# Chapter e23: Geriatrics: Physiology of Aging

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## CHAPTER SUMMARY FROM THE PHARMACOTHERAPY HANDBOOK

For the Chapter in the Schwinghammer Handbook, please go to Appendix 2, Geriatric Assessment and Pharmacotherapy.

## KEY CONCEPTS

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1. The population of people 65 years and older is increasing.
2. Age-related changes in physiology affect the functions of various organ systems and contribute to the onset of diseases.
3. Age-related changes in physiology can affect the pharmacokinetics (PK) and pharmacodynamics (PD) of numerous medications.
4. Successful aging is determined by individually defined measures of well-being that include maximizing health-span and socio-environmental engagement.

## BEYOND THE BOOK

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Pair up with a classmate and brainstorm a list of age-related changes that occur in the human physiology and the effects they may have on pharmacokinetics (PK)/pharmacodynamics (PD) of medications in older adults.

Interview an older adult and obtain a medication history. Using their medication list, determine the effects that age-related changes in PK/PD will have on the medications and ensure they are appropriately dosed for older adults.

## INTRODUCTION

Medications can cure or palliate medical conditions in older adults; however, they can also cause a number of drug-related problems. Prevention of drug-related problems requires that health professionals be knowledgeable about the changes that occur with aging and the implications this has on prescribing, monitoring, and evaluating medication regimens in older adults. This chapter will focus on the epidemiology of aging, mechanisms of aging, physiologic changes due to aging with an emphasis on the age-related changes in pharmacokinetics (PK) and pharmacodynamics (PD) of medications, and successful aging to maximize healthspan and quality of life.

## EPIDEMIOLOGY OF AGING

1 The proportion of persons 65 years and older is increasing worldwide. In 2019, the worldwide number of people aged 65 years or older was 703

million, and this is projected to double to 1.5 billion by 2050.[1] In the United States, the population of older adults has changed from a pyramidal shape to a pillar.[2] The rectangular shape will be top heavy in 2050 because of the large numbers of births in the latter half of the 20th century. In 2018, 16% of the population was considered geriatric in the United States, and in 2050 it is projected to be 22% and 23.4% by 2060.[3] In 2034, the older adult population will outnumber children under 18 years old for the first time in US history.[2]

The population is aging due to people having fewer children and living longer. In the United States, the life expectancy in 2018 at birth is 76.2 years for men and 81.2 years for women.[4] At age 65 and 85 years old, respectively, men are projected to have 18.1 and 6 years of life remaining, compared to 20.7 and 7 years for women.[3] However, based on provisional data for the first half of 2020, US life expectancy has declined due to COVID-19 global pandemic.[5]

Older adults often have multiple chronic conditions and thus need to see a number of specialists and healthcare providers. In 2018, the three most frequently reported chronic health conditions in the United States for adults 65 and older were hypertension, arthritis, and heart disease.[3] Women have a higher prevalence of arthritis (54% vs 46%) and asthma (14% vs 9%), while men have higher rates of heart disease (35% vs 24%), cancer (27% vs 25%), and diabetes (25% vs 19%).[3] In 2018, the six leading causes of death among persons 65 years and older were: heart disease, cancer, chronic lower respiratory diseases, stroke, Alzheimer's disease, unintentional injuries, and influenza and pneumonia. Heart disease and cancer were the top two leading causes of death.[3] COVID-19 has had a significant impact on life expectancy and mortality during the global pandemic.[5]

Older adults have a high prevalence of chronic diseases, and this means they are using numerous medications on a long-term basis. This "polypharmacy" can lead to potential drug-related problems, such as drug-drug interactions.[6-8] To provide the best pharmacotherapy for this diverse and heterogeneous population of older adults, their health-care providers need to understand the mechanisms of physiologic changes that occur with aging and resulting pharmacokinetic and pharmacodynamic implications, especially with respect to the common chronic conditions and medications that are used to treat them.

## MECHANISMS OF AGING

Aging is associated with alterations in physiologic and homeostatic mechanisms. These alterations affect multiple organ systems and contribute to the presence of common chronic diseases.[9-14]

2 Aging affects the various organ systems in parallel and this contributes to the majority of older adults having multiple chronic conditions. The aging-associated physiologic and homeostatic alterations that contribute to the pathogenesis of chronic conditions also influence the responsiveness to medications. Therefore, older adults are more likely than younger adults to have medication-associated adverse events (eg, hypotension, hypoglycemia, constipation, delirium, bleeds, cognitive decline, urinary retention, functional decline, and falls).[15,16]

Historically, the exact mechanisms of aging that affect organ function have been difficult to identify. However, the powerful research tools of the current era are revealing some insights into the mechanisms of aging. Comprehensive translational studies have revealed that centenarians have lower chronic disease burdens, lower levels of systemic inflammation, lower frequencies of genetic variants that contribute to chronic disease burdens, and better epigenetic profiles when compared to noncentenarians.[17–23] Therefore, some are considering centenarians as models of healthy aging; other older adults with higher burdens of chronic diseases are being considered accelerated agers. The mechanisms of aging that are being clarified may contribute to the healthcare community's ability to optimize pharmacotherapy for older adults.

## HUMAN AGING AND CHANGES IN DRUG PHARMACOKINETICS AND PHARMACODYNAMICS

3 Many theories have been proposed to explain the human aging process. Clinical manifestations of aging include changes in the biochemical makeup of tissues, reduced capacity of body systems, reduced ability to adapt to physiologic stress, and increased vulnerability to disease.[24,25] Interindividual variability in physiology increases with age,[26] as individuals experience aging at different rates along with the development of disease processes and geriatric syndromes (see Chapter e25, "Geriatrics: Assessing Health and Delivering Health Care to Older Adults"). Table e23-1 reviews some common physiologic changes associated with aging, with an emphasis on those changes that can affect pharmacotherapy. For more detailed information, readers are referred to excellent reviews.[24,25]

TABLE e23-1

**Physiologic Changes with Aging**

| Organ System | Manifestation |
|---|---|
| Body composition | ↓ Total body water |
| | ↓ Lean body mass |
| | ↑ Body fat |
| | ↔ or ↓ Serum albumin |
| | ↑ $\alpha_1$-acid glycoprotein (↔ or ↑ by several disease states) |
| Cardiovascular | ↓ Cardiovascular response to stress |
| | ↓ Baroreceptor sensitivity leading to decreased exercise tolerance |
| | ↓ Cardiac output |
| | ↑ Systemic vascular resistance with loss of arterial elasticity and dysfunction of systems maintaining vascular tone |
| | ↑ Systolic blood pressure and increased risk of arrhythmias |
| | ↓ Compliance of the left ventricle increasing the risk of positional hypotension |
| Neurological | ↓ Size of the hippocampus and frontal and temporal lobes |
| | ↓ Number of receptors of all types and ↑ sensitivity of remaining receptors |
| | ↓ Short-term memory, coding and retrieval, and executive function |
| | Altered sleep patterns |
| | ↑ Blood-brain barrier permeability |
| Endocrine | ↓ Estrogen, testosterone, growth hormone, thyroid hormone, |
| | Altered insulin signaling |
| | Decreased basal metabolic rate |
| Gastrointestinal | ↓ Gastric motility |
| | ↓ Vitamin absorption by active transport mechanisms |
| | ↓ Splanchnic blood flow |
| | ↓ Small bowel surface area |

| | |
|---|---|
| Genitourinary | Atrophy of the vagina with decreased estrogen |
| | Prostatic hypertrophy with androgenic hormonal changes |
| | Detrusor hyperactivity and decreased bladder muscle tone may predispose to incontinence |
| Hepatic | ↓ Hepatic mass |
| | ↓ Hepatic blood flow |
| | ↓ Phase I (oxidation, reduction, hydrolysis) metabolism |
| Oral | Altered dentition |
| | ↓ Ability to taste salt, bitter, sweet, and sour |
| Respiratory | ↓ Respiratory muscle strength |
| | ↓ Chest wall compliance |
| | ↓ Arterial oxygenation and impaired carbon dioxide elimination |
| | ↓ Lung tissue elasticity |
| Renal | ↓ Glomerular filtration rate |
| | ↓ Renal blood flow |
| | ↓ Number of functioning neurons |
| | ↓ Tubular secretory function |
| | ↓ Renal mass |
| Sensory | Presbyopia (diminished ability to focus on near objects) |
| | ↓ Night vision |
| | Presbycusis (high-pitch, high-frequency hearing loss) |
| | ↓ Sensation of smell and taste |
| Musculoskeletal | ↓ Skeletal bone mass (osteopenia) |
| | ↓ Muscle mass |
| | Joint stiffening due to reduced water content in tendons, ligaments, and cartilage |
| | Altered gait and posture |
| Skin/hair | Thinning of stratum corneum |

| | |
|---|---|
| | ↓ Melanocytes |
| | ↓ Depth and extent of the subcutaneous fat layer |
| | Atrophy of sweat glands |
| | Thinning and graying of hair |

*Data from References 24,27.*

Age-associated physiologic changes may result in reduced functional reserve capacity (ie, ability to respond to physiologic challenges or stresