, therefore, one of the enablers of the IoT.

During the last couple of years NFC has been utilized in a number of projects to empower mHealth-based systems in support of chronically ill patients. Most of these systems incorporated AMS elements and concepts [37, 38], some of them where specifically designed as AMS [39–42].

Fig. 4 Example for a medication box with both barcode and RFID tag which can be used to identify the type of medication [44]

Drug Identification

A pivotal element in any AMS is to identify medications unequivocally. If not done automatically, e.g., by means of electronic blisters or bottles (eBlisters, eBottles) this task becomes part of the patient interaction at some point in the process chain. One way of identifying medicines is to scan the barcode which is available on each medication package. The barcode can be used to look-up the medication in a corresponding database. A similar method which does not need the 'line of sight' and which is less difficult to handle for patients is to do it via RFID. Figure 4 shows both methods used for identification of medicinal products.

Whereas barcodes representing the International Article Number (EAN-13) are readily available on all medication boxes today, RFID tags are not. However, RFID tags can be expected to be utilized for a variety of reasons like supply chain optimization and monitoring, counterfeiting prevention and, last but not least, AMS applications in the foreseeable future.

Results of the clinical study with 20 patients indicated that a multimodal mHealth concept utilizing barcode and RFID tags facilitates easy-to-use identification of medications in an AMS context [43]. Although further clinical evaluation is needed to assess whether such a tool can also enhance adherence, the system shows the potential for targeting the problem of medication management with mHealth methods.

AMS in the Geriatric Population

Adherence to drug therapy is a special challenge for elderly patients with an increasing prevalence of co-morbidities and disabilities which go along with an increasing number of different drugs to be taken simultaneously (polypharmacy). The difficulty with adherence in this population is often underestimated and adds complexity to

AMS. Discrepancy in the perception of ease or difficulty of adherence to a therapy schedule between physicians and patients have been described for severe diseases conditions like chronic heart failure that are frequent in older adults [44].

AMS need to provide appropriate ways for monitoring all of the prescribed drugs. Since older individuals may not have been exposed to the technologies used in AMS today [45], AMS who are demanding a high degree of technology skills should, therefore, be tested for appropriateness in such patient groups. As described above, on the other hand, recent developments in mobile and wireless technologies, e.g., smartphones featuring NFC, provide new and intuitive ways for patients to collect data in telehealth settings.

Provision of a weekly therapy in pill organizers is a common practice to simplify the drug therapy for older adults with polypharmacy. Although it remains a challenge to track individual pill intakes when such 'containers' are used, such devices need also be included in AMS.

Summary and Conclusions

Until now, most AMS deal with just one or a maximum of two different data sources from the medication process chain as described above. In the future this is likely to change and AMS may tap into different data sources from different links in the chain to draw a more comprehensive picture of the adherence situation in individual patients. However, to follow this concept, a number of issues need to be addressed by research and application development. The two most important ones that need to be solved are issues of standardization and of privacy regulations and patient concerns. Standardization is required to facilitate combining data from a variety of different and so far disparate information sources like Adherence Apps and medication lists from EHR systems. This would allow to assess adherence from both ends and include the patient's and the doctor's healthcare provider's perspective. New concepts for privacy protection are needed for such approaches, however that respect current and future data protection and privacy regulations and enable patients to stay in control of their data in a complex and networked environment. In all those scenarios - the direct link between the patient and the persons coordinating his/her healthcare will be pivotal, since adherence, after all, is very much about keeping these partners in touch across space and time.

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Medication Compounding in the Provision of Drug Therapy

Linda F. McElhiney

Abstract The geriatric patient population is growing. These patients naturally undergo physiological changes and may not be able to use some commercial drug products for their therapies. There is an increasing need for pharmacists to compound alternative dosage forms for these patients that meet their treatment needs. Pharmacists who work with geriatric patients need to be trained in providing compounding services, maintain a good compounding reference library, and develop good investigative skills to search for the information needed to prepare alternative, compounded dosage forms to meet the patient-specific needs of geriatric patients. This chapter is an overview of sources for compound training, reliable compounding resources that are available as references, and how to search these resources for alternative treatment options for geriatric patients.

Keywords Compound · Alternative dosage form · Training · Resources · References

Introduction

Prior to World War II, over 75 % of medications were compounded by trained pharmacists based on physician orders or prescriptions. There were very few drug manufacturers that mass-produced drug products. The art and science of compounding was taught in all pharmacy schools as part of the required pharmacy curriculum. With the discovery of penicillin and the Industrial Revolution, drug manufacturers increased and reduced the need for compounded medications. By the 1970s, pharmacy schools focused on dispensing and patient counseling because less than 1 % of all prescriptions required compounding [1].

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S. Stegemann (ed.), *Developing Drug Products in an Aging Society*,
AAPS Advances in the Pharmaceutical Sciences Series 24,
DOI 10.1007/978-3-319-43099-7_32

With the emergence of homecare services, hospice care, and total parenteral nutrition in the 1980s and 1990s, the number of compounded preparations started to increase. By 1995, 11 % of all prescriptions were compounded [2]. Based on economic decisions by the drug manufacturers, less dosage form options, and strengths are produced to decrease expenses and improve profit margins. In the twenty first century, the medical community has been focused on individualizing treatments for patients rather than relying on the 'one dose fits all' mentality of the mass-produced drug products.

Today, the geriatric patient population is increasing and this has created some new treatment challenges. Aging is a natural process with gradual change of various physiological, biological, physical, and social functions for all human beings [3]. Physiological changes in absorption, distribution, metabolism, and elimination (ADME) can significantly affect the geriatric patients' drug therapy. Their kidney or liver function may have decreased and they cannot take the commercial drug products because the doses are too high. Some geriatric patients develop problems with swallowing or have co-morbidities that prevent them from taking certain drugs or dosage forms. The need for compounding medications in dosage forms that are suitable for these patients can be met by pharmacists who have been specifically trained in compounding.

Training and Education

Since the Doctor of Pharmacy (Pharm.D.) curriculum is now the entry-level degree offered by all pharmacy schools in the United States, the focus is on clinical practice, medication management, and being part of the healthcare team to provide patient care. Routine dispensing functions in hospitals and pharmacies are now delegated to trained or licensed pharmacy technicians or automated. Prior to 2015, most pharmacy curriculums eliminated required pharmacy compounding courses; however, the Accreditation Council for Pharmacy Education (ACPE) approved and released the standards in early 2015 for the Doctor of Pharmacy degree to include extemporaneous compounding.[1] Accredited schools of pharmacy must provide instruction for the "preparation of sterile and non-sterile prescriptions which are pharmaceutically accurate regarding drug product and dose, free from contamination, and appropriately formulated for safe and effective patient use." The schools must also provide instruction in the mastery of pharmaceutical calculations to accurately prepare these prescriptions and compounded preparations that are therapeutically sound and safe for patient use.

[1]Accreditation Council for Pharmacy Education. Accreditation Standards and Key Elements For The Professional Program in Pharmacy Leading To the Doctor of Pharmacy Degree. Chicago, IL. 2015.

There are thousands of practicing and licensed pharmacists, however, that received little or no education in compounding skills and techniques. Fortunately, there are several chemical wholesalers and professional organizations all over the world that offer a variety of different compounding courses for pharmacists and technicians:

- General and advanced non-sterile compounding
- Sterile compounding
- Compounding for Hospice Patients
- Compounding for BioIdentical Hormone Replacement Therapy (BHRT)
- Compounding for Pain Management
- Hazardous compounding

The non-sterile and sterile compounding courses will cover most dosage forms that are used in the geriatric patient population: oral liquids, topicals, and transdermal delivery systems, suppositories, capsules, troches, medicated lollipops and gummies, ophthalmics, inhalations, otic preparations, nasal preparations, and injectables. These courses also offer hands-on experience in using the latest compounding equipment and technologies. The pharmacist should do some research in the local area and find out what the local patients' needs are to better serve them. There are also courses, presentations, and seminars that focus on compounding needs for specific patient populations or morbidities, such as diabetes, arthritis, neuropathies, transplants, and bariatrics.

Education and training doesn't end in the classroom setting. To obtain more education, knowledge, and expertise specific to compounding for geriatric patients, subscribe to professional pharmacy, medical, and compounding journals. They often contain information on new drugs, case reports, clinical studies, and formulations. Since geriatric patients may require lower doses or unique dosage forms, such as oral liquids, transdermal delivery systems, or suppositories, look at pediatric journals too. Information about these dosage forms are more likely to be found in pediatric journal articles because pediatric patients also require lower doses and dosage forms that are not commercially available.

Local, national, and international professional pharmacy, compounding, and medical organizations also offer opportunities to learn about compounded treatment options. They provide current information through newsletters, journals, regularly scheduled meetings and seminars. It can also be the opportunity to network with other compounding pharmacists that may also specialize in treating geriatric patients or various morbidities.

Compounding Resources

Proper training and education is not enough to become a compounding pharmacy expert in treating geriatric patients. Compounding pharmacists need good investigative skills and tools in order to develop new drug formulations or dosage forms

to treat the elderly. Unfortunately, there is no single resource available that can provide all of the information needed to develop compounded drug formulations. Building a good library collection of compounding texts and resources is the key and main tool that every compounding pharmacist must acquire and maintain.

Technical Support

Most chemical wholesalers, compounding suppliers, and professional organizations offer compounding technical support at no cost, for a nominal fee or with a paid membership. The technical support staff usually consists of pharmacists and technicians who respond within 24 h or less. Questions may be submitted through online requests on the companies' websites, via email, or called directly by phone. Some of these companies will post copies of published stability studies that can be downloaded and printed.

Journals

Although medical journals will provide good, updated information on the latest treatment options for various medical conditions that affect geriatric patients, these adult-based studies are probably not going to have any compounding information because these studies usually use commercial drug products. Search peer-reviewed pediatric journals or compound-based journals for stability studies for compounded formulations or case reports. These journals are usually provided as part of the pharmacist's membership in a professional organization.

The *International Journal of Pharmaceutical Compounding (IJPC)* is the most comprehensive journal for compounding information and is indexed by the International Pharmaceutical Abstracts, the Cumulative Index to Nursing and Allied Health Literature print index and database, the Chemical Abstracts Service and the Elsevier Bibliographic Databases. *IJPC* contains information articles on compounded treatments and case reports, formulations, peer-reviewed stability studies, pharmaceutical calculations, legislative updates, and basic compounding information to improve and enhance pharmacists' and technicians' compounding skills and knowledge. Subscribers can obtain a bi-monthly hard copy, as well as an electronic version. This journal also offers the opportunity to join a compounders' list serve which allows subscribers to network and share information with other compounders globally. It can be a valuable resource when trying to find compounding information.

Texts

The gold standard reference for compounding in the United States is the *United States Pharmacopeia (USP).* The *USP* is published by the United States Pharmacopeial Convention, which is a private, nongovernment organization that has several appointed, volunteer Committees of Experts who write the standards or best practices for compounding. All of the chapters below 1000 are legally enforceable in the United States. The *USP* is a 'living document' that is continuously updated by the Committees. It is used and recognized internationally as a compounding resource that provides information based on scientific evidence for good compounding practices, quality assurance, assigning beyond-use dates, and tested compounded drug monographs. An abbreviated online version is available for a subscription fee called the *USP Compounding Compendium.*

The *British Pharmacopeia*, also a private nongovernment organization, offers similar information as the *USP* and more commonly used in Europe. Individual European countries, such as Spain, Germany, France, Italy, the Netherlands, and the United Kingdom, also publish national formularies through their governments and provide legal guidance regarding compounding for their respective countries. Unfortunately, not all of the government-provided formulations are current. As of 2004, the Spanish formulary had not been updated in years and contained less than 25 formulas.

The compounding pharmacist must choose references that are most applicable for the pharmacy's location, as well as the patient population, to build a good compounding reference library. Compounding pharmacy practice is popular in other countries, such as Australia, Brazil, and Canada. Professional organizations from these countries also publish and sell references that may be useful for compounding.

Other good text references published in the United States that are recommended for a compounding library include the following:

- *Trissel's™ Stability of Compounded Formulations* (Trissel LA)
- *Extemporaneous Formulations for Pediatric, Geriatric and Special Needs Patients* (Jew RK, Soo-Hoo W, Erush SC)
- *Pediatric Drug Formulations* (Nahata MC, Pai VB)
- *Suppositories (*Allen LV Jr)
- *The Art, Science, and Technology of Pharmaceutical Compounding* (Allen LV Jr)
- *Compounding Guide to Ophthalmic Preparations* (McElhiney LF)
- *Handbook of Pharmaceutical Manufacturing Formullations* (Naizi SK)
- *Handbook of Pharmaceutical Excipients* (Kibbe AH).

Online Resources

Physicians may need help with dosing and treatment options for geriatric patients. They may not realize that pharmacists can compound dosage forms that can meet the needs of their patients. It is very useful for a pharmacist that specializes in compounding to have access to medical libraries online with good, reliable search engines, such as Medline, OVID, or PubMed. They are a great resource to find clinical evidence to support non-approved use for medications, compounded formulations, and compounding stability information. If an article is found but unavailable through the medical library, the librarian can often "borrow" or obtain the article from another medical library upon request.

Pharmacists can also subscribe to drug databases, such as Lexi-Comp Online or MicroMedex. Lexi-Comp contains extemporaneous preparation information, usually under the pediatric section, that is based on a published stability article. MicroMedex is a good resource to find information on unapproved uses for medications based on published studies. The citations from MicroMedex can then be used to obtain articles from the medical libraries. These databases also provide general information about the drugs, monitoring parameters, and dosing guidelines which can be used to determine the optimum dose for geriatric patients.

The best comprehensive compounding resource available online via subscription if CompoundingToday.com. It contains numerous databases, tools, formulas, information on training courses, and standard operating procedures, *Kings Guide to Parenteral Administration*, links to regulatory bodies in the United States, and up-to-date compounding information. It saves a lot of labor time in researching compounding information because it is literally a 'one-stop shopping' resource for compounding information. If there are no articles published about a compounded medication, the databases provided by CompoundingToday.com can help pharmacists develop compounded formulas for their patients. The databases include base-salt-ester weight conversions, flavorings, sodium-equivalent values, information on commercial vehicles and bases, recommendations on preservatives and antioxidants, and physicochemical properties of drugs. CompoundingToday.com is owned by the same company as the *International Journal of Pharmaceutical Compounding*.

Developing Compounded Medications

Solutions to geriatric medical problems may not always be taught in a classroom or seminar, found in a textbook, or searched online. A compounding pharmacist may need to be creative in developing a formulation to meet the needs of a geriatric patient. For example, an elderly female patient was often admitted to a local hospital and experienced severe anxiety because of it. The hospitalist wanted to prescribe oral fluoxetine for this patient; however, the patient could not swallow

capsules and could not tolerate the commercial oral liquid. From the information found in several of the compounding resources available, the pharmacist found a formula for a transdermal fluoxetine dosage form, fluoxetine 4 % pluronic lecithin organogel (PLO) gel. The compound was prepared and dispensed in a special metered-dose dispensing device called a Topi-Click which delivered 20 mg of fluoxetine in 0.5 mL or 2 'clicks' of the device. The patient tolerated the medication very well and it controlled her anxiety with minimal side effects. The patient was even discharged on the compounded medication and routinely uses it at home.

According to a few published studies, inappropriate medication use is the major cause of adverse reactions or events and can significantly affect compliance and positive clinical outcomes in geriatric patients [4, 5]. A medication may be appropriate but not available or administered to a geriatric patient in a dose or dosage form that is suitable for that patient. For example, some diabetic patients develop diabetic neuropathies as they age and their disease progresses. These neuropathies are routinely treated with oral tricyclic antidepressants (amitriptyline), anticonvulsants (gabapentin), and narcotics. All of these medications taken together systemically can cause major side effects, including profound drowsiness. Quality of life can deteriorate quickly. Again, these medications can be mixed into a transdermal cream and applied locally at the site of the neuropathic pain. The pain is controlled and the patient does not experience the significant adverse effects from taking the same medications orally.

Physical changes from aging can alter a geriatric patient's ability to swallow tablets and capsules. It is easier for these patients if their medications are in an oral liquid dosage form. Since most medications have no official pediatric medications, they are often not available in oral liquid dosage forms. Fortunately, most medications can be compounded into oral liquids for these patients to improve compliance. They can also be flavored with flavorings that are more appealing to the adult population, such as butterscotch, pina colada, crème de menthe, or teaberry. The key to finding these formulations is to look in reliable compounding references or published pediatric studies.

The compounding pharmacist needs to really assess the individual needs of each geriatric patient to develop a dosage form that is suitable for that patient.

- Does the patient have any difficulties in swallowing?
- Is the patient sensitive to experiencing adverse effects with systemic medications?
- Can the medical problem be treated locally rather than systemically?
- Does the patient have any physical limitations to administering medications?

It is up to the compounding pharmacist to find a way to administer the medication to geriatric patients that is needed to optimize treatment, improve compliance, and minimize adverse events. With the proper training, education, expertise, tools, and resources, a compounding pharmacist can provide a valuable service in treating geriatric patients who are unable to take commercial drug products.

Compounding medications can meet the needs of this fast-growing patient population.

Since the geriatric patient population is growing, drug manufacturers also need to assess the needs of these patients and develop doses and dosage forms to meet those needs. It is difficult for some elderly patients to split tablets or crush them to be added to liquids and these patients often need smaller doses or easier-to-swallow oral liquids. Developing these doses and dosage forms could also serve a dual purpose to meet the needs of pediatric patients. Currently, the only option for several of the medications is for the pharmacist to compound it.

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Geriatric Pharmacotherapy: Optimisation Through Integrated Approach in the Hospital Setting

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Abstract Since older patients are more vulnerable to adverse drug-related events, there is a need to ensure appropriate prescribing in these patients in order to prevent misuse, overuse and underuse of drugs. Different tools and strategies have been developed to reduce inappropriate prescribing; the available measures can be divided into medication assessment tools, and specific interventions to reduce inappropriate prescribing. Implicit criteria of inappropriate prescribing focus on appropriate dosing, search for drug-drug interactions, and increase adherence. Explicit criteria are consensus-based standards focusing on drugs and diseases and include lists of drugs to avoid in general or lists combining drugs with clinical data. These criteria take into consideration differences between patients, and stand for a medication review, by using a systematic approach. Different types of interventions exist in order to reduce inappropriate prescribing in older patients, such as: educational interventions, computerized decision support systems, pharmacist-based interventions, and geriatric assessment. The effects of these interventions have been studied, sometimes in a multifaceted approach combining different techniques, and all types seem to have positive effects on appropriateness of prescribing. Interdisciplinary teamwork within the integrative pharmaceutical care is important for improving of outcomes and safety of drug therapy. The pharmaceutical care process consists of four steps, which are cyclic for an individual patient. These steps are pharmaceutical anamnesis, medication review, design and follow-up of a pharmaceutical care plan. A standardized approach is necessary for the adequate detection and evaluation of drug-related problems. Furthermore, it is clear that drug therapy should be reviewed in-depth, by having full access to medical records, laboratory values and nursing notes. Although clinical pharmacists perform the

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S. Stegemann (ed.), *Developing Drug Products in an Aging Society*,
AAPS Advances in the Pharmaceutical Sciences Series 24,
DOI 10.1007/978-3-319-43099-7_33

pharmaceutical care process to manage the patient's drug therapy in every day clinical practice, the physician takes the ultimate responsibility for the care of the patient in close collaboration with nurses.

Keywords Geriatric pharmacotherapy · Optimization · Integrated approach

Introduction

Older individuals are more susceptible to adverse drug reactions (ADRs), which can occur while they are hospitalized due to multiple comorbidities, the progression of these conditions, the complexity of the therapeutic regimen or even drug-drug interactions, but can also be the primary cause of hospitalization [1, 2]. While the percentages of ADRs for all hospitalized patients vary between 2.4 and 10.9 % [3, 4], the incidence of ADRs is higher in older people as they take far more drugs than younger individuals, the higher frequency being a common risk factor for the development of ADRs. Therefore, it is of utmost importance that physicians to understand the therapeutic schedule prescribed, the drugs being used by the patients and the drug effects being experienced by the patients being submitted to the hospital. However, obtaining accurate figures for older people is complicated by the voluntary ADR reporting system in which it is known that under-counting is an issue [5, 6]. Consequently, to avoid under-reporting, thought should be given to combining information from physicians and nurses with data obtained directly from the patient, perhaps via direct interview while staff members are making ward rounds.

Although as a cause of hospital admissions, the percentage related to drug issues varies considerably from 4 to 30 %, the majority are related to ADRs which are considered avoidable in 50–97 % of the cases [7–9]. Moreover, while only 5.6 % of the 13,000 unplanned hospital admissions analyzed in the prospective Hospital Admissions Related to Medications study (HARM) were classified as drug-related, the mean age of this population was significantly higher compared to overall mean population age, suggesting drug-related hospital admissions were more common in older individuals [10].

It is also important to separate out the general factors responsible for the high incidence of drug-related problems in older people [11–17], versus other factors that further modulate the rate of ADRs in the hospital setting. In regard to the former, it is common for older people to have many diseases at the same time that may be treated with a variety of different drugs, which obviously increases the complexity of the drug therapy for patients as well as the risk for adverse drug events, including undesirable drug-drug interactions. Second, physiological and biopharmaceutical changes in older people may be responsible for different pharmacokinetic and pharmacodynamic profile of drug products contributing to unanticipated ADRs due to the lack of focus on the older and complex patient populations in the clinical trial program during the development and marketing of

the drug product. Another important consideration is the fact that, in an age in which many older patients see several specialists in addition to and independently from their primary care physicians, lack of coordination can increase the difficulty to evaluate the overall medication schedule of the patient. This lack of coordination can relate to indications for drug prescription, courses of therapies, the monitoring of ADRs, and assessing drug effectiveness for the different medical problems for which they were prescribed. Last but not least, older persons are also often challenged cognitively and physically to handle their medications (for example, removing tablets or capsules from blister packs, or using inhalation devices appropriately including the required inhalation techniques), which can results in unsatisfactory compliance or inappropriate drug use and therapeutic outcomes. Finally, it must be remembered that while older people are typically prescribed the same drugs as younger adults often based on a "single disease" examination and treatment view, many more drugs are being prescribed simultaneously (polypharmacy) with the possibility that some of the drugs may not exhibit the expected and desired efficacy and safety profile [8–10].

In the hospital setting, older patients are often placed into acute geriatric wards. But, despite good professional care that includes evidence-based pharmacotherapy, inappropriate drug prescription still continues to occur thus elevating the risk of ADRs [18–20]. The major reason is continuation of drug therapy initiated prior to hospitalization plus additional drug prescription based on the acute treatment plan. This practice gives rise to simultaneous administration of previously and newly prescribed drugs without complete evaluation as to which drugs are really required, should be continued, changed, temporarily or definitely stopped, as well as lacks the necessary follow-up of the therapeutic effects and side-effects.

Designing strategies to prevent drug-related problems (DRPs) in older people requires close attention to the associated factors in the hospital itself and incrementally must address the transition between settings: admission to other hospitals and discharge to the home or long-term care facilities. Consequently, admission to the acute geriatric wards of a hospital affords both an opportunity to identify patients at high risk for DRPs and evaluation of medication discrepancies that already exist without compounding them further [21, 22].

Identification of Older Patients at Risk for Developing Adverse Drug Reactions

As a matter of fact, staffing resources within hospitals are often limited particularly when it comes to groups of individuals who need more attention than the 'average' patient. Consequently, within the multistep paradigm of geriatric pharmacotherapy, the first critical step is identification of those older patients who are most at risk for developing ADRs. This requires a continuous training of clinicians, nurses, and pharmacists in recognizing ADRs, which in daily practice is unfortunately not

achieved to the extend needed. Often an ADR is diagnosed and judged as a part of a disease-related clinical symptom rather than a drug-related problem per se, which may lead to further drug prescribing to control the ADR symptoms. In addition, such ADRs are complicating the definition of the medical diagnosis and increasing the chance for more drug-drug interactions, which, in turn, increases the odds that more ADRs will occur in a phenomenon termed 'the prescribing cascade' [23]. Consequently, any differential diagnosis should *always* include the possibility that presenting symptoms may be caused in part or wholly by an ongoing ADR. If a high-risk patient can be identified at admission those patients will receive extra attention from physicians, nurses, and pharmacists in regard to existing and new medications that will benefit most which in turn will mitigate the resource problem —as well as lower the chance of avoidable ADR occurrences and prescription cascading.

Two approaches have been recently reported in the literature which identify older patients at high risk for developing ADRs, both of which are simple and efficient: the GerontoNet ADR risk score [24] and the Brighton Adverse Drug Reactions Risk (BADRI) Model [25].

The GerontoNet risk score comprises those variables associated with ADRs and includes: four or more comorbid conditions (1 point); heart failure (1 point); liver disease (liver function test results that are more than twice the upper limit of normal) (1 point); number of daily drugs (maximum 4 points for ≥8 drugs, 1 point for 5–8 drugs, 0 points ≤5 drugs); previous ADRs (2 points); and renal failure (estimated GFR <60 mL/min) (1 point). Within the score range of 0–10 points a cut-off point of 3–4 presents a balance between optimal sensitivity (68 %) and specificity (65 %) in classifying those patients most at risk for an ADR.

Although the GerontoNet ADR risk score is simple to use, not requiring any clinical tests or complex biological parameters to be calculated, and can easily classify patients according to risk, it still has limitations. For example, in an observation study comprising 513 acutely ill patients aged ≥65 years, the GerontoNet ADR risk score incorrectly classified 38 % of patients as low risk [26].

The alternative more recent approach to assess ADR risk is the BADRI model [25], which is based on five clinical parameters with equal weighting: >8 drugs, hyperlipidaemia, elevated white cell count, use of antidiabetic agents, and length of hospital stay (>12 days). The best trade-off was found at a cut-off score of 1, yielding a good sensitivity of 80 % but a poorer specificity of 55 %. A major disadvantage of the BADRI model is that it requires length of the hospital stay in its calculation, which means that the score will not be assessed until 12 days have elapsed from initial admission. Validation results from European centres for both approaches were similar, although the BADRI results reflect a higher patient age and included possible ADRs rather than just definite and probable ADRs that were used in construction of the GerontoNet ADR risk score. Thus, although a promising start in this field, this methodological assessment of risk patients for ADRs will require further refinement with the addition of other variables and perhaps reweighting of its applicability and usability in routine practice where assessment of ADRs and identification of risk patents will have the highest impact. In addition,

such approaches will gain better acceptability and implementation when the assessment tools for ADRs will become more accurate.

Strategies to Reduce Inappropriate Drug Prescribing in Older Patients

One obvious solution to reducing ADRs in older people in any kind of clinical setting is to create a framework in which inappropriate drug prescribing is prevented or at least diminished. Specific settings may require different sets and combinations of interventions, explicit approaches include pharmacist-driven interventions, educational interventions, and instruments to detect inappropriate prescribing in older people, computerized decision support systems and geriatric medical services interventions (Table 1).

Pharmacist-Driven Interventions

Traditionally, pharmacists just dispensed the drug products according to the prescriptions. However, in the last 20 years there has been a gradual evolution towards a patient-centred viewpoint in which pharmacists are taking increasing responsibility for the drug therapy and welfare of their patients. Applying their specific pharmaceutical expertise, clinical pharmacists contribute to the overall assurance for the patient's safety and effectiveness of the prescribed drugs [27]. This evolution stems in part from a cyclical process applied each time a patient is prescribed a new medication whereby the pharmacist will perform pharmaceutical anamnesis, medication review, design of an individualized pharmaceutical care plan, and follow-up of the plan [28].

This process is far from perfect in practice because it is assumed that someone—the primary treating physician in most cases—actually takes responsibility for working through the cycle elements based on available medical records, laboratory values and nursing notes. Because electronic health records are not universally available and certainly not linked between healthcare institutions, the available information may be incomplete or even inaccurate, leading to erroneous conclusions. Nevertheless, the first step is identification of all medications the patient is taking, along with dosages, frequency, and route of administration. The second step is to review the medications in the context of what is known about the patient medically in a structured manner to identify inappropriate drug prescriptions taking into account the patient's limitations that could lead to misuse, overuse, underuse, or medication errors. This process should lead to the identification of possible DRPs. Discussion with the patient and other physicians prescribing existing medications should then take place so that a medication management plan can be

Table 1 Advantages and limitations of approaches to lower inappropriate drug prescribing

Approach	Advantages	Limitations
Pharmacist-driven intervention	• Pharmacist has more in-depth knowledge about drug adverse effects that treating physician • Can educate other healthcare professionals	• Mixed/insufficient evidence for effect on health outcomes, health related quality of life and cost-effectiveness of care • Working outside of the multidisciplinary team often fails
Educational intervention	• Ongoing individualized, interactive, multidisciplinary, and multifaceted programs can be helpful	• Need to define what is required to assess adequacy for a given level of intervention • Mere dissemination of guidelines unlikely to be effective
Instruments to detect inappropriate prescribing in older people	• Implicit: comprehensive and systematic approach; includes operational definitions, clear instructions and examples; good as an educational tool • Explicit: relatively easy to remember and to detect; provide support to identify inappropriate prescribing in older people	• Implicit: knowledge-dependent, time-consuming and does not assess underprescribing • Explicit: time-consuming unless process is automated and the patient's perspective is often not taken into consideration
Computerized decision support systems	• Have the potential to alert the prescribing physician to drug-prescribing issues	• Existing systems are not geriatric specific; insufficient evidence for improvement in patient outcomes; high volume of alerts: risk of unimportant warnings
Geriatric medical services interventions	• Integrated care and detailed geriatric assessment can reduce length of hospital stay and the number of readmissions	• Pharmacotherapy must be part of the initial geriatric assessment for approach to work well • Heterogeneity in terms of structural components and care processes

generated to address any issues [29]. Finally, the pharmacist discusses with the patient how the medications are best taken and the medication scheduled can be implemented into the patient's daily life.

Authors of a recent literature review concluded, that in general, pharmacotherapy for older patients improved when pharmacists played a proactive role in performing medication reviews and were involved in the active education of other healthcare professionals. Nevertheless, a specific positive impact of pharmacists' interventions on health outcomes, quality of life or cost-effectiveness could not always be established [30]. Illustrative of this point is a randomized clinical trial (RCT) investigating pharmacist-assisted medication reconciliation, inpatient

pharmacist counselling, low-literacy adherence aids, and individualized telephone follow-up after hospital discharge. In the trial population of 851 adults hospitalized for acute coronary syndromes or acute heart failure the per-patient number of clinically important medication errors (incidence rate ratio, 0.92) or adverse drug events (incidence rate ratio, 1.09) was not significantly different between the intervention and control groups [31]. The primary reason that the trial failed to demonstrate any significant effects could be seen in a lack of integration between the pharmacists and other professional caregivers which is critical and was not insufficiently addressed in the study. This was confirmed by Spinewine et al. [30] who noted that results of pharmacist-driven interventions tend to show better results when pharmacists are skilled and work as part of a multidisciplinary team composed of physicians, nurses and other caregivers. For example, in the RCT conducted by Spinewine et al. [32] in which pharmaceutical care was delivered to hospitalized older patients by an experienced clinical pharmacist who worked contextually with the existing geriatric team, the results were superior in the intervention arm compared to the control arm. Specifically, intervention subjects experienced a significant improvement in the appropriateness of prescribing from hospital admission to discharge. In addition, when team-based care included pharmacists, meta-analysis demonstrated that a 47 % reduction in adverse drug events was possible [33].

These findings illustrate the complexity in globally assessing geriatric patients in regard to appropriate pharmacotherapy and judgment of ADRs. The research also suggests that isolated pharmacist-driven interventions are not likely to succeed; rather, team-based approaches in which pharmacists are fully appraised in the pharmacotherapy of older people are required. Finally, to better direct this kind of research, larger multicentre trials are needed as sample sizes of available RCTs are small [34–37].

Educational Interventions

Educational interventions of healthcare professionals vary broadly ranging from teaching, interactive workshops, and face-to-face interactions to providing decision algorithms. A systematic review of such interventions found mixed results [38] and especially singled out limitations of several studies as they did not define what data would be required to assess adequacy for a given level of intervention nor sample size calculations to determine acceptable type I and type II errors. Another review also suggested that mere dissemination of guidelines is unlikely to be effective, whereas active educational interventions in the form of workshops, meetings, and regular reports could improve drug treatment [39]. Taking together the results of the studies clearly imply that ongoing individualized, interactive, multidisciplinary, and multifaceted educational programs are a critical and important intervention to

succeed in increasing awareness of healthcare professionals in regard to prescribing medication in older patients.

Instruments to Detect Inappropriate Prescribing in Older People

Several tools are available to clinicians to assess whether medication is appropriate for older and multimorbid patients. These tools are either implicit, judgment-based, instruments that include clinical information available about the patient or explicit, criteria-based tools. The MAI is the most comprehensive and validated implicit tool available to date. The MAI is based on ten elements of drug prescribing: indication, effectiveness, dose, correct directions, practical directions, drug-drug interactions, drug-disease interactions, duplication, duration, and cost. Summation of the ratings produces a weighted score that is representative of whether prescribed drugs are appropriate whereby lower scores are indicative as being more appropriate [40]. While straightforward, calculating the MAI score is time-consuming and does not assess underprescribing. A study using adapted MAI scores found considerable utility in detection of drug-related problems in geriatric inpatients and was reliable with a low inter-rater variability as well as positive correlation between high score and drug-related hospital admission [41].

Explicit tools, on the other hand, are consensus-based standards focusing on drugs and diseases and include lists of drugs to avoid in general or lists combining drugs with clinical data. Although many explicit tools have been developed over the years [42–52], only the Beers criteria [53, 54] and Screening Tool of Older Persons' Prescriptions (STOPP) [55, 56] criteria have been examined in terms of their predictive validity.

Almost 25 years ago, Beers and his coresearchers set about developing a list of criteria using the Delphi approach that would lower the risk of drug prescribing in older persons [53]. The Beers criteria have since undergone several updates, with the latest revision in published in 2012 by the American Geriatrics Society using an evidence-based approach that identifies 53 drugs or drug classes divided into three categories: potentially inappropriate drugs to avoid independent of comorbidities; potentially inappropriate drugs to avoid in older adults with certain diseases and syndromes because they might cause exacerbation, and medications to be used with caution [54]. Based on the most recent criteria and using a community-dwelling sample of U.S. older adults (N = 18,475). Davidoff et al. [57] estimated that the potentially inappropriate medication (PIM) prevalence rate in the USA declined from 45.5 % in 2006–2007 to 40.8 % in 2009–2010. While this is an encouraging trend in the USA there is evidence that such criteria cannot be so easily applied in European countries; for example, several drugs listed in the 2003 Beers criteria were rarely prescribed or were not available in Europe and 2003 Beers-listed PIMs were not associated with ADRs in some studies [58].

Alternative tools initiated in 2008 and updated in 2015 termed STOPP (Screening Tool of Older Person's Prescription) and START (Screening Tool to Alert doctors to Right—appropriate, indicated—Treatment), include potentially inappropriate drugs (STOPP) as well as screening for omissions of indicated, potentially beneficial drugs (START) [55, 56]. The authors took a different approach by organizing criteria according to physiological systems and include both potentially inappropriate prescribing, and omission of potentially beneficial pharmacotherapy, which is missing from the Beers criteria. These START and STOPP criteria have now been endorsed by the European Union Geriatric Medicine Society (EUGMS). Perhaps what is most interesting about this approach is that their application leads to significant and durable improvements in the appropriateness of prescribing at discharge and for *up to 6 months after discharge*, indicating that this is a pragmatic tool capable of producing long-lasting, beneficial effects for older people [59, 60]. As an example of validation, a prospective study conducted involving 600 consecutive inpatients aged 65 or more utilizing STOPP criteria demonstrated an association with avoidable adverse drug events that cause or contribute to urgent hospitalization, a result that could not be shown with the Beers criteria [61].

Computerized Decision Support Systems

Another method to detect inappropriate drug prescribing and drug interactions and reduce the risk of iatrogenic drug problems has been the 'intelligent' computerized decision support system (CDSS). This is basically a series of algorithms implemented through the use of specially designed software. Such algorithms are generally rule based. For example, based on known data about drugs in geriatric populations upon a physician entry of a prescription order the software will check whether the drug dosage is appropriate and whether it is contraindicated given the patient's comorbidities. Although the CDSS has the potential to alert the prescribing physician to drug-prescribing issues, a recent review article concluded that improvements in patient outcomes have not yet need established [62]. Part of the reason for this is that physicians usually have the ability to override the system. When a 'hard stop' is employed in conjunctions with computerize order entry this could lead to a more effective system but could also delay critical patient medications [63]. Performance issues depend on how specific the information in the system is as well as the system is by itself considering that if the system does not recognize a geriatric patient, or impairments in individuals—for example, cognitive deficits—it will be of little use in older people as a means of stopping inappropriate drug prescribing.

Geriatric Medical Services Interventions

The use of multidisciplinary teams in medicine always confers advantages over non-integrated healthcare providers within any system, and geriatrics is no exception. When the medical and physiological complexity of older patients is considered by the team prior to any pharmacotherapy, the risk of an ADR can be lessened. Ideally, integrated medicine management is delivered starting with hospital admission and following up after discharge in a manner that is transparent to the patient with continuous information flow between hospital physicians and nurses, clinical pharmacists inside or outside the hospital, and primary care physicians. An ultimate patient benefit is that this process leads to optimized drug therapy with reduced length of hospital stay, longer time to readmission, and decreases the number of readmissions [64].

The traditional medical approach to treatment of older patients, even within a multidisciplinary framework, is not always enough to fully assess all problematic areas. Therefore, a more comprehensive geriatric assessment may be required to improve the pharmacotherapy and reduce the ADR rate. When this is done via the production of an individual care plan tailored to an older person that includes a more thorough evaluation it will result in enhanced care planning and better quality of care [65]. In this process, the issue of pharmacotherapy is not seen as a separate issue, but as part of the overall treatment plan, embracing a more holistic program in which drug prescribing is one avenue of treatment that is integrated into others. One further benefit is that the drug prescription plan may be simplified based on pharmacological and healthcare needs of the individual patient with concurrent reductions in drug-related adverse events and increases in the quality of drug prescribing [66–69]. In a large study employing a randomized 2×2 factorial controlled design utilizing patients in 11 Veterans Affairs (VA) hospitals, inpatient geriatric unit and outpatient geriatric clinic teams evaluated and managed patients according to published guidelines and VA standards in the intervention arms [70]. A 35 % reduction in the risk of serious ADRs compared with usual care was observed in outpatient geriatric clinic care and inpatient geriatric unit care with a significant reduction of unnecessary and inappropriate drug use and underuse. Moreover, outpatient geriatric clinic care reduced the number of clinical conditions that were caused by the omission of drugs significantly.

In the context of comprehensive geriatric assessment, the CRIteria to assess appropriate Medication use among Elderly complex patients (CRIME) project generated 19 recommendations relating specifically to five chronic conditions commonly experienced in older persons: diabetes, hypertension, congestive heart failure, atrial fibrillation and coronary heart disease. The intent of the project was to make healthcare providers more aware that goals of treating older people in respect of pharmacotherapy may be different from younger persons due to patient related factors and the presence of conditions routinely experienced by this patient population, such as limited life expectancy, functional and cognitive impairment and

geriatric syndromes. These conditions frequently limit drug benefits or can cause negative outcomes in respect of drugs and need to be considered when prescribing to such patients [71].

Conclusion

Single interventions as described in this review rarely achieve significant enhanced patient outcomes by themselves, but are far more effective when bundled together in a rational and integrated fashion—for instance, the effectiveness of a medication review by including a pharmacist in the context of a multidisciplinary team. Approaching the subject of complex clinical and therapeutic problems of geriatric patients with a global review that includes assessing each patient's clinical and functional parameters before tackling the pharmacological issues is likely to succeed better than merely reviewing pharmacotherapy by itself. If future clinical research focuses on better integration of all methods with demonstrated improvements in patient outcomes, more healthcare providers are likely to see the benefits of such approaches and adopt them.

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Part VII
Regulatory Guidance on Geriatric Medicines

European Medicines Agency (EMA): Regulatory Perspectives on Geriatric Medicines

Francesca Cerreta and David Bowen

Abstract The European Medicines Agency (EMA) recognises the challenges of new medicines development for older patients, particularly in the context of steadily increasing demand. The EMA Geriatrics Medicines Strategy has been established in response to this challenge and to the International Conference on Harmonisation (ICH) E7 guidance. The importance of this strategy is reinforced by the recently repealed Regulation of the European Parliament on Clinical Trials. The EMA strategy will encourage pharmaceutical companies to consider inclusion of appropriate patients in drug development programmes for medicines to be used in older patients. In addition the goals are to improve the assessment process for Market Authorisation and encourage post-authorisation studies when data at the time of Market Authorisation are perhaps lacking in older patients with co-morbidities and polypharmacy concomitant medication. EMA is now working actively with Health Technology Assessment (HTA) bodies for which data on drug development should align demographically and clinically with the target population in routine clinical practice.

Keywords Regulatory · Drug development · Pharmacovigilance · Clinical trials

Abbreviation

ADR	Adverse Drug Reaction
AE	Adverse Event
CHMP	Committee for Evaluation of Human Medicinal Products
EC	European Commission

The original version of the book was revised: The name of the co-author was missed to be added in this chapter. The erratum to this chapter is available at 10.1007/978-3-319-43099-7_38

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S. Stegemann (ed.), *Developing Drug Products in an Aging Society*,
AAPS Advances in the Pharmaceutical Sciences Series 24,
DOI 10.1007/978-3-319-43099-7_34

EFPIA	European Federation of Pharmaceutical Industries and Associations
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
EU	European Union
EMA	European Medicines Agency
EPAR	European Public Assessment Report
FDA	Food and Drug Administration
GEG	Geriatrics Expert Group
GMS	Geriatrics Medicines Strategy
GVP	Good Pharmacovigilance Practice
hERG	Human Ether-a-go-go
HTA	Health Technology Assessment
ICH	International Conference on Harmonisation
NCA	National Competent Authority
MA	Marketing Authorisation
MAH	Marketing Authorisation Holder
MS	Member State
PMDA	Pharmaceutical and Medical Devices Agency
PAS	Post-authorisation Study
PASS	Post-authorisation Safety Study
PRAC	Pharmacovigilance Risk Assessment Committee
PSUR	Periodic Safety Update Report
RMP	Risk Management Plan
SA	Scientific Advice
SAG	Speciality Advisory Group
SmPC	Summary of Product Characteristics
SPPB	Short Physical Performance Battery

Introduction to the European Regulatory Process

The approval of medicines for use in Europe proceeds via one of two routes: a *centralised* Market Authorisation procedure administered by the European Medicines Agency (EMA) or a *decentralised* procedure in one or more Member States with mutual recognition then administered at EMA as appropriate. For the centralised procedure, following a request from the applicant/sponsor, EMA will provide scientific advice (SA) to assist with the medicine's development programme. SA is in the form of responses to specific questions from the sponsor and does not constitute a comprehensive overview of the proposed development programme. Nevertheless, the SA process maximises the potential for authorisation of the product from a scientific regulatory perspective [1]. SA is provided by coordinators from the National Competent Authorities (NCA) of Member States (MS) in collaboration with coordinating EMA scientific staff and internal clinical and preclinical EMA experts. NCA coordinators consult internal experts from each MS; as such the SA process is inclusive and networked throughout Europe. EMA is the coordinating hub. Regulatory advice (non scientific) may also be sought from EMA.

Once the development programme is considered sufficiently mature, the sponsor submits the Market Authorisation Application via an electronic common technical document, largely harmonised with the US FDA and Japan's PMDA. This document includes Clinical Study Reports for the pivotal and supportive studies, and also the Risk Management Plan. The process of evaluation by the Committee for Evaluation of Human Medicinal Products (CHMP) then proceeds through a series of fixed steps at days 80, 120, 180 and 210. Clock stops are allowed at days 120 and 180. CHMP rapporteurs are appointed from the NCAs and the networked assessment process is similar to that of SA. Occasionally expert external groups may be consulted, usually as Specialty Advisory Groups (SAG). CHMP issues a recommendation on the benefit–risk ratio, which is then discussed and usually ratified at the European Commission (EC). The average time from submission via market authorisation to EC approval in 2013 was 478 days. Three options are currently available for MA:

1. Full MA—the standard approval where the benefit–risk ratio is favourable, the evidence base sufficiently solid with relatively lower uncertainty. The pivotal trial is typically a randomised controlled trial.
2. Conditional MA—approved for one year on a lesser evidence base with greater uncertainty around the robustness of the benefit–risk ratio but with sufficiently promising a signal to justify granting wide access to European patients. Conditions are imposed, usually a requirement to collect more robust data to inform the benefit–risk ratio.
3. MA under Exceptional Circumstances—typically granted for an ultra-orphan disease where the medicine has a reasonable probability of, or confirms a positive benefit–risk ratio and robust data to inform a level of uncertainty usually required for a full MA are unlikely to be able to be collected. Nevertheless it is expected that registry data will be collected in the post-authorisation phase.

The Regulatory Challenge of Population Ageing

Population Demographics

A fundamental premise of drug development and regulation is that new medicines for use in human patients should be efficacious and safe in the patient population with the appropriate demographic composition for the disease to be treated. As repeatedly emphasised in previous chapters, the population demographic of Europe is changing rapidly and headline metrics include an estimate of 50 million European citizens (12 % of the population) projected to be >80 years in 2060, almost triple than that in 2010. The proportion of people aged 65 years or over in the EU is expected to grow from around 17.4 % in 2010 to around 29.5 % by 2060. Although life expectancy is increasing steadily, so is quality of life in older age. No totally reliable data are available to quantify this, but it also has ramifications for the consequences of medicines consumption in older patients. Eurostat measures the concept of healthy ageing as healthy life years; a combined dataset for mortality

statistics and self-perceived disability surveys. The latest data (2009) indicate that the number of healthy life years at birth was 60.9 years for men and 61.6 years for women in the 27 EU member states; this represented 79.4 and 74.5 % of total life expectancy at birth for men and women. For survivors at the age of 65, the number of remaining healthy life years was 8.2 years for men and 8.3 years for women; the life expectancy of those who survive to the age of 65 is 17 years for men and 20 years for women indicating that the last 9 years for males and 12 years for females on average will include some form of (self-perceived) disability.

Representation of Older Patients in Clinical Trials

Clear data are now emerging demonstrating the mismatch between the age demographics of diseases and the clinical trial population recruited for market authorisation of drugs to treat those diseases. Recent studies from EMA/Italy (Fig. 1) [2] and Japan [3] show how great this disparity is, and its distribution by therapeutic area. The Japanese study considered new medicines approvals up to 2012 in six disease areas. The proportion of patients included in clinical trials compared with those of comparable age in clinical practice was <50 % in four disease area namely hypertension, rheumatoid arthritis, non-small cell lung cancer and depression. Only in Alzheimer's disease medicines trial was the recruited population truly age-appropriate. This study considered age only and no other

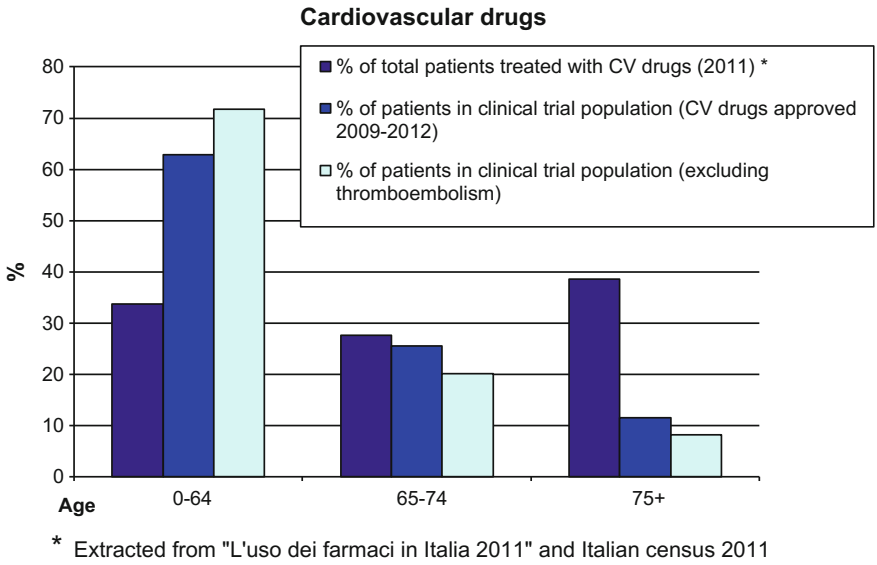

Fig. 1 The example of cardiovascular drugs: percentages of all patients in a given age group treated with cardiovascular drugs (Italy) versus percentages in each age group included in cardiovascular drug. Trials (globally) [2]. Copyright © (2015) Massachusetts Medical Society. Reprinted with permission

co-morbidities, frailty or self-reported quality of life perspectives. Similar observations have been made for older cancer patients by FDA [4].

Some caution with data interpretation is required however. Initial perceptions that women were underrepresented in cardiovascular studies have been questioned [5]; however older women and older men were under-recruited to the cardiovascular landmark studies but not to primary prevention studies.

EMA accepts that representation of older patients in a clinical trial need not be equivalent to an exact percentage match with the disease demographics, but enrichment of older patients should be demonstrated where appropriate, such that a valid scientific assessment can be made for the benefit–risk ratio in this population.

Reasons for Underrepresentation of Elderly Patients in Clinical Trials

Conventional approaches to new medicine development have appropriately proceeded through phase 1 dose finding studies, phase 2 studies to reassure on toxicity profile and seek an efficacy signal followed by phase 3 studies to demonstrate superiority over existing standards of care. Given the duality of minimising the trial subject (health) and company's (financial) damage through excess toxicity it is understandable that trial populations are typically at lower risk of toxicity than an unselected population with the disease of interest would be. These and other reasons for underrepresentation of elderly subjects in clinical trials include:

- Restrictive inclusion and exclusion criteria, for example
  - Age upper limit; infrequent now.
  - Organ function

    Occasionally inappropriate, e.g. drugs that are predominantly metabolised in the liver having a renal exclusion criterion, drugs that have a low hERG QTc prolongation signal in preclinical studies, yet still the study excludes patients with borderline prolonged QTc.
- Co-morbidity, for example
  - Trials often exclude cancer survivors.
- Concomitant medication, for example
  - Often inappropriate exclusions based on preclinical knowledge of hepatic enzyme metabolism.
- Practical
  - Difficulty in obtaining patient informed consent.
  - Difficulty travelling to the trial centre.
  - Difficulty in completing trial documentation, e.g. patient reported outcome or health-related quality of life questionnaires.

Regulatory Framework Documents

EC Regulation on Clinical Trials on Medicinal Products for Human Use: 536/2014

The European Parliament and Council adopted this regulation [6] on 16 April 2014, repealing the 2001 directive.

Amongst many amendments intended to promote and facilitate effective clinical trials in the EU, the regulation strengthens the statements for recruitment of representative populations into the clinical trials. Examples include:

Point (14) 'Unless otherwise justified in the protocol, the subjects participating in a clinical trial should represent the population groups, for example gender and age groups, that are likely to use the medicinal product investigated in the clinical trial'. Point (15) 'In order to improve treatments available for vulnerable groups such as frail or older people, people suffering from multiple chronic conditions, and people affected by mental health disorders, medicinal products which are likely to be of significant clinical value should be fully and appropriately studied for their effects in these specific groups, including as regards requirements related to their specific characteristics and the protection of the health and well-being of subjects belonging to these groups'.

Article 6: Assessment report

Member States will assess… "the relevance of the clinical trial, including whether the groups of subjects participating in the clinical trial represent the population to be treated, or if not, explanation and justification is provided in accordance with… Annex I…"

Annex I paragraph 17 point (y)

"…justification for the gender and age allocation of trial subjects….if a specific gender or age group is excluded from or underrepresented in the trials, an explanation of the reasons and justification for these exclusion criteria…"

International Conference on Harmonisation (ICH) E7

The International Conference on Harmonisation (ICH) of technical requirements for registration of pharmaceuticals for human use (ICH) agreed a common regulatory position on 'Studies in support of special populations: Geriatrics' in 1993. This guidance noted the special characteristics of the older patients that warranted specific attention: the frequent occurrence of concomitant illnesses (and the polypharmacy that is often concomitant), and the necessity to elucidate

pharmacokinetic differences that may derive from altered renal and hepatic function. A minimum of 100 patients over the age of 65 was advised for inclusion in a clinical development programme.

Regulators recently examined whether this advice still provides for appropriate elucidation of the benefit/risk balance in this major group of drug users, particularly considering the facts that the older old (over 75) are the fastest growing population segment in many countries. In July 2010, recognising the rapidly changing demographic environment, ICH E7 was updated with the addition of a question and answer document [7].

The main points emphasised in this addendum to the guideline are:

(1) A representative number of older patients should be included in the clinical trials. In the world of ageing baby-boomers, this means that 100 patients are unlikely to be sufficient for most indications. Data should be presented for three separate age brackets 65–74, 75–84 and ≥85 years.
(2) The guideline applies both to drugs intended for the geriatric patient population and for drugs used in diseases present in, but not unique to, the geriatric population. For diseases specific to the elderly, geriatric patients are expected to constitute the majority of those enrolled in the pivotal and supportive clinical trials.
(3) The importance of specifically recruiting older old patients (>75 years) is emphasised.
(4) Arbitrary upper age cut-offs in the inclusion criteria should be avoided.
(5) Inclusion of patients with frequently occurring concomitant illnesses is encouraged.
(6) The preference is for inclusion of older patients in the pivotal Phase 3 trials, because this allows comparison of responses with younger patients in the same study, but it is recognised that this may not always be optimal. For example, where specific measurements (e.g. cognitive function) are critical but not typically carried out, a separate trial in the elderly may be more informative (even post-authorisation). Also, in some cases it may be necessary to protect potentially more vulnerable patients until the drug profile is better known.
(7) The pharmacokinetics in geriatric patients (over the *entire* spectrum of the geriatric patient population) should be evaluated to identify age-related differences that are not explained by other factors such as reduced renal function or weight differences. If a sufficient, representative number of patients in different age ranges (including patients >65 and >75 years) is included in the clinical trials, then population pharmacokinetic analysis could provide such data; otherwise, a specific pharmacokinetic study comparing non-geriatric and geriatric subjects in the same study (matched for relevant covariates, e.g. weight, sex) could be performed.

The EMA Geriatric Medicines Strategy

In 2006, the EC asked the EMA to provide an opinion on the adequacy of guidance on the elderly regarding medicinal products. In 2011, the agency's CHMP adopted the EMA Geriatric Medicines Strategy (GMS) marking its commitment to promoting effective evaluation of the benefit–risk ratio for a medicine in older patients (Fig. 2).

Aims

(1) A recognition that older people are the main users of medications not a minority or special population (a fundamental difference between the geriatric and paediatric populations), and a strategy that therefore strives to ensure that medicines used by geriatric patients are of high quality, appropriately researched and evaluated for use in this population throughout the lifecycle of the product. Therefore, legislative and regulatory frameworks must be designed to ensure that the use of newly approved medicines in the intended population is supported by relevant data on the benefit–risk balance.
(2) To improve the availability of information to patients and prescribers, to support safer use of medications.

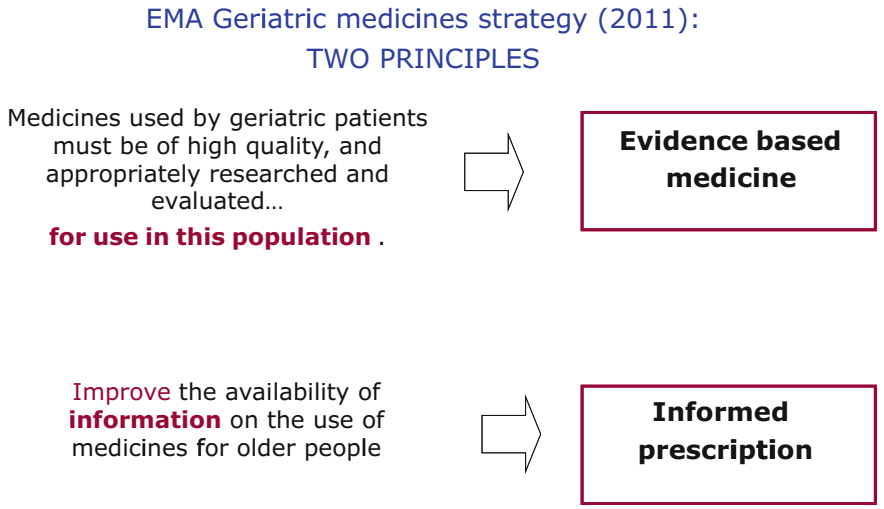

Fig. 2 The EMA geriatrics medicines strategy

These aims will be achieved by:

- ensuring that the development and evaluation of new medicines takes into account specific safety and efficacy aspects related to ageing, in accordance with current guidelines, particularly ICH E7;
- identifying gaps in regulatory and scientific knowledge and taking appropriate measures to tackle them (e.g. in the provision of SA, in the drafting of guidelines, and during business pipeline meetings);
- consideration for the need of specific pharmacovigilance activities;
- ensuring relevant regulatory guidelines contain appropriate guidance on the development and assessment of products to be used in geriatric patients;
- provide advice to applicants on regulatory requirements for the development of products likely to be used in the elderly;
- and, finally, by fostering and utilising a relevant experts' pool to address specific issues as requested by the CHMP, making full use of its Working Parties and experts groups where appropriate.

The practical delivery of these objectives is managed as follows.

Establishment of Geriatrics Expert Group

In 2011, the Geriatrics Expert Group (GEG) was convened to advise on issues that would benefit from the input of expert geriatrics physicians to assist with the implementation of the EMA GMS. The GEG currently comprises ten European physicians with diverse clinical and academic expertise in geriatrics medicine. Since its' inception the GEG has provided opinions on:

- Frailty guidance—document created by the GEG members in line with the EMA GMS (expected release late 2016).
- CHMP Assessment Report/European Public Assessment Report (EPAR)/ Summary of Product Characteristics (SmPC) content from a geriatrics perspective—consultation to inform the revision of the CHMP Assessment Report, which in turn feeds the EPAR and SmPC content.
- A specific pharmacovigilance proposal for authorised medicines with a new safety signal relevant to older patients.

Medicines Development

EMA Scientific Advice

Scientific Advice (SA) may be sought by a sponsor for any new medicine and takes the form of a nonbinding response by EMA to specific questions asked by the sponsor. Such advice relevant to geriatrics is typically Protocol Assistance, which may include

early or later stages of clinical development programme or indeed both. Parallel SA and Health Technology Assessment (HTA) advice has been offered since 2010.

Given that most SA is sought at an early stage of the development programme there is a considerable opportunity to promote the aims of the EMA GMS during this process. With that in mind the EMA GMS implementation group have

- encouraged the recruitment of a clinical geriatrics physician onto the Scientific Advice Working Party.
- committed to screen all SA requests for questions relevant to the aims of the GMS.

Protocol Assistance is often provided on inclusion/exclusion criteria, suitability of endpoints (which should reflect clinically relevant outcomes in a representative patient population) and comparators which should be a recognised standard of care where feasible.

Opportunities for the implementation of the GMS in SA procedures for medicines intended for use in older patients include:

- Review of inclusion criteria establish that the included population is representative of the disease demographics, unless appropriately justified to be otherwise.
- Review of exclusion criteria with particular emphasis on ensuring adequate justification of exclusion criteria such as hepatic and renal dysfunction, QTc prolongation, and concomitant medication based on sound preclinical or early phase trial data and evidence. Excessive 'confounder cleansing' may result in the study of nonrepresentative populations.
- Endpoints that are clinically relevant to older patients. Increasing emphasis is likely to be given to patient reported outcomes and health-related quality of life metrics in older patients, in addition to overall survival. Depending on patients' frailty and disability status, the desirable outcome and treatment choices might vary: different patients place different values on benefits and risks. The design of a clinical trial should consider age-appropriate end points; for older people, functional outcomes may be most important, and an emphasis on such outcomes could lead to reduced costs for healthcare systems.
- Comparators that reflect standard of care across all age ranges within the disease demographic.
- For parallel SA-HTA advice procedures, the GMS emphasises the importance of real-world data in the form of relevant comparators, and if necessary post-authorisation studies including registries to collect relevant data for more precise HTA evaluation.

EMA Guidance Documents

EMA Regulatory Guidelines

The GMS implementation group is consulted for all EMA Guidelines. Where relevant, the draft Guideline is also circulated to the GEG for external expert input.

Such regulatory guidelines are intended to provide guidance to industry and other stakeholders involved in drug development programmes. Recent examples include:

- Venous thromboembolic diseases—'Generating clinical data in older (≥75) and frail oldest older persons (≥85 years) patients with high co-morbidity is a matter of utmost importance, as they will represent an important part of the target population in standard practice. Any dose adaptation in these populations should be appropriately explored and justified'.
- Chronic Renal insufficiency—'Older age is an important risk factor in CKD and the age of transplant recipients is increasing. Confirmatory studies should reflect this and generally there should be no restriction because of old age and a sufficient number of elderly should be included'.

Points to Consider on Frailty

EMA recognises that few clinical trials in older patients describe the baseline frailty status of the trial population at study entry. Chronologic age alone is inadequate for characterising the population enrolled in a clinical trial. Frailty is often an important variable influencing outcome which is neither captured nor measured in clinical trials. The goals of the document are to encourage the baseline description of four aspects of frailty, namely physical frailty, cognitive decline, malnutrition and multi-morbidity for all subjects enrolled in clinical trials where frailty could contribute to outcome. A menu of validated instruments has been agreed with an external group of opinion leaders (GEG) and any of these instruments may then be used commensurate with the indication and outcome measures relevant to the medicine under development. It is recognised that other 'frailty' instruments may also be valid for specific purposes. These instruments are not intended for routine clinical assessment or for endpoint/outcome evaluation, but may nevertheless be associated with outcome for example the Short Physical Performance Battery (SPPB) [8, 9].

Reflection Paper for Quality Aspects of Medicines for Older People

EMA will provide comprehensive guidance to encourage developers of medicines to consider the needs of older patients. Inappropriate formulations and packaging may contribute to low adherence, medication errors and safety and efficacy problems. Additional considerations for an elderly trial population will include the need for ease of administration, simple and clear instructions for dose adjustment, consideration of the effects of visual and motor impairment, and the impact of polypharmacy on administration of the clinical trial medicine. If appropriate, protocols should be designed for evaluating patients' ability to manage their own medications. Regulators should also look favourably on novel non-drug technologies to monitor adherence.

Medicines Evaluation

CHMP Assessment Report Template

Rapporteurs from CHMP have been assigned to steer and contribute to the GMS. An early task has been to invite the GMS implementation group to review and revise the Assessment Reports for CHMP in order to ensure, where appropriate, that the assessment of an application for Market Authorisation in a population including older patients has a clear and comprehensive perspective of geriatrics issues. This includes creating a summary section of the AR for geriatrics-specific assessment relevant to the medicine undergoing assessment. Revisions to the AR with a focus on older patients have included inclusion of more detailed age breakdown for adverse event reporting, including grouped AEs (Table 1), and more specific statements to guide assessors in their review of geriatrics-specific issues. Such an example is population pharmacokinetics or a specific pharmacokinetic study including the very elderly which should be performed whenever possible (Table 2).

Table 1 CHMP assessment report: distribution of adverse drug reactions by MedDRA term in different age groups of older patients

MedDra terms	Age <65 number (%)	Age 65–74 number (%)	Age 75–84 number (%)	Age 85+ number (%)
Total ADRs				
Serious ADRs–total				
−Fatal				
−Hospitalisation/prolong existing hospitalisation				
−Life-threatening				
−Disability/incapacity				
−Other (medically significant)				
AE leading to drop-out				
Psychiatric disorders				
Nervous system disorders				
Accidents and injuries				
Cardiac disorders				
Vascular disorders				
Cerebrovascular disorders				
Infections and infestations				
Quality of life decreased				
Sum of postural hypotension, falls, black outs, syncope, dizziness, ataxia, fractures				

Table 2 CHMP assessment report: pharmacokinetic studies conducted by age group

	Age 65–74	Age 75–84	Age 85+
PK trials	Number/total number		
Controlled trials			
Non controlled trials			

Pharmacodynamic differences related to age are less frequent than PK ones; specific clinical studies by age group are usually not needed, unless early data and past experience suggest such differences. Modelling can assist in indicating whether an age relationship may exist and further investigation is advisable, discussed in detail at a recent EMA workshop (http://www.ema.europa.eu/docs/en_GB/document_library/Presentation/2015/01/WC500179819.pdf).

A greater focus on geriatric-specific issues during the assessment process will inform later relevant documentation including the European Public Assessment Report, the Summary of Product Characteristics and the Patient Information Leaflet, all of which have their basis in the CHMP Assessment Report content. There must be greater focus on the package insert, the regulatory document most widely referred to by the public, which must explain clearly how to take the medication, whether dosage adjustments are advised for older patients, and what is known about use with concomitant medications.

Pharmacovigilance

EMA has a strong focus on pharmacovigilance, enshrined in EU Law and updated in 2012. EMA works in partnership with the NCAs to promote a lifecycle approach to the development of new medicines. Sponsors are encouraged to develop plans for pharmacovigilance at an early stage of medicine development and with parallel SA and HTA advice there is an increasing emphasis on collection of safety data post-authorisation given the high level of uncertainty at the time of Market Authorisation. The Pharmacovigilance Risk Assessment Committee (PRAC) reviews all Market Authorisation Applications, focusing on the Risk Management Plan submitted by the company as a component of the MAA. Following MA, the company must submit a Periodic Safety Update Report (PSUR) at defined time points during the post-authorisation phase, which is in turn reviewed by PRAC. Signal detection for adverse events is rapidly improving with the development of more sensitive systems and algorithms. PRAC can be alerted to a safety signal from varied sources including the company (Market Authorisation Holder, MAH), or the NCAs, via the EuDRAVigilance network portal (https://eudravigilance.ema.europa.eu/human/index.asp). EMA is producing a Guideline on good pharmacovigilance practices (GVP). A module for ‘Medicines used by the older population’ is in preparation (expected publication early 2017).

Risk Management Plan

The Risk Management Plan (RMP) template mandates a comprehensive discussion of risk management in older patients studied within the pivotal and supportive clinical trials, to inform the proposed RMP. Importantly the RMP template mandates presentation of the limitations of the medicine development programme in this context with a series of subsections including:

- 'Populations not studied in clinical trials' which should be cross-referenced with the detailed disease demographic data presented earlier in the RMP.
- Limitations of adverse drug reaction detection common to clinical trial development programmes.
- Effect of exclusion criteria in the clinical trial development plan.
- Limitations in respect of populations typically underrepresented in clinical trial development programmes.

Patient exposure to the trial medicine is presented by age breakdown and by number of patients/person time exposure (Table 2).

Post-authorisation Studies

Although EMA expects the age distribution of patients to be representative in studies presented for marketing authorization, post authorisation studies (PAS) might also be required to consolidate knowledge regarding higher risk subpopulations. Such populations would often include older patients and those with more co-morbidity. Post authorisation safety studies (PASS) are typically registries which may be disease based or product based. In 2006, EMA established the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) as a platform for research and management of pharmacovigilance including PAS. ENCePP is a network of over 170 research centres, existing networks and providers of healthcare data, coordinated by the EMA. In collaboration with the EU and European Federation of Pharmaceutical Industries and Associations (EFPIA) through the Innovative Medicines Initiative funding, EMA has recently led a methodological research programme to develop new tools for pharmacovigilance.

Consultation on PRAC Referral for Product Safety

The EMA GMS implementation group responds to requests from PRAC on Article 31 pharmacovigilance referral of Directive 2001/83/EC. A recent example is 'New restrictions to minimise the risks of effects on heart rhythm with hydroxyzine-containing medicines' (http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/referrals/Hydroxyzine/human_referral_prac_000043.

jsp&mid=WC0b01ac05805c516f). Expert pharmacodynamic and clinical advice from consultation with the GEG as a component of the referral process led to the following actions: 'the product information of hydroxyzine-containing medicines will be updated with new dosing recommendations and warnings on use in patients who have risk factors for heart rhythm disturbances or who are taking certain other medicines'.

Health Technology Assessment and the Regulatory Interface

Efficacy in clinical trials does not always reflect efficacy in real-world data sets [10], and safety/tolerability may also prove to be different [11].

Although not the direct responsibility of, or a mandate for the regulators, managing the introduction of new medicines into healthcare systems in Europe usually involves a form of HTA of clinical and/or cost-effectiveness. EMA recognises this and now offers parallel scientific and HTA advice. The goal of such an initiative is to promote a development programme that is responsive to the needs of the HTA process. Shortcomings in the development programmes often include an inappropriately small population of older patients in diseases of older age, and an inappropriately fit/healthy population in clinical trials compared to the target population in the real world. Sponsors are encouraged to consider the full product lifecycle and to collect data over a lifetime horizon where possible. Comparison with real-world data sets may be feasible with evolving initiatives such as the UK NHS Systemic Anticancer Therapy data set (http://www.chemodataset.nhs.uk/home), which will by definition collect data from older patients treated with chemotherapy and other modalities of cancer therapy. Inappropriate development programmes generate high levels of uncertainty during the HTA process, which in turn leads to a higher bar for approval of a medicine, particularly in countries that employ a cost-effectiveness approach (including a relative effectiveness assessment) such as the UK.

EMA is collaborating with European Union and Industry funded initiatives such as GetReal (http://www.imi-getreal.eu/) which aim to develop processes for generating real-world data relevant and usable for HTA. This demonstrates an increasing recognition of all parties that healthcare systems are resource-limited and all components of drug development programmes must respond to this.

Challenges in the Era of Adaptive Licensing/Breakthrough Therapies with Earlier Approvals

Advances in scientific understanding of disease are rapidly evolving into novel targeted therapy, particularly in cancer. This creates many regulatory challenges, with medicines in development for smaller patient populations, often with

comparators that may not be well defined, and with sample sizes too small for traditional phase 3 clinical trials. The regulatory process must adapt in line with these advances but inevitably the consequence of the pressure to bring such medicines to market as early as possible means a high level of uncertainty around the benefit–risk ratio at the time of MA. Inevitably these MAs are likely to be Conditional (contingent on the acquisition of more robust data to inform a full MA) or Exceptional Circumstances where such post-authorisation data are unlikely to be able to be collected.

EMA is developing an Adaptive Pathways process comprising early dialogue with sponsors and with early parallel SA and HTA in order to design a development programme that actively and continuously manages the uncertainty throughout the product lifecycle. The principles of the GMS are the same as for a conventional medicines development programme. However there is a greater requirement for collection of real-world data in the post-authorisation setting to ensure a continuing valid benefit–risk ratio in the face of greater uncertainty at the time of MA.

Conclusions

Regulators must ensure that the development and evaluation of drugs take into account global demographic changes, so that safe and effective drugs reach the patients who ultimately use them. Medicines development for elderly patients (and children) is the paradigm and an increasing challenge of considerable magnitude and importance. EMA is responding to this challenge with the implementation of the Geriatrics Medicine Strategy which aims to influence all stages of the medicines development and assessment programmes. Ultimately the challenge is for industry and other sponsors to respond to this, and to better manage the risks associated with developing drugs for older patients with frailty, co-morbidity and polypharmacy by including such patients in their clinical trial populations. EMA is now well placed to advise on, and to assess the outcomes of such adapted programmes.

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Views on the Therapeutic Needs of Older Adults

S.W. Johnny Lau and Raman K. Baweja

Introduction

A few decades ago a term was coined for pediatric drug development, or lack thereof, calling children "therapeutic orphans" [8, 66]. Since then, tremendous strides have been made in developing drugs to benefit children. We are in a similar conundrum now for drugs of the older adults. Therefore, it is appropriate to mention that the current situation for the older adults is that of "therapeutic overlook." Perhaps this recognition can set the wheels in motion to seriously understand the issues related to the older adults from a clinical perspective and also from the viewpoint of sociocultural and physical limitations that come with advancing age.

The world population is aging [72, 73]. An understanding of aging means changes at the molecular, cellular, and tissue levels of a human being. Involved therefore are changes in body composition and organ function. These changes are different amongst people of the same age or even these changes are different in an individual that one organ may be fully functional while another is compromised. Therefore, age-related changes in physiology can affect the pharmacokinetics (PK) (absorption, distribution, metabolism, and excretion) and pharmacodynamics (PD) (effect) of a drug. In turn, the changes in both PK and PD in older adults can affect the dose, the dosing frequency, treatment duration, and choice of medications.

Who is an "ideal patient?" A patient's own understanding and knowledge of their disease conditions can play a vital role in the adherence of their therapy [46]. Therefore, an ideal patient is one who first of all fundamentally recognizes that he

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S. Stegemann (ed.), *Developing Drug Products in an Aging Society*,
AAPS Advances in the Pharmaceutical Sciences Series 24,
DOI 10.1007/978-3-319-43099-7_35

or she has a disease or a host of diseases. An individual's understanding of his or her disease(s) coupled with the importance of taking his or her medications as prescribed should lead to an improved quality of life. In prescribing a medication to the patient, a prescriber considers that the patient receives the drug safely, completely, and comfortably [8]. For the older adults this means bringing discipline to the intake of their medications leading to strict adherence to their daily medical routine. Furthermore, obtaining insight and gaining knowledge about their diseases and the accompanying risk to benefit consequences are advantageous.

The Changing United States Demographics in the Coming Decades

According to the United States Census Bureau, the age group of 65 years and above will be the fastest growing segment of the population in the United States for the next four decades due primarily to the migration of the Baby Boom generation into this age group. In 2050, the projected number of people in the United States aged 65 years and above will be 88.5 million, more than double the population estimate of 40.2 million in 2010 [75]. Figure 1 shows the age distribution of the United States population in the next four decades.

This aging trend is consistent with that of other developed countries like Canada, Denmark, France, Germany, Italy, Japan, United Kingdom, and Australia [4, 12]. For example, Fig. 2 shows the age distribution of the German population in the next four decades. The proportion of global population at age 65 years or above will increase from 8 % in year 2013 to 15.6 % in year 2050 [72]. The aging trend is evident in both developing and developed countries [73].

Aging is a complex and multifactorial process that is an outcome of an accumulation of various functional deficits of multiorgan systems occurring over time at varying rates. No reliable biological marker for aging currently exists despite numerous research efforts. We rely on the chronological age to stratify the aging population. Due to the expected increase in the aging population, it may be advisable to divide the older population into three subgroups: young-old, age 65–75 years; old, age 75–85 years; and old-old, age ≥ 85 years to better understand the processes and changes of aging as well as its impact on drug therapy [40].

Therapeutic Needs of Older Adults

Drug therapy is an important medical intervention for care of the older adults. Persons aged 65 and above are the most medicated group of patients and receive the highest proportion of medications [63]. Older patients usually have more disease burden and thus receive multiple drug therapies that results in polypharmacy.

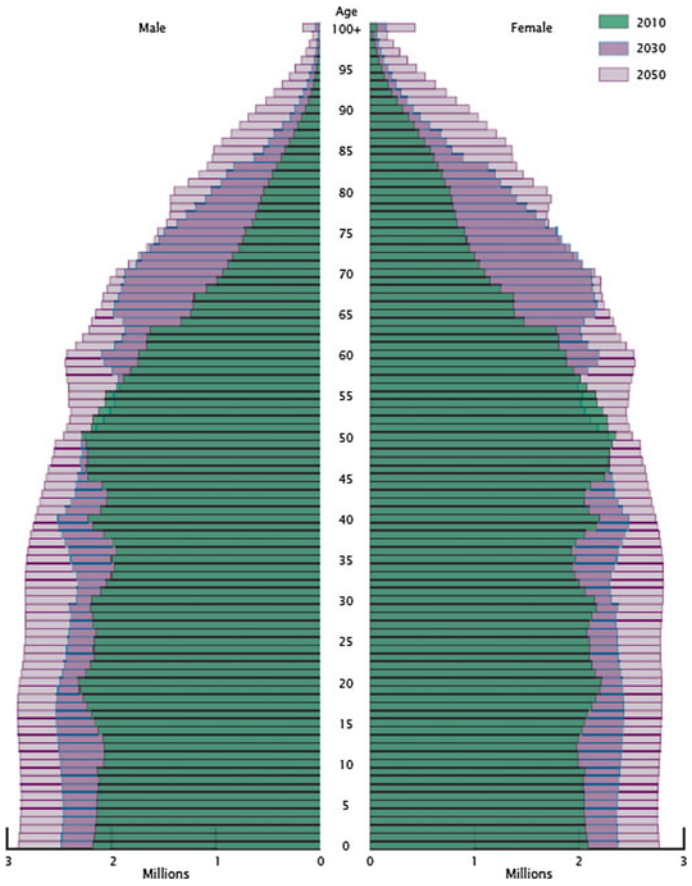

Fig. 1 Age and sex structure of the population for the United States: 2010, 2030, and 2050 (*Source* United States Census Bureau)

Polypharmacy is commonly defined as the use of multiple medications [10]. Polypharmacy can cause multiple drug interactions and results in adverse drug events [32].

The main reason that older adults are in a state of polypharmacy is because they suffer from comorbid disease states, such as diabetes, hypertension, prostate or breast cancer, arthritis, osteoporosis that can coexist in an individual. Simply put, drug therapy in the older patients is complex due to comorbid disease states and polypharmacy. Thus, older individuals may have at a given time different diagnoses. Each drug therapy aligned to each disease state may be singularly benefitting to the older adult patient. However, the summation of all cotherapies may result in considerably increased medication exposure and likely increases the risk of adverse drug–drug interactions. Thus, there is the possibility of an uneven increase in the number and severity of adverse drug reactions. Recognizing the importance of

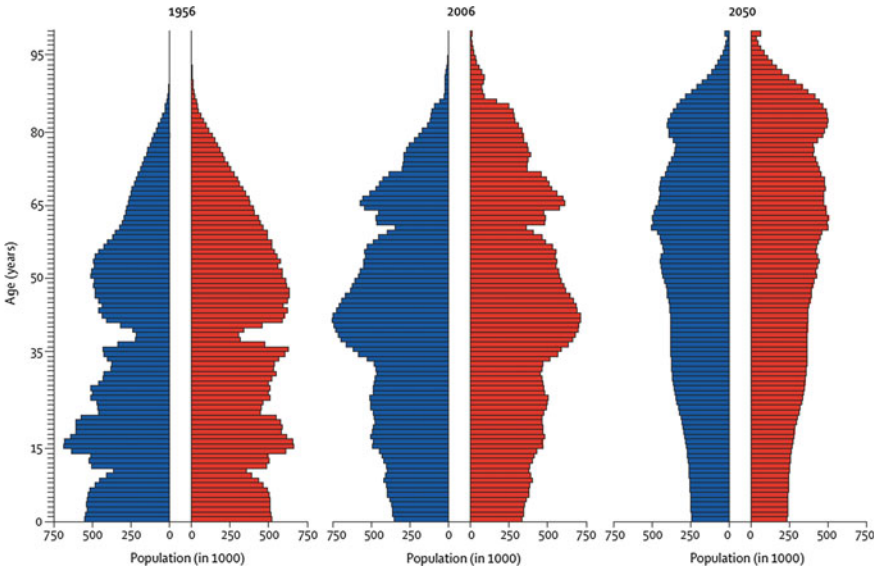

Fig. 2 Population pyramids for Germany in 1956, 2006, and 2050 (*Source* [12]). *Horizontal bars* are proportional to number of men (*blue*) and women (*red*). Data for 2050 are based on the German Federal Statistical Office's 1-W1 scenario, which assumes a roughly constant total fertility rate of 1.4, yearly net migration of 100,000 and life expectancy in 2050 reaching 83.5 years for men and 88.0 years for women

comorbid diseases in an individual that his or her daily routine revolves around multiple medications, it is not surprising for us to see the shift now from disease-centered care to patient-centered care.

Older adults have physical limitations besides the disease state itself that they are contending with. Some of these limitations are decreased motor ability including difficulty in swallowing or splitting open a scored tablet, and reduced vision. For example, older adult patients suffer from a decline in their motor ability, nimbleness, and agility particularly with diseases like rheumatoid arthritis (RA) that directly impact motor functions [8, 51, 68]. These limitations are even more pronounced when medication containers further pose difficulties in the physical complexity of administration of the drug thereby leading to decreased adherence by the older adult patients. Therefore, pharmaceutical packaging of the dosage form also plays an important role so as not to hinder but rather facilitate the ease of administration [49].

Another factor to consider in the older adults is poor vision. While poor vision may be a factor to recognize in the older adults, it is surprising that age does not seem to affect color identification, and perception. Nevertheless, the vivid use of color and colorful displays in dosage forms and in their packaging has received the attention of the pharmaceutical industry [68].

The ease of swallowing of oral dosage forms is taken for granted. However, difficulty in swallowing amongst the older adults is a major concern. Mini-tablets and viscous liquid dosage forms seem to be well received and support better acceptance and adherence by older adult patients [68].

Documents to Guide Drug Development in the United States for Older Adults

Currently, the inclusion of older adults in clinical trials of drugs under evaluation for registration in the United States is guided by the "Guideline for the Study of Drugs Likely to Be Used in the Elderly" published in November 1989 [17]. The general theme of this guideline is "drugs should be studied in all age groups, including the older population, for which they will have significant utility."

In 1997, the Food and Drug Administration established the Geriatric Use subsection, as a part of the PRECAUTIONS section, in the labeling for human prescription drugs to include more comprehensive information about the use of a drug or biological product in persons aged 65 years and above [18].

Other useful documents for developing drugs in the older adults include the following:

- General Considerations for the Clinical Evaluation of Drugs (prior to February 1997) [19]
- Providing Clinical Evidence of Effectiveness for Human Drugs and Biological Products 1998 [20]
- Exposure-Response Relationships—Study Design, Data Analysis, and Regulatory Applications 2005 [21]
- Population Pharmacokinetics 1999 [22]
- Pharmacokinetics in Patients with Impaired Hepatic Function: Study Design, Data Analysis, and Impact on Dosing and Labeling 2003 [23]
- Pharmacokinetics in Patients with Impaired Renal Function: Study Design, Data Analysis, and Impact on Dosing and Labeling 2010 [24]
- Drug Interaction Studies—Study Design, Data Analysis, Implications for Dosing, and Labeling Recommendations 2012 [25].

Dosage Forms Considerations for the Older Adults

Attributes related to the physical characteristics of the dosage form and its drug delivery system (such as the physical nature of container) for drug administration to older adults cannot be overemphasized. Coverage of age-appropriate dosage form has received considerable attention in children. As about 70 % of all prescription

drugs are for the older adults, it is apt now to focus on age-appropriate formulations for the older adults [49]. Furthermore, self-administration of drugs by the older adults has always been a challenging issue. Recognizing this fact at the outset will allow for tangible solutions to the problem at hand. Drug delivery systems do pose obstacles to older adult patients particularly those who are self-medicating. Further, the impending switch from prescription to over-the-counter categories for many drugs implies that in the future a larger group of older adult patients will be self-medicating. The proportion of the older adults in the total population is increasing. These are the reasons to enhance and improve drug delivery systems and medication containers for older adult patients. The outcome of these measures can meet the needs of the older adult patients so that they may independently manage their medications with minimal support of caregivers [49].

The above features in the older adults make one realize that dosage forms need to be appropriate from a clinical perspective (such as dosing and dosing regimen), and just as important, from a practical perspective (namely ease and handling of administration) [68].

There are issues for considerations when it comes to dosage forms and their dosing strategies. Starting with simple formulations for the first-in-human trial to the eventual "to-be-marketed" dosage form(s) and their appropriate strengths require both intuition and farsightedness. Specifically from an older patient's point of view, it means empathizing with their physiological, psychological, and sociocultural limitations. The major areas of consideration in developing age-appropriate formulations for older adults are the correctness of the dose strengths and the simplicity of the dosing regimen, the ease of identification and maneuverability of the packaging, and swallowability [68]. For example, buccal drug formulations or lyophilisates which are placed on the tongue (orally disintegrating tablet) combine the advantages of oral solid dosage forms and their ease of administration [8]. A key problem associated with any dosage form is the accuracy of dosing [8]. Splitting of tablets or the sprinkling of capsule contents onto soft foods is cumbersome and less accurate than the easy adjustment of doses in liquid formulations. For example, even for dosing with liquid formulations the delivered dose is only accurate if the dropper is held vertically [8]. Thus, older adults need novel formulations that can provide accurate dosing. For oral dosage forms the accuracy of dosing is therefore governed by improved tablet geometries. Use of de-blistering machines has its advantages in facilitating the ejection of tablets and capsules from blister packages. Sociocultural acceptability is important as with insulin application devices known as "pens," and in the application of transdermal patches. Many immediate release dosage forms are being reformulated to modified release dosage forms in order to provide for extended release administration. The once-daily dosing seems to be the most common dosing frequency for these dosage forms currently [46].

Routes of Drug Administration and Aging

Oral

The most common route of drug administration is oral. Aging results in many physiological changes in the gastrointestinal tract such as increased gastric pH, delayed gastric emptying, decreased splanchnic blood flow, decreased absorption surface, and decreased gastrointestinal motility. Despite these changes, oral absorption does not appear to alter in advanced age especially for drugs that show passive diffusion mediated absorption [41, 56, 62].

However, older adults usually have multiple comorbidities and require multiple drug treatments which make it difficult for older adults to swallow multiple tablets daily. Difficulty swallowing is prevalent in older adults that can result from the medication itself, weak tongue, poor control of muscles in the mouth, and from the diseases being treated such as stroke, surgery after cancer, esophagus and nervous disorders [69].

Of note, orally disintegrating tablets may have the potential to aid drug delivery for the older adults. Orally disintegrating tablet is a patient-friendly dosage form which disintegrates upon contact with saliva within seconds on the tongue thereby avoiding the need to swallow tablets [53]. However, orally disintegrating tablet has the following major challenges for development:

- Orally disintegrating tablets need a balance between high mechanical properties such as hardness and friability and low disintegration time [1]. Thus, orally disintegrating tablets need the mechanical strength to withstand physical forces during manufacturing and transportation yet be able to rapidly disintegrate in the oral cavity.
- Difficulties to mask the unpleasant or unpalatable taste of some drugs [14].
- Development of controlled release technologies suitable for orally disintegrating tablets [1].

Prevalence of dry mouth or xerostomia increases with age and about 30 % of people aged 65 years and above experience xerostomia [65]. Thus, orally disintegrated tablets may not be convenient for use in patients with xerostomia because low volume of saliva would be present for tablet disintegration. Also, assessment of disintegration for orally disintegrated tablets needs standardization such as the volume of saliva rather than different experimental parameters from different laboratories [55].

Transdermal

The transdermal route of drug delivery has good potential for application in older adults because it is simple to use, convenient, noninvasive, and visible that increases patient adherence. Transdermal drug delivery may reduce adverse effects

especially for the management of pain and neurological conditions that require sustained effective plasma drug concentrations. Age-related changes in hydration and lipids result in increased barrier function of the stratum corneum for relatively hydrophilic drugs. Highly lipophilic drugs may dissolve readily into the stratum corneum even when the available lipid medium is reduced. No significant differences in absorption of drugs from transdermal delivery systems appear to exist between young and older adults [36]. Transdermal absorption of fentanyl was thought to be reduced in the older patients resulting in dose adjustments, whereas transdermal absorption of buprenorphine is little affected by age [2, 74]. Nevertheless, more research is necessary to better understand how age-related skin changes may affect transdermal drug absorption and consequently the need for dose adjustment in older adult patients.

Subcutaneous

The subcutaneous route of drug delivery is of particular interest because it is the most common route of administration for therapeutic proteins, which is likely to become important in the therapeutic arena for older adults. Subcutaneous drug absorption is through the vascular capillaries and lymphatic channels. Molecular size primarily determines the passage across the capillary endothelium. Polypeptides of less than about 5000 g/mole primarily pass through the capillary pathway, whereas those of greater than about 20,000 g/mole primarily enter blood via the lymphatic pathway [58]. The skin blood supply and lymphatic drainage will age [60]. Thus, subcutaneous absorption of drugs may be affected with aging and has clinical consequences.

Pulmonary

Lung anatomy and physiology change with age. Older adults show a decrease of the alveolar surface, a variation of lung elasticity, a decrease of the alveolar capillary volume combined with a decline of the ventilation/perfusion ratio, a decrease of the pulmonary diffusion capacity for carbon monoxide, and an increase of the pulmonary residual volume. Thus, age is an important parameter that affects the pharmacokinetics of inhaled drugs [67].

In a study of young (mean [SD] of 40.7 [5.1] years) and older (70.1 [4.2] years) patients with type 2 diabetes, exposure was comparable among the two groups following a single inhalation of insulin but the older patients had less glucose reduction suggesting the need for higher doses in the older patients. There were no statistically significant differences for the mean insulin AUC and C_{max} values between the young and older patients [31]. To the contrary, the concentrations of

isoflurane and sevoflurane necessary to maintain adequate depth of anesthesia are less in older age [48].

There is very little research on the pharmacokinetic and pharmacodynamic characteristics of new inhaled drugs in older adults and the effects of lung aging and copathologies are not known, especially in the very old. Moreover, decrements in cognition, praxis, and executive function that are highly prevalent in frail older adults have a profoundly detrimental effect on inhaler technique. Thus, a large proportion of older patients are unlikely to be able to use drugs targeted for alveolar absorption because accurate and reliable inhalation performance may not be achievable. However, cognitively intact older individuals with good neurological, pulmonary, and musculoskeletal performance may be able to use inhaled treatments in the same manner as younger individuals [3].

Intramuscular

Intramuscular drug absorption is very similar to subcutaneous drug absorption [58]. Based on the limited data for the 2 benzodiazepines (diazepam and midazolam), intramuscular drug absorption does not appear to change with old age [16, 33].

Ocular

Cornea shows decreases in permeability to a variety of compounds with different physicochemical properties between young and old rabbits [37]. Human and rabbit eye are very similar; their anatomical and physiological differences are well documented [26]. Choroidal thickness becomes thinner with older age, whereas Bruch's membrane thickens with older age in humans. Thickness changes of choroid and Bruch's membrane may affect drug permeability from subconjunctiva or episcleral space into the retina and the vitreous [42]. More research is necessary for better ocular drug delivery in older adults who suffer from age-related macular degeneration, cataract, glaucoma, and diabetic retinopathy [29].

For a more comprehensive discussion on newer methods of drug delivery to care for older adults, readers can refer to two recent articles [53, 55].

Issues in Medicating the Older Adults

Compliance has become a less widely used term as it implies patronizing toward the patient, and therefore it has been replaced by the term "adherence" which appears to be nonjudgemental [9, 46]. Nowadays, medication "adherence" is the preferred terminology. Adherence in a patient means acting in accordance with the prescribed

dose and dosing regimen. Quantitative metrics to measure adherence can be: (a) the proportion of days with the correct number of doses consumed and (b) the proportion of correct number of doses taken. Factors such as demographics, medical conditions of the patients, medication, behavior, and economic situations can affect adherence [5, 46]. Examples of aids to improve adherence are the weekly pill box, marking on calendar, self-coding of prescription vials with large letters or colored labels, and newer computer aided tools like computerized refill reminders. The rapid expansion in the area of modified release dosage forms including extended release pharmaceuticals has alleviated the adherence issue somewhat [61]. Less frequent dosing results in better adherence. For example, less frequent dosing of medications in patients with chronic ailments improves medication adherence in both once-daily versus twice-daily dosing, and in once-daily versus thrice-daily dosing [61].

There is a general belief that cognition declines with aging such that older patients may not be able to manage their medications. Prescribers need not subscribe to this assumption. Age is indeed a risk factor for adherence but surprisingly the younger adults rather than the older adults are more prone to making medication errors [52]. A study of RA patients showed no age-related differences in the use of external aids (such as use of organizers, writing notes or putting the medications in a prominent location), nor was there a relationship between the use of these strategies and medication adherence [52]. The high adherence rates in older RA patients are likely due to their understanding of their health. RA provides an example where older patients organized their daily activities around their medication timetable. The key therefore is being vigilant about one's health [52].

An opposite example is in the treatment of patients with glaucoma where there is poor patient adherence [9]. This may be due to the difficulty in administering topical antiglaucoma therapy, and therefore, physical disabilities like visual acuity and manual dexterity may prevent proper eye-drop instillation. Therefore, nonadherence is a serious problem in this disease state.

Methods exist for assessing medication adherence yet no single method is sufficiently reliable and accurate [46]. Clinicians can now select one or more methods to gauge medication adherence and can choose from a blend of traditional methods and newer electronic medication adherence devices. An ideal approach would be to select a method that monitors drug adherence and a primary clinical outcome [46].

Emerging Methods to Study Pharmacology in Older Adults

Underrepresentation of the older population in clinical trials is very common across multiple therapeutic areas such as cancer, dementia, epilepsy, incontinence, transplantation, and cardiovascular disease [7, 13, 30, 43–45, 50]. This underrepresentation phenomenon is also common to the pharmacokinetic and pharmacodynamic studies [11, 47]. Understanding the effect of aging on the pharmacokinetics and pharmacodynamics of drugs is important since it can help maximize the therapeutic

effects and minimize the adverse effects of medications for better care of older patients. An increased participation of older patients in clinical trials should provide benefit.

Population pharmacokinetic and pharmacodynamic approach with sparse sampling through covariate analysis in clinical efficacy and safety trials is an option to evaluate the effects of age on pharmacokinetics and pharmacodynamics of a drug. Some scientists refer to this approach as the "top-down approach" [71]. The population pharmacokinetic and pharmacodynamic approach is particularly suitable for the older patients since extensive blood sampling for the older patients may be too invasive and the studied patients more resemble the intended patient population than a dedicated pharmacokinetic or pharmacodynamic study that requires extensive blood sampling in rather healthy older participants. A recent example is the application of population pharmacokinetics to study participants living in the community and in nursing homes and found that advancing age (relevant only to men) and concomitant medications with cytochrome 3A4 inhibitors lowered the apparent clearance of orally administered atorvastatin [64].

Physiologically based pharmacokinetic (PBPK) modeling is another tool that has the potential to study drug disposition and action in the older population [57]. Some scientists refer to this approach as the "bottom-up" approach, which is more mechanistic in nature [71]. Recent examples of the application of the PBPK modeling approach include understanding the effect of renal impairment on the pharmacokinetics of diltiazem, paroxetine, and repaglinide as well as pharmacometrics in pregnancy [38, 59].

Scientists have compiled physiological parameters for healthy and health-impaired people 65 years of age and older for the PBPK models [70]. Others used the PBPK modeling approach to predict metabolic drug clearance with advancing age [54]. Scientists are applying the PBPK modeling approach to estimate drug dosing in children [6]. Thus, applying the PBPK modeling approach to understand drug disposition and action for the older adults seems appropriate [15, 34]. However, application of PBPK models to predict pharmacokinetics in older adults is with low to moderate confidence now. This is because knowledge of the abundance of cytochrome P450 enzymes (CYP), non-CYP enzymes, and transporters is limited or lacking in older adults. Also, understanding of changes in gut physiology is limited. Thus, confidence for applying the PBPK modeling in older adults may increase as more human data become available [35].

Scientists have been working on the systems biology of aging, which is intrinsically complex, being driven by multiple causal mechanisms [39]. In general, the systems biology approach combines the following:

- data-driven modeling, often using the large volumes of data generated by functional genomics technologies
- hypothesis-driven experimental studies to investigate causal pathways and identify their parameter values in an unusually quantitative manner, which enables us to better understand the contributions of individual mechanisms and

their interactions as well as allows for the design of experiments to explicitly test the complex predictions arising from such models.

The learning from these systems biology studies will help us understand healthier aging.

Compression of Morbidity to the End of Life Is the Eventual Goal of Healthy Aging and Drug Treatments

Healthier aging focuses on the compression of morbidity in older age [51]. The Compression of Morbidity hypothesis states that the age of onset of chronic illness may be postponed more than the age at death, squeezing most of the morbidity in life into a shorter period with less lifetime disability [27, 28]. Thus, the ideal goal of healthier aging and drug treatment should help older adults maintain physical independence and biological reserve as well as enjoy psychosocial well-being well into older ages.

Conclusions

Healthcare professionals, older adult patients, and caregivers need to work closely together in order to maximize the benefits and minimize the risks of medications taken by older adult patients. Thus, effective communication between them is absolutely essential. Medications taken by an older adult patient need an ongoing systemic review namely to adjust the dose(s), change to better options, discontinue unnecessary medications or duplicate medications from different prescribers. Practically, the pharmacist and caregiver are in a unique position to inform the prescribers for the medications that the older adult patient is taking. The pharmacist can also check for potential drug–drug and drug–disease interactions especially when an older adult patient receives a new medication. If an interaction were to occur, the pharmacist can alert the prescriber and the caregiver of the older adult patient. To prevent serious interactions, the primary care prescriber may need to intervene and stop the interaction from further happening. Overall, the healthcare community and general population recognize the need to care more for the older adult patients. Thus, the time is ripe to start putting recognition into practice. A genuine understanding of the therapeutic needs of older adults coupled with the recognition that the population worldwide is aging can help the health care community transform its thinking from regarding older adults as “therapeutic overlook” to one of “therapeutic dedication and enthusiasm.” Also, it has been almost 50 years since children were declared to be therapeutic orphans and one of the tremendous strides in developing drugs to benefit children is the development of

age-appropriate pediatric formulations. Now is the time to consider advancing older-adults-friendly dosage forms and their packaging.

Disclaimer This chapter reflects the views and opinions of the authors and does not represent the views and opinions of the authors' present and former employers.

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Part VIII
Concluding Remarks

Future Perspectives in Drug Therapy of Older Adults

Amanda Lavan, Paul Gallagher and Denis O'Mahony

Abstract The global population is aging and the prevalence of multimorbidity is increasing in tandem. With increased age-related multimorbidity, global consumption of medication is on the rise. Greater consumption of pharmaceuticals by an expanding global population of older people will inevitably lead to increasing levels of inappropriate prescribing (IP), polypharmacy, adverse drug events (ADEs), and iatrogenic morbidity and mortality. This chapter focuses on these changing prescribing patterns, the challenges associated with them and the potential strategies to optimize drug therapy for older adults. Any strategies to be employed need to address prescribing challenges from multiple angles including improvements in education among doctors and patients, encouraging the use of proven pharmacotherapy optimization tools, and embracing the use of computerized prescribing systems where appropriate. However, governments and pharmaceutical agencies need to work together to produce appropriate protocols and incentivized schemes in order to continue to provide effective and affordable drug therapy to the growing aging global population.

Keywords Elderly · Multimorbidity · Polypharmacy · Prescribing optimization · Adverse drug event

Introduction

Over the last century, life expectancy has increased dramatically due to many factors including advances in the treatment of infectious diseases, improvements in sanitation, nutrition, and drinking water, and in particular improvements in childhood survival. Over the next century, it is predicted that life expectancy will continue to increase, with birth rates remaining static, as the post-World War 2 generations reach retirement. Thus, between 2013 and 2080, the working sector of

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S. Stegemann (ed.), *Developing Drug Products in an Aging Society*,
AAPS Advances in the Pharmaceutical Sciences Series 24,
DOI 10.1007/978-3-319-43099-7_36

the European population (15–64 years) will decline in numbers, whilst those aged over 65 year will increase, particularly, the over-80s who are expected to double in numbers. Hence, the so-called European population pyramid is forecast to evolve wherein the over-65 population will be larger than any other group [1]. Internationally, similar trends are expected. In 1990, approximately 9 % of the world's population was 60 years or older. By 2013, this proportion had increased to 11 % [2]. By 2050, the global over-60's population is expected to double to 22 %, with the numbers of people aged over-80 expected to quadruple in the same time interval [2]. By 2050, the largest numbers of older adults will reside in developing poorer countries, unlike now where most are residents of developed nations.

The phenomenon of global population aging will inevitably bring a major increase in the prevalence of multimorbid chronic illness and a corresponding increase in medication consumption in general and major polypharmacy in particular. Currently in the United Kingdom, more than 80 % of primary care attendees over 65 years have multimorbidity, i.e., the concurrent presence of 3 or more chronic medical conditions [3]. Multimorbidity increases with age, with reported prevalence estimates of 62 % for those aged 65–74 years and 81.5 % for those 85 years and older [4]. At age 85 compared to age 70, the prevalence of chronic multimorbidity increases threefold [5]. In those persons over 85 years, approximately 1 person in every 5 will have chronic cognitive impairment, 2 persons in every 5 will have frequent urinary incontinence, and 1 person in every 2 are dependant in basic and instrumental activities of daily living [5]. Thus, the highest rates of multimorbidity are seen in the oldest old, who are predicted to be the fastest growing global population group in the coming decades.

The predicted demographic changes outlined above present many challenges for the future, particularly in the area of healthcare and drug therapy. This chapter will focus on two areas in particular, i.e., (i) current prescribing patterns of concern in older adults and what this means for the future of pharmacotherapy in this age group, and (ii) potential strategies for addressing these challenges and optimizing drug therapy in older individuals in the future.

Current Prescribing Practices of Concern in Older Adults

Polypharmacy

Over recent decades, the incidence and prevalence of polypharmacy has been increasing steadily secondary to a rapidly increasing aging population and advances in the treatment of chronic diseases. Major polypharmacy, i.e., the daily consumption of 10 or more prescription drugs is a characteristic feature of multimorbid older people and will therefore very likely increase markedly in prevalence as an epiphenomenon of global aging in the twenty-first century. Major polypharmacy is in turn intimately associated with inappropriate prescribing and adverse drug

reactions (ADRs) and adverse drug events (ADEs). Hence, some epidemiologists now regard drug-related morbidity as one of the emerging major public health problems of the modern era.

Historically, polypharmacy has been defined in two ways. The first, as "concomitant use of multiple drugs, which is measured by a simple count of medications," with many using 3–5 medications as a cutoff point [6]. Another definition is "the administration of one medication or more that is not clinically indicated" [6]. Recently, a clear distinction has emerged to differentiate between appropriate and inappropriate or problematic polypharmacy, the latter being the area of concern both for now and in the future [7]. Appropriate polypharmacy has been defined as "prescribing for an individual with complex or multiple conditions in circumstances where medicine use has been optimised and the medicines are prescribed according to best evidence" [7]. Maintaining a good quality of life, improving life-span and minimizing drug-related harm are the aims of appropriate polypharmacy [7]. Problematic, or inappropriate polypharmacy occurs when "multiple medications are prescribed inappropriately, or where the intended benefit of the medication is not realised" [7]. The causes of inappropriate polypharmacy are several, principally the lack of an evidence base for particular prescriptions and an unfavorable risk/benefit ratio from particular drugs in individual patients. On other occasions, the demands of taking multiple medications compromise adherence. Finally, inappropriate polypharmacy can result from so-called 'prescribing cascades,' i.e., the prescribing of additional drugs to counteract symptoms that are not recognized as adverse effects of other drugs taken by the same patient [8].

Currently, the highest rates of polypharmacy are seen in older people [9]. In the UK, approximately 20 % of the population is aged over 65 years, but receive 45 % of all dispensed drugs [10]. Similarly in the United States (US), people aged 65–79 years proportionately take five times more medication than young adults aged 19–25, with those over 80 years remaining the largest per person users of prescription drugs [11]. Inappropriate polypharmacy exists to similar degrees in the community ambulatory setting and hospital setting, i.e., approximately 1 in 2 older persons take one or more medications that are not medically necessary [9]. In nursing home residents, approximately 15–40 % of residents take ≥ 9 medications [9]. This is a cause of concern because the risk of clinically significant adverse drug reactions (ADRs) increases in a linear fashion in proportion to the number of daily prescription medicines taken by hospitalized patients [12]. This relationship is observed also in older community-based patients, i.e., those taking 2, 4, and more than 7 daily medication concurrently experience ADR risks of 13, 38, and 82 %, respectively [13].

The combination of predicted demographic changes and current trends toward ever increasing levels of inappropriate polypharmacy inevitably point toward rising levels of iatrogenic morbidity and mortality. This means that one of the core objectives for future safe prescribing will be the swift and accurate detection of inappropriate polypharmacy and rapid correction of the problem.

Inappropriate Prescribing (IP), ADRs, and Adverse Drug Events (ADEs): Cause and Effect

There is an intimate link between polypharmacy, inappropriate prescribing (IP) and ADR/ADE risk, illustrated schematically in Fig. 1. There is firm evidence of substantial prevalence rates of IP in older people in a variety of clinical settings [14, 15]. Recent data from southern Ireland using both Beers criteria and STOPP/START criteria are illustrated in Table 1. Not surprisingly, identification of potentially inappropriate medications (PIMs) and potential prescribing omissions (PPOs) increases steadily from primary care through secondary acute hospital care to long term nursing home care. The avoidance of PIMs is important from a clinical perspective, since STOPP criteria PIMs are significantly associated with excess ADEs in older people [16]. As expected from previous studies, PIMs are significantly related to polypharmacy in these three clinical settings. Therefore, future software-based strategies to minimize iatrogenic morbidity and mortality arising from PIMs and PPOs will need to be implemented in all clinical settings where prescriptions are initiated and reviewed.

In the ambulatory setting, ADR prevalence is approximately 5 % in the under 65 population and 16 % in those over 65 years [17]. In one recent systematic review, 4 % of hospital admissions in young adults resulted directly from ADRs, compared to 6 % in older patients [18]. In the same review, the rate of hospital-acquired ADRs was higher in older adults at 10 % compared to 6.3 % in younger adults [18]. Importantly, Beijer et al. [19] in their meta-analysis have estimated that 80 %

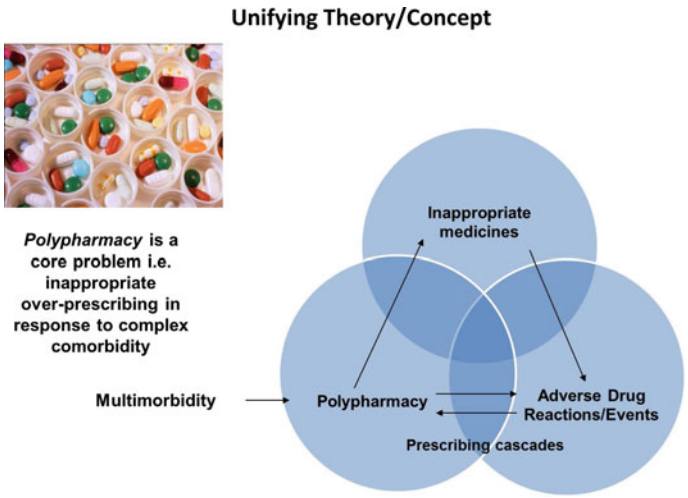

Fig. 1 The relationship between polypharmacy, inappropriate prescribing and adverse drug reactions (ADRs)/adverse drug events (ADEs) is a close and intertwined one. In some cases, ADRs/ADEs are not recognized for what they are leading to further prescribing, so-called 'prescribing cascades'

Table 1 Inappropriate prescribing tools designed specifically for older patients

1	McLeod criteria [91]
2	IPET (Improved prescribing in the elderly tool) [92]
3	Zhan criteria [93]
4	French consensus panel list [94]
5	Rancourt [95]
6	Australian prescribing indicators tool [96]
7	Norwegian general practice (NORGEP) criteria [97]
8	Priscus list [98]
9	Thailand criteria [99]

of hospital-related ADRs in older adults are preventable compared to 25 % in younger patients. Not surprisingly, the frail older populations are at considerably higher risk of ADRs. In one study, Cooper et al. noted that almost 70 % of nursing home residents developed one or more ADRs in a 4-year observation period. In the same study, many residents had recurrence of the same ADRs, especially related to the use of anti-psychotics, non-steroidal anti-inflammatory drugs and insulin [20].

The mortality rate attributable to ADRs in hospitalized patients is reported to be between 0.14 and 4.7 % [21, 22]. In the USA, annual mortality rates of 0.08–0.12/100,000 have been reported, with this rate significantly increasing over the last 7 years [23], with those at greatest risk being aged 75 years and older. Mortality associated with ADRs is due to commonly prescribed drugs with predictable side effects, such as anticoagulants, opioids, and immunosuppressant drugs [23]. In the future the demand for these drugs will increase as the incidence and prevalence of illness requiring these drug treatments increases with age, i.e., atrial fibrillation, stroke, cancer, and arthritis. In the USA, the overall incident rates of serious and fatal ADRs are reported as 6.7 and 0.32 % respectively during a hospital episode, thus ADRs are now listed as being between the fourth and sixth leading cause of death [22]. The implication from all these studies is that while ADRs are highly prevalent in older sicker patients, they are also predictable, and therefore, preventable in most cases.

Economic Effect of IP and ADRs/ADEs

It is now recognized that IP and related ADRs/ADEs represent a major drain on health budgets. In one study, it was estimated that 5–9 % of all hospital costs were related to ADRs [24]. Several recent studies demonstrate the magnitude of health budget wastage resulting from ADRs/ADEs. In 2004, Pirmohamed et al. [22] estimated that ADRs were costing the UK National Health Service approximately 700 million euros per annum, i.e., approximately 1 billion euros in 2015. The recent HARM study in the Netherlands estimated that the average cost of preventable medication-related acute hospitalization was 6009 euros [25]. The authors extrapolated this average cost to represent approximately 0.5 % of the total national

Dutch hospital budget [25]. Of note, the median length of stay of patients hospitalized as a result of medication adversity in the HARM study was the same as that recorded by Pirmohamed et al. [22] in the earlier UK study, i.e., 8 days. In another recent German study, Rottenkolber et al. [26] calculated that approximately 3.25 % of all acute hospital admissions were directly related to ADRs. In that study, the median age of affected patients was 74 years, the median length of stay was once again 8 days and the extrapolated cost to the national exchequer was 434 million euros, i.e., approximately 650 million euros in 2015 terms. These European studies indicate a consistent level of ADRs/ADEs resulting directly in acute hospitalization, affecting older people in the majority and imposing very serious strain on healthcare budgets.

Another cost relating to medication use is the overall amount spent on prescribed medications, drug costs being one of the fastest growing areas of all healthcare expenditure. In Ireland, state-funded community drug expenditure has increased sixfold in a decade from approximately €300 million in 1998 to €1.9 billion in 2008 [27]. In Europe, annual expenditure on prescription medicines is currently expected to increase by up to 2 % per annum to 2016 [28]. In the US, spending on prescription drugs grew by 9.9 % annually between 1997 and 2007 [29]. With the global demographic shift toward aging populations, these rising costs are expected to continue in tandem. Despite the global increase in prescription medication consumption by older people, it is known that in the US as many as 2 out of 3 medications dispensed to older adults are not used, accounting for $2.4 billion annually in unnecessary or wasted drug expenditure [30].

Added to rising healthcare costs associated with IP and ADEs/ADR are increasing so-called age dependency ratios. Age dependency ratios look at the ratio of dependents (whether 15 years and younger or 65 years and older or both) to the working age population (15–64 years). In January 2010, the old-age dependency ratio for Europe was 27.5 %, i.e., approximately four persons of working age for every person aged 65 years or over. In the coming years, with the number of persons of working age expected to decline and the number of older persons expected to increase steadily, the old-age dependency ratio is predicted to almost double from 27.5 % in 2013 to 51.0 % by 2080, i.e., two persons working for every person over 65 years. To increase healthcare funding governments will either increase taxes, reduce available services or both [30]. The medical and pharmaceutical communities globally need to work alongside governments to devise effective strategies that ensure that inappropriate drug expenditure is minimized so that the funds that are available are used appropriately.

Paucity of Clinical Trials Evidence in Older Persons

Prescribing for the older patient is often a complex task, particularly for multimorbid older people. One continuing challenge is the paucity of clinical trial evidence to support drug treatment regimens in this group. Older people with multimorbid illness are often excluded from clinical trials and when they are

included they are, more often than not, underrepresented [31, 32]. Recent reports have highlighted serious levels of exclusion of older people from common age-related conditions including heart failure [33], diabetes mellitus [34], and cancer [35]. There are many reasons for this underrepresentation. A recent study of professional views of clinicians in nine European countries as the main barriers to greater participation by older people in clinical trials concluded that legislative and healthcare system restrictions were paramount [36]. There is no firm evidence that older people themselves or their carers are more resistant or have more negative attitudes to participation in clinical trials than any other age group [37].

A clinical trial's aim is often to prove that a new drug is beneficial and trial participants are usually selected by particular exclusion criteria to avoid the potential influence of other factors on trial results, i.e., other diseases and treatments. These potentially confounding factors are seen more commonly in older people, making them less attractive clinical drug trial participants. When included in clinical trials, older patients can be more difficult to follow up, particularly those who are frail. Ethical concerns can also arise around obtaining valid informed consent, in particular from those older patients with dementia or communication/comprehension deficits. In these circumstances, it is not surprising that many older adults are excluded from clinical trials.

In the future, in order to improve older adult representation in trials, discussion with older patients needs to improve, trust needs to be built between clinical trial organizers and older people as an increasingly important population group. Data from the recent PREDICT study indicate that clinical trials in the future need to include real-life older people with multimorbid illness and complex polypharmacy in order to fully understand the benefits and limitations of particular drugs in the older population [38]. In addition, those older people who participate in clinical trials need to be financially compensated accordingly. Only then can an evidence base that is truly representative of multimorbid older people be developed, which can guide prescribers toward appropriate drug therapies for the broad variety of older adults in the future.

Potential Strategies for Optimizing Drug Therapy in the Future

Strategies to address these core issues around optimizing pharmacotherapy in older people and their associated healthcare implications in older adults discussed above areas are several.

Role of Education

Improvements in undergraduate and postgraduate medical education are paramount if prescribing practices relating to older patients are to improve. Doctors, whether

trained in Geriatric Medicine or not, need to be prepared to prescribe for older patients, as older people will attend many different specialties. Prescribers need to be cognizant of the age-related changes that affect drug pharmacokinetics and pharmacodynamics. They also must be aware of the multiplicity of potential drug-drug interactions and drug-disease interactions in multi-morbid older people with polypharmacy. A heightening of such awareness among prescribers is likely to improve IP and polypharmacy, and to lessen ADR occurrences and consequent excess healthcare costs. Although some progress has been made in preparing doctors for treating the aging population [39], most physicians to date still receive inadequate training in geriatric pharmacotherapy [40]. Evidence suggests that educational strategies, predominantly interactive teaching with direct feedback could improve doctors' prescribing knowledge with positive effects on clinical outcomes [41]. Among medical students, the WHO guide on prescribing can improve their prescribing skills, but this has only been shown in a simulated environment [42]. More recently, researchers in The Netherlands have demonstrated that prescribing skills in medical students can be significantly enhanced by means of a software-based pharmacotherapy skills teaching tool which focuses of avoidance of inappropriate prescribing [43]. Further research on educational strategies applied to medical students and postgraduate doctors, particularly on their long term benefits to older patients, is required.

The global aging demographic shift also demands more specialized geriatricians than are currently available. Unfortunately, in some countries including the US, the proportion of geriatricians to the number of persons aged over 75 is diminishing [44]. Two major reasons for this phenomenon are the lack of awareness of Geriatric Medicine as a clinical specialty and healthcare systems that favor the number of reimbursable clinical procedures over time spent with a patient as a marker for healthcare efficacy. Such a system financially rewards doctors who assess and treat many patients using a multiplicity of diagnostic and therapeutic procedures, often of a highly invasive nature [45]. Patients attending geriatricians are often multimorbid, require fewer treatments and generally need more consultation time. Hence, Geriatric Medicine is one of the lowest paid specialties in the US, discouraging many medical graduates from embarking on this specialty as a career, despite its high career satisfaction [46]. Providing the appropriate number of geriatricians for the global aging population will be pivotal for leading the education of all doctors, providing high standard care for older adults and avoiding inappropriate prescribing with its negative sequelae.

Methods to Enhance Adherence/Compliance

It is essential that those who prescribe for older adults are knowledgeable about pharmacotherapy in late life, but it is also important that older patients and their carers are equally educated about their medications. A paternalistic approach is less acceptable nowadays and increasingly older patients are active participants in their own health

care. If patients of any age do not understand their treatments, noncompliance may result which can in turn lead to adverse outcomes and greater financial cost health systems. If this occurs in a trial setting, results will be affected. Doctors need to ensure that patients are informed about their medications and to reinforce the importance of medication adherence. Clinical pharmacists have an important role here also, with research evidence showing that pharmacist intervention has favorable effects on therapeutic outcomes, safety, hospitalization and medication adherence in older adults [47]. As with doctors, not all pharmacists are trained in geriatric pharmacotherapy. The impact of specialty training on prescribing appropriateness and avoidance of drug adversity in older people has not been studied to date.

Medication adherence is influenced by many factors and is a complex area to address. One factor is the burden of taking many medications. Combination medications and the polypill have been shown to improve adherence and avoid medication wastage [48, 49]. Patients find medications given in this manner to be convenient and are more inclined to comply as a result [50]. In diabetes and hyperlipidaemia, greater medication adherence is associated with lower disease-related medication costs including lower hospitalization rates [51]. Encouraging the use of combination medications could improve adherence in older people and reduce healthcare costs but in isolation does not fully address medication adherence. Public health campaigns on medication adherence could possibly have benefit in older people, although this has not been demonstrated to date.

Role of Prescribing Optimization Tools

Over the last 30 years, prescribing tools advising on potentially IP in older adults have been introduced and will play a role in the future of drug therapy of older adults. These aim to highlight potentially inappropriate medications (PIMs) and consequently reduce IP, adverse events and cost. The two most commonly used explicit IP criteria sets are Beers Criteria [52–55] and the Screening Tool of Older Person's potentially inappropriate Prescriptions (STOPP)/ Screening Tool to Alert to Right Treatment (START) criteria [56, 57] although there are several others (Table 1). Both these criteria have been developed from expert consensus techniques [58] and contain lists of drugs that are known to cause harm in older adults (through predictable pharmacological or physiological mechanisms) and should be avoided or prescribed with greater caution. To complement the detection of common or more important instances of PIMs by means of validated criteria sets, sets of criteria that highlight the more common and important instances of potential prescribing omissions (PPOs) have also been developed recently. The only validated set of explicit PPO criteria in the literature is START criteria. Recent studies have shown PPO prevalence rates as high as 60 % in older people admitted to hospital with unselected acute illness [16, 59].

Using Beers and STOPP criteria, varying prevalence rates of PIMs have been reported in different older patient cohorts (Table 2). STOPP criteria PIMs, unlike

Table 2 Reported inappropriate prescribing rates according to Beers criteria and STOPP criteria

Cohort	Beers criteria (%)	STOPP criteria (%)
US community dwelling (n = 18,475) [100]	42.6	–
Spain community dwelling (n = 407) [101]	44	35.4
Sweden community and institutional dwellings (n = 1,346,709) [102]	24	–
Brazil community dwelling (n = 142) [103]	51.8	33.8
Ireland community dwelling (n = 2051) [104]	30.5	52.7
US nursing home (n = 696) [105]	51.9	–
Ireland nursing home attending ED (n = 165) [106]	89.1	84.8
Ireland primary care (n = 931) [107]	28	42
Italy hospitalized inpatients (n = 871) [61]	58.4	50.4

Beers criteria PIMs have been associated with avoidable clinically significant ADEs in older adults [60, 61]. A recent study has shown that the application of STOPP criteria within 48 hours of admission reduces hospital-acquired ADRs, with an absolute risk reduction of 11.4 %, i.e., number needed to treat with STOPP criteria to prevent one nontrivial ADR was 9. In the same study the median monthly medication cost was significantly lower in the intervention group (73.16 [38.68 – 121.72]) compared to the control group who's median monthly medication cost was (90.62 [49.38 – 162.53]) and reduces costs significantly [62]. However, the full clinical and economic benefit from routine deployment of PIM criteria is yet to be fully appreciated and is the subject of many ongoing research endeavors [63]. Their role in the future may be enhanced by dedicated software systems wherein they can be applied in seconds rather than being manually applied.

Another pharmacotherapy assessment tool called the medication appropriateness index (MAI) is based on implicit prescribing assessment criteria. MAI can be used to evaluate the appropriateness of prescribing in all patients and not just older adults. It consists of 10 domains: drug indication, dose, efficacy, practicality, directions, drug–drug interactions, drug-disease interactions, duplication of drugs, duration of treatment, and cost [64]. Each medication is assessed according to these 10 domains and given a score. This tool requires the user to have clinical pharmacology expertise and is very time consuming to apply, such that, it remains essentially a research tool. However, it does encompass elements for drug prescribing that are applicable to any medication and any clinical condition. A more concise, implicit assessment tool may have a role in routine clinical practice but as yet has not been developed.

Prescribing criteria are likely to play a role in the future drug therapy of older adults to assist with optimzsation of medications. However, it is important that those using them are aware of their limitations. First, they are designed to assist decision-making and not to substitute good clinical decision-making and so need to be applied by appropriately trained people. In order for these tools to continue to be applicable, they need regular updating as new evidence emerges and new drugs enter the market.

Role of Computers

Computers have the potential to improve pharmacotherapy in older people through many mechanisms such as automated alerts to drug contraindication, potentially adverse drug-drug and drug-disease interactions as well as best value drug selection from lists of generic medicines. Electronic prescribing (e-prescribing) allows prescribers to compile a new prescription list or to renew an old prescription list as well as to transfer it quickly to the appropriate dispensing pharmacist. A clear account of a person's medication history is recorded in this manner. It is fast and efficient and prescriptions are not misidentified because of poorly legible prescriber's writing. E-prescribing has been shown to reduce medication errors and ADRs and is cost effective [65, 66]. Although e-prescribing software systems are available and have proven to have many associated benefits, most health services in developed countries do not use them mainly because they are generally costly and challenging to install [66, 67]. Those e-prescribing systems that are commercially available have been developed for the general adult population and are not specifically for use in older adults. In order for e-prescribing systems to be of benefit to the future of drug therapy in older adults, they need to be adapted for the older, multimorbid patient population with altered pharmacokinetics and pharmacodynamics, multimorbidity and complex polypharmacy.

In conjunction with e-prescribing, computerized drug-laboratory alert systems could potentially be of benefit. Inadequate monitoring of drugs has been associated with as many as 6 out of 10 preventable ADEs [68]. The aim of computerized drug alerts is to remind prescribers when a laboratory test is required with a certain drug or to advise regarding cessation of a drug when a laboratory value is abnormal. To date there is nothing to indicate that these alerts, in daily practice, are associated with clinical benefits. However, their use can improve surrogate outcomes (i.e., time in therapeutic range for vitamin K antagonists) in selected cases and thus the potential for tangible clinical benefit is there. They could be of particular use in the older population where organ function can change over time and in situations where a drug that was once clearly indicated and well tolerated is now contraindicated and likely to cause an ADR, e.g., dabigatran in context of worsening renal function in the context of chronic kidney disease [69].

Computers may also improve prescribing in the older adult by means of software engines designed to optimize prescriptions based on inappropriate prescribing criteria (e.g., STOPP/START) alongside electronic databases that identify potentially adverse drug-drug interactions and drug-disease interactions. Research is ongoing in the area of prescribing optimization software development and validation, e.g., the Software ENgine for the Assessment and optimization of drug and nondrug Therapy in Older peRsons (SENATOR) trial currently in progress in 6 large-scale teaching hospitals in Europe [70]. This is likely to be a growing area in health software research and will likely evolve toward commercialization for routine clinical use if clinical trials of these prescribing optimization software engines prove their efficacy.

Role of Pharmacogenetics

The science of pharmacogenetics looks at genetic variations in individual patients that predict individual patients' response to particular drugs. It examines genetic variability in drug metabolic pathways, drug receptors, and transporter systems that can have clinically relevant influences on individual patients' responses to particular drugs. With the surge in the study of genomics over the last 20 years, pharmacogenetics has been revolutionized. Following the discovery of a wide range of genetic polymorphisms within the cytochrome P450 system of metabolizing enzymes in the liver, there followed a rapid expansion in the number of drugs whose variability of pharmacokinetic and pharmacodynamic effects could be readily explained. In general terms, drugs with a narrow therapeutic range which are metabolized by polymorphic cytochrome enzymes are more likely to be considered inappropriate for older people. There are three pharmacogenetic mechanisms that influence patients' clinical response to pharmacotherapy: (i) genetic polymorphisms that alter (increase or decrease) drug metabolism and thus change drug concentrations; (ii) unexpected events in response to a drug via genetic variants (haemolysis in glucose-6-phosphate dehydrogenase deficiency); (iii) genetic variation in drug targets which can in turn alter clinical response and frequency, e.g., variants of the beta-adrenergic receptor which can alter response to beta-agonists in asthma patients [71].

There is a growing list of adverse drug-drug interactions that arise through pharmacogenetic mechanisms. Although much research has been done in this area, how to translate it to routine clinical practice poses a major challenge for the future. Among the biggest challenges highlighted in the literature are the incorporation of pharmacogenetic data into drug development and the use of pharmacogenetic profiling in routine therapeutic decision-making [72], the latter being a key part of so-called 'personalized medicine.' Pharmacogenetic profiling has already been shown to have the capability of minimizing individual patients' difficulties with certain commonly prescribed drugs that can cause very serious ADRs e.g. warfarin [73], statins [74], and phenytoin [75]. Another example of the practical value of pharmacogenetic testing in defining risk of serious ADRs is the CYP2CP polymorphism profiling in predicting gastroduodenal ulceration and bleeding when exposed to oral nonsteroidal anti-inflammatory drugs (NSAIDs). In this instance, persons with the CYP2CP*1/*3 polymorphism have a substantially higher risk of NSAID-related gastrointestinal bleeding [76]. Pharmacogenetic testing can also be used to define higher likelihood of positive response to certain drugs. For example, research data show that persons in whom there is low or absent CYP2D6 activity have a significantly higher likelihood of positive clinical response to donepezil [77].

Although pharmacogenetic profiling has the potential to reduce drug-related problems in some instances and to predict drug-related benefit in others, its implementation in routine clinical practice would mean substantial extra costs over and above current routine costs of traditional prescribing and dispensing of pharmacotherapy. It is unclear whether the cost of investment in pharmacogenetic profiling would be balanced by

fewer adverse clinical events through prediction and prevention of serious adverse drug-drug and drug-disease interaction events in older people. However, as with most novel technologies applied to clinical practice, the associated costs of routine pharmacogenetic profiling will very likely diminish over time.

Generic Prescribing

Increased generic prescribing has perhaps the greatest potential to reduce current drug expenditure costs with minimal investment. At the present time, there is a steady annual increase in overall pharmaceutical spending in most developed countries. The two main reasons for this are the growth in prescriptions items and the prescribing of newer more expensive medicines. The evidence shows that doctors in more affluent countries generally have positive views toward generic prescribing, in contrast with doctors in less wealthy countries who tend to have mixed views on the benefits of generic prescribing, including views on costing [78]. Previous research has shown that if doctors are educated on drug costs, generic prescribing behavior can improve accordingly [79].

Many countries to date have promoted generic prescribing through different policies such as mandatory generic substitution and incentivized generic prescribing with varying levels of success [80]. In 2002, mandatory generic prescribing was introduced in Sweden. Prior to its introduction patient and society's expenditure on drugs had been increasing steadily year after year. Following the implementation of mandatory generic prescribing, annual overall prescription medicine costs fell steadily and substantially in Sweden, with major exchequer savings [81]. This policy was not without drawbacks, however. For example, 40 % of Swedish patients experienced at least one subjective difficulty relating to the change in their medications following the switch from branded drugs to generic medicines [82]. Recent work by Kesselheim et al. indicated that variation in drug appearance, which often occurs in the context of generic as distinct from branded drug prescription, can adversely affect drug adherence [83, 84]. It is likely that for generic prescribing to work effectively it needs to be undertaken on in a large scale, i.e., at national or regional level. Continued prescriber incentivization schemes are also likely to be necessary to sustain high levels of generic prescribing.

Electronic prescribing software systems are considered a key element to successfully introducing fully generic prescribing. As with all software systems used in prescribing, the quality and reliability of the updated drug files is crucial to enhancing prescriber acceptability and continued use.

Pharmacist and Nurse Prescribing/Medication Review

To help deal with the increased demand on the health service by the demographic shift, it is highly likely that nursing and pharmacy roles will expand,

particularly with nurses taking on more prescribing tasks. The nurse prescribing initiative has, in general, been successful, with high levels of satisfaction among nurse prescribers and their patients [85]. If the number of nurse prescribers is to increase to deal with the prescribing demands of an expanding older population, it is expected that nurse prescriber education will need to evolve and diversify in order to prepare nurse prescribers for the growing aging population. Pharmacist prescribing has been in place in several countries over the last 15 years, including the UK where pharmacists were granted limited prescribing rights in 2003, shortly after the introduction of nurse prescribing [86].

Medication reconciliation (MR) is an important and understated part of accurate and detailed medication history taking. It is a process of creating the most accurate list of a patient's current medications in order to detect potential inconsistencies and potential drug-drug and drug-disease incompatibilities. The structured history taking of medication use (SHiM), pioneered by the Dutch Ephor group, has been shown to detect discrepancies in almost all patients' medication histories, with clinically significant consequences occurring in up to 20 % of older patients [87]. The same study noted that 1 in 2 of these clinically significant consequences related to over-the-counter drugs [87]. The practical value of MR as it currently exists remains uncertain, however. Christenen et al., in a recent meta-analysis found MR reduced emergency department contacts but did not significantly reduce mortality or overall healthcare cost [70]. In contrast, another recent meta-analysis of MR impact found that MR significantly reduces medication discrepancies and ADEs [88]. The inconsistent clinical and economic value of MR may possibly relate to the wide variability of the scope of MR as described in the literature and the fact that most MR programs deal more with medication formulation, dose, and adherence issues rather than with appropriateness of prescription.

As well as carrying out software-supported structured medication reconciliation (MR), pharmacists will have a key role in the future in pharmacotherapy optimization in the expanding older populations of most countries. It is expected that sophisticated and fast software engines will come into clinical use in the next 10–15 years designed specifically for detailed assessment of complex pharmacotherapy in older people. Such software engines will check drug indications and contraindications, potential drug-drug and drug-disease interactions, dose appropriateness, drug adherence, and best value brand selection. It is expected that routine medication review in older people will thereby become much faster and more comprehensive than at present.

The Role of Government and Pharmaceutical Companies

For effective strategies to improve pharmacotherapy quality and impact and reduce associated costs in older people, they need to be supported by the health professions (universities, higher training bodies), medication regulatory bodies and by governments. Healthcare in most countries is a service supported primarily by public

funding. To deal with increasing healthcare demands of aging populations, it is expected that taxation will need to increase. With aging demographics expected to continue into the latter half of this century, governments are beginning to appreciate that optimizing pharmacotherapy and minimizing drug-related wastage in older people is an essential part of any forward-looking economic strategy. Equally important is the need to minimize older people's level of dependency, which is gradually being recognized as imperative given the fact that care of the frailest older people is highly costly. The central role of pharmacotherapy in so-called 'preventive gerontology' as an emerging strategy for keeping older people healthier for longer will be very considerable. Several of the common debilitating conditions of late life are preventable through careful screening and application of appropriate pharmacotherapy (Table 3).

The pharmaceutical industry will continue to play a central role in the enhancement of pharmacotherapy for the older global population over the coming decades. In the last 20 years, the rate of expenditure on pharmaceuticals has grown faster than the gross national product (GNP) in all European countries [89]. In the USA, pharmaceutical expenditure has grown faster than any other healthcare area of healthcare expenditure; the same pattern is evident in Europe [90] and in many other low to middle income countries and is likely to continue to grow with the predicted aging demographic changes. Keen competition between the major global pharmaceutical companies will very likely continue. It is expected that the total number of pharmaceutical companies globally will continue to contract as the bigger and more powerful international corporate companies continue in the trend

Table 3 Common age-related conditions and appropriate preventative therapy

Common conditions	Preventative therapies
Musculoskeletal	
– Frequent fallers with osteoporosis	Vitamin D and calcium supplementation with anti-resorptive therapy to prevent fractures
Cardiology	
– Atrial fibrillation	Anticoagulation to prevent stroke
– Coronary artery disease	Antiplatelet therapy, beta blockers, and statin therapy to prevent myocardial infarction
– Hypertension	ACE-inhibitors, calcium channel blockers, beta blockers, or diuretics to control hypertension and prevent stroke and cardiovascular morbidity and mortality
– Heart failure	ACE-inhibitors, beta blockers, spironolactone to prevent cardiovascular morbidity and mortality
Respiratory	
– Chronic obstructive pulmonary disease (COPD)	Inhaled corticosteroids to prevent exacerbations of COPD
Neurological	
– Dementia (mild—moderate)	Acetyl-cholinesterase inhibitors to slow progression of disease
Endocrinology	
– Diabetes mellitus with renal disease	ACE-inhibitor or angiotension receptor blocker to prevent progression of renal disease

of buying out and taking over smaller companies. Oncological, immunological, and inflammatory conditions are likely to be the drivers for new pharmaceutical product innovation in the future [28], with new drugs expected to arrive on the international market for treatment and prevention of common conditions of late life in which current therapeutic options are very limited, such as Alzheimer's disease, osteoarthritis, macular degeneration, and sarcopenia. Government regulation of the pharmaceutical industry will likely increase since health economists appreciate that an unregulated pharmaceutical market will not produce effective competition and will not reduce the cost of medicines currently or in the future.

Rationing of expensive pharmaceuticals in older people is a reality in some countries and will likely continue and grow as an unavoidable aspect of pharmacotherapy in aging populations in increasing numbers of countries. Reliance on cost-effectiveness models by drug regulatory bodies in developed countries in particular is an increasing phenomenon. The need to prove cost-effectiveness of new drugs before their patents expire will be a greater influence on availability of these drugs in the future, particularly for more expensive 'biological' drugs such as monoclonal antibodies.

Conclusion

The future of drug therapy in the older adult will continue to be complex and challenging. IP, polypharmacy and ADEs will continue to be a problem unless effective counteractive strategies are devised, validated, and introduced into routine clinical practice. Improving undergraduate and postgraduate therapeutics education and increasing the number of specialist geriatricians will help with this increasing demand. Even if the number of specialist geriatricians increases globally, the majority of prescriptions for older people will still originate from practitioners who are not geriatricians. Other clinical specialties need to have a greater awareness of their role in the pharmacotherapy of older people. Prescribing support software tools can assist prescribers in geriatric pharmacotherapy but they cannot replace knowledge and experience, hence ongoing education at a postgraduate level is required.

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Opportunities in Drug Product Development in an Aging Population

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Abstract Drug product development is a lengthy and highly regulated process that requires substantial investment at high risk. The changing demographic of society towards older people is a fact that will impact healthcare provision, including drug product development and prescribing. While it presents many challenges, demographic evolution should be seen as an opportunity rather than a threat. Rapid progress in science and technology, as well as multidisciplinary research, will be important sources for innovation in providing healthcare to patients, and especially older patients.

Keywords Drug therapy · Older adults · Drug product development · Patient centricity

Introduction

A demographic change is occurring on a global level, affecting both mature and emerging markets. This demographic trend is associated with an increase of the number of people 65 years and older, and more importantly, with the existence of a significant number of people at old (85–94 years) and very old ages (95+ years), which can be considered a newly evolving patient population. This demographic change is often considered a major issue for healthcare systems grappling with the sustainability of the quality of medical and pharmaceutical care over the coming decades. However, one should not forget that already in October 1960, *Harper's Magazine* published a special supplement titled "The crisis in American medicine", suggesting the unsustainability of the healthcare system due to soaring costs and the crisis of the uninsured in the 1960s. Just a few years later, in 1968, Paul Ehrlich

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S. Stegemann (ed.), *Developing Drug Products in an Aging Society*,
AAPS Advances in the Pharmaceutical Sciences Series 24,
DOI 10.1007/978-3-319-43099-7_37

published his book *The Population Bomb*, predicting that within the following 15–20 years, the world would experience mass starvation of humans due to overpopulation along with other major societal upheavals, and thus that limiting population growth was urgently needed [8]. That none of these scenarios has come true is the result of continuous advancement in food production, income, education, technology and societal coexistence. With the current progress in medicinal and pharmaceutical sciences as well as in other technologies, there is no reason to doubt that we will be able to sustain and improve healthcare delivery in an aging population in an affordable manner.

Dynamic changes and technological advances are incremental, and are essential for mankind and the wealth of our society. The ambition of every generation is to move forward and solve unresolved issues to increase wealth around the world. This dynamic progress, however, may not be without risk; it can create new challenges that cannot be predicted or judged, just as it can generate new opportunities that were not visible or obvious earlier. Refraining from embracing every possible technological advancement without precautions has helped us to survive, while at the same time taking some risk has helped us to make disruptive innovations possible [4]. It is also a matter of fact that innovative technologies come at high cost in their beginnings but then drop down very quickly as the technology is further developed and matures. Sequencing the first human genomes generated costs of about US$100 million per person in 2001 and took several years; in contrast, the sequence of a human genome can be done within 24 h at less than US $5000 in 2013 [7].

Developing medicinal products and prescribing them to patients have always been a matter of a risk-benefit assessment, as every desired therapeutic effect comes with certain undesired adverse drug reactions. To protect patients from any harm, regulatory guidance and processes as well as prescription guidelines have been put in place with the best intentions. Overregulation, on the other hand, bears the risk of denying effective treatment to patients that would benefit, even though the views of scientists, medical doctors and the patients might not concur on the benefit–risk judgement. Significant changes in the patient population, therapeutic and medicinal advances, and patient empowerments are leading to new dynamics across the spectrum of healthcare provision, including the entire group of healthcare stakeholders and the patients. The challenges are equal for each and every stakeholder and patient, and thus the solutions to these challenges remain a shared responsibility.

Beyond the Drug

With the increasing number of patients beyond 65 years of age, including the old and very old, the prevalence of typical age-related diseases will further increase [21]. Today, heart diseases and cancer are the major causes of mortality in the USA followed by stroke, chronic lower respiratory diseases, Alzheimer's disease and

diabetes [5]. An increasingly significant number of patients will live with multimorbidity and complex health impairments and disabilities. This is also reflected within the healthcare costs: chronic diseases account for 95 % of the spending, and the costs for people 65 years and older is three to five times as high as those for younger people [5]. To maintain the independence and well-being of these patients, treatment schedules with several drugs and polypharmacy are required, and are very often essential. This moves drug therapy away from the focus on a single disease and single drug therapy, towards a therapy that will be stratified towards the specific patient or patient population. This includes not only the disease parameter as such, but also the physiological changes occurring with age, the other disease parameters and symptoms, as well as the co-treatments and the potential drug–drug interactions. In multimorbid and especially frail patients, therapeutic decisions will have to be prioritized, focusing on those that most critical and causing the greatest disease burden for the patient [22]. Transforming prescription from independent disciplinary prescribing to a holistic prescribing model is expected to prevent unintentional inappropriate prescribing. Different models have been proposed, such as the Beers or PRISCUS s list containing the medicines that are considered inappropriate for older adults, the Medication Appropriateness Index (MAI), the application of START (Screening Tool to Alert doctors to Right Treatment) and STOPP (Screening Tool of Older Persons' potentially inappropriate Prescriptions) criteria to prescribe the right drugs and doses to an individual patient [12, 23] or applying pharmacometrics in defining the best treatment plan for the patient to achieve the clinical and personal objectives of the therapy [20]. When reviewing prescriptions and medication schedules of older adults based on such guidance, it was found that under-prescribing was an even more important issue than over-prescribing, suggesting that older adults might still benefit from additional prescription [10, 18]. Considering multimorbid patients early on in the clinical trial program provides important data on the clinical benefits of new drugs and drug products, and helps to identify subpopulations at risk or at benefit for a certain intervention or specific dosing schedule. This will increasingly include pharmacogenomics information, helping to tailor drug benefits to the right patient population in their overall clinical context.

Since the first sequencing of the human genome in 2001 [32], genomics, proteomics, metabolomics and other -omic technologies have become an integral part of modern drug discovery, providing tools for understanding the disease on a molecular level. Screening the genes of hundreds of thousands of people and patients with a specific disease, and combining these genomic data with phenotypic and environmental variables, has enabled scientists to form multilayer disease modules (MLDMs). Several studies have confirmed the association of an altered function in one module with other diseases, revealing the relationship between different diseases as an interactive network. With an increasing set of data and powerful computational tools, it is expected that the understanding of such disease networks might change our disease taxonomy and classification [13]. From the broader perspective, systems medicine will help to move from a reactive, disease-oriented approach to a predictive, preventive and personalized medicine [31].

Beyond the Traditional Disease Model

The basic requirement today for a therapeutic entity to become a drug or medicinal product is decided in conjunction with the definition of a physiological condition that is considered a "disease". There is still a lack of clear definition as to what a "disease" is, even though we may believe that there is universal agreement. In general, disease is understood to be any deviation from or disruption of the normal physiology of an organ, body part or system that is accompanied by a characteristic set of symptoms and signs with a known or unknown etiology, pathology and prognosis. However, what is considered normal or not normal depends on various factors, such as differing personal philosophies and the cultural and environmental context. For many years, homosexuality was classified as a disease caused by a pathological hormone status until this view was largely corrected. In contrast, osteoporosis was seen as a normal aging process, but since the World Health Organization (WHO) concluded in 1994 that osteoporosis was a pathological process, it is now considered a disease [28].

These concepts follow the traditional principles of the disease model, which is based on the manifestation of a defined and generally agreed-upon set of criteria for a pathological process, the clinical parameters, symptoms and diagnostic evidence. With the changing age groups of future patient populations, this disease model will have to be modified and further developed. Patients will suffer concurrently from more than one diagnosed chronic disease; and two or three different chronic diseases in one patient may act synergistically or additively on health impairments, which are associated with disability and frailty. As discussed by Fried et al. disability, frailty and comorbidity are distinct conditions, which significantly impact patients and drive healthcare costs. Disabilities are characterized by difficulty or dependency in carrying out essential activities of independent living, including activities that are important for a person's quality of life. Frailty is a physiological state of increased vulnerability to stressors as a result of decreasing physiological reserves and dysregulation of multiple physiologic systems [11]. Comorbidity, disability and frailty are highly interrelated and cause a significant health burden for the patient. Dealing with these conditions requires different interventions, of which the preventive and acute drug therapy is largely established for the comorbidities but not yet for conditions of disability and frailty associated with chronic diseases and the aging process. Developing effective drug therapies to treat such conditions would have a significant impact on both patient and society, as each condition is independently associated with healthcare needs and costs and with the risk for hospitalization [11].

During recent years, substantial work has been done by various physicians to create awareness of the fast growing issue of cachexia and sarcopenia as a result of the increasing age and multimorbidity of patient populations. Cachexia, an involuntary weight loss of more than 5 % in 12 months, is present in a number of infectious as well as chronic diseases such as cancer, heart or respiratory disease,

HIV and central nervous system (CNS) degenerative disorders, today affecting nine million people, with a prevalence of 1 % of the population in America, Europe and Japan [9]. For sarcopenia, which involves tissue loss, the prevalence today is estimated to be 5–13 % of people aged 60–70 years and 11–50 % for people 80 years and older [33]. The numbers of affected individuals in our society can be expected to further increase in the coming years, as the concerned patient population will continue to rise over the coming decades. Sarcopenia and cachexia are conditions of a rapid functional decline leading to a high risk of frailty and disability due to falls, hospitalization, institutionalization and a loss in quality of life [25]. While the number of patients affected is growing rapidly, pharmacological interventions for the prevention and treatment of cachexia and sarcopenia are still lacking [3, 26, 34]. One of the major reasons is a lack of general consensus on the clinical development and relevant end points to prove efficacy and earn acceptance by the regulatory authorities. Besides demonstrating the benefit for the patient, the new treatments would also need to prove their economic value and benefits to society and the payers [2]. Recognizing the clinical importance of sarcopenia and cachexia and the high impact of hospitalization and institutionalization (due to disabilities resulting from sarcopenia and cachexia) on healthcare costs, it becomes obvious that there is an urgent need for effective pharmacological interventions and therapies. Sarcopenia and cachexia are just some examples for new and evolving therapeutic areas in which research and development must be considered as an opportunity for the pharmaceutical industry.

The shift in the patient population towards older and multimorbid patients will continue to challenge the practice of treating a single disease and disease symptoms, independent from individual patient comorbidities, functional impairments and medical interventions. Introducing new clinical trial programs that go beyond the investigation of a single drug in a homogeneous patient population, and use heterogeneous but well-characterized patient populations with regard to disease profiles and progress, genetic information, risk factors and co-medications, could be used with the goal of identifying subpopulations with commonalities of such characteristics that benefit from a drug or a combination of drugs [1]. Taking into account the heterogeneity of the increasingly older and multimorbid patients, improvement of therapeutic outcomes in such patients will be essential for enhancing the efficiency of the healthcare system and balancing the increasing need for healthcare services. Developing new therapies in the clinical context of multimorbid patients and providing tailored products can significantly reduce the exponentially rising costs seen with the increasing numbers of chronic diseases. For example, studies found that in patients 65 years and older without a chronic disease, treatment costs were only US$211, but that this tag price increased to US$13,973 for a patient with four chronic diseases in 1999 [35]. Data from the Chronic Conditions Data Warehouse showed annual Medicare payments for a single chronic disease of US$ 7121, which increased exponentially, to US$14,931 for two and US $32,498 for three or more chronic conditions [27].

Beyond the Clinical Disease Focus

In developed economies, people value their health very highly and want to receive the best healthcare. Thanks to the significantly increased accessibility to healthcare information through the Internet and modern information technology (IT) technologies, people and patients are able to play a much more active role in their own healthcare, which includes prevention and therapy. Patients today are no longer automatically accepting the therapeutic decisions made by a physician; they want to be part of the decision in a variety of different ways. More highly educated patients are more likely to view therapeutic decisions as a shared responsibility and seek to verify the different options independently. Moreover, they consider their experience as being important to others, and use various ways of sharing these experiences [30].

According to The King's Fund [17], older adults have an increasing spending power that will rise from £76 billion in 2011 to £127 billion by 2030, representing a growth of 68 %. According to a recent study, 29 % of older adults take five or more prescription drugs with a steady prevalence increase by age. Sixty-eight percent of the older patients using prescription drugs also use at least one non-prescription product (over-the-counter [OTC] dietary or nutritional supplement), among which one in eight patients took five or more non-prescription products concomitantly [24]. This clearly shows that older patients are getting more involved in their health and healthcare decisions and are willing to invest in their health and well-being.

Considering that the future older patient generations will be very familiar with modern IT applications, e-health tools will increasingly be accepted by patients and implemented in future drug therapy. Monitoring adherence, clinical parameters and patients' daily quality of life through wearable diagnostic technology increases the potential to tailor treatment towards individualized therapeutic regimens and schedules. Especially for older adults living independently, having mobility limitations or living in a rural environment, e-health technologies offer a new way of receiving healthcare services and enable early preventive interventions, reducing the risk of preventable serious disease events and their consequences. This implies that pharmaceutical drug products will become part of an e-health solution, requiring additional features and integrated electronics to serve patient and healthcare provider needs.

This greater patient involvement in the therapeutic decision process will increasingly include the design of the drug product and its usability geared towards the patients themselves. The age- or disease-related context of a patient, especially in the case of multimorbidity and polypharmacy, will become a criterion for the prescription of a specific drug compound, and its dosage form and design. Reducing the complexity of the therapeutic schedule and simplifying the therapy alone can have a significant impact on patient adherence. For long-term prescribed cardiovascular drugs, the impact of complexity has been demonstrated in a recent study where higher non-adherence was correlated with a higher number of prescribed drugs, involving prescribers as well as pharmacies and less refill consolidation [6].

In addition, avoiding unnecessary manual operations with the dosage form, increasing product recognition and differentiability, and improving ease of administration will become important selection criteria for patients and prescribing physicians as they increase drug safety and effectiveness by reducing medication errors, inappropriate alteration and poor adherence. This also accounts for varying generic prescriptions, whereby a change in the appearance of the drug products determined by color, shape or both during the treatment with cardiovascular drugs [15] or antiepileptic drugs [16] has been shown to have a negative impact on patient adherence. Thus, developing simplified therapeutic schedules by modified-release or fixed-dose combination products and continuing the prescription long term is an important factor for long term adherence as patients can establish their individual implementation plan and contextual cues into their daily routine [19].

The provision of patient-centered drug products might include new ways of drug product manufacturing and dispensing. Developing small and flexible manufacturing units that can be installed and operated closer to the patient, coupled with secure direct hospital or home delivery services, can offer a new business model in healthcare provision to individual patient populations with special needs. Such small and flexible manufacturing units will also be required for the manufacturing and delivery of personalized medicines, where drugs and their doses are adapted to the special genetic disease patterns and pharmacogenetic profile of an individual patient.

Patients and caregivers will recognize the benefit of patient-centric drug products and will actively ask for these instead of accepting drug products that are difficult to handle or administer.

Conclusion

Since the beginning of the new century, the healthcare environment has undergone significant changes, which will continue and further evolve over the coming decades. The future patients and patient populations that will require effective drug therapy will be characterized by high to very high age as well as by multimorbidity. Such patients require patient-centric therapeutic solutions that will include patient-centric drug products, product design and simplified therapeutic schedules, as well as intensive communication and monitoring by healthcare professionals. The increasing personalization in drug therapy—based on the use of pharmacogenomics information, biomarkers and innovative diagnostic tools—will shift the therapy for the patient from a reactive and clinical parameter-focused treatment to a predictive, preventive and personalized therapy. The application of new portable or wearable monitoring devices applied within the patient's living environment will measure the clinical parameters, adherence performance and general behavioral aspects of the patient. These acquired data will provide predictions for eventual newly occurring healthcare issues that will allow new ways of managing the health of independently living people in the future. The next generation of patients will be able to take more responsibility for their health, moving healthcare further forward from the reactive, disease-focused model to a model

that is predictive, preventive, personalized and participatory [14]. Even though there are still some questions to resolve and research to be done, there is a common understanding that there is substantial value for the patient and the healthcare system that will drive its implementation [29].

These approaches will require collaboration between healthcare professionals and other stakeholders in the healthcare profession and might change the traditional way of developing, prescribing and delivering the drug therapies to patients. This will become especially true where the traditional processes lack effectiveness due to the increasing complexity of the patient's therapeutic plan and drug therapy; new approaches will help prevent poor therapeutic outcomes, hospitalization, disability or therapeutic failure. The acceptance of changes by healthcare professionals and payers in any healthcare system will depend on the evidence that such changes will increase efficiency in healthcare delivery and reduce the overall costs of the treatment, as well as increase the quality of life and well-being of the patients.

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Erratum to: European Medicines Agency (EMA): Regulatory Perspectives on Geriatric Medicines

Francesca Cerreta and David Bowen

Erratum to:
"European Medicines Agency (EMA): Regulatory Perspectives on Geriatric Medicines" in: S. Stegemann (ed.), *Developing Drug Products in an Aging Society*, 10.1007/978-3-319-43099-7_34

The name of the co-author, David Bowen, was missed in the chapter titled, European Medicines Agency (EMA): Regulatory Perspectives on Geriatric Medicines, and also in the Table of Contents and List of Contributors. The original chapter and the erratum book has been updated with the correction.

The updated original online version for this chapter can be found at 10.1007/978-3-319-43099-7_34

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S. Stegemann (ed.), *Developing Drug Products in an Aging Society*,
AAPS Advances in the Pharmaceutical Sciences Series 24,
DOI 10.1007/978-3-319-43099-7_38

Index

S. Stegemann (ed.), *Developing Drug Products in an Aging Society*,
AAPS Advances in the Pharmaceutical Sciences Series 24,
DOI 10.1007/978-3-319-43099-7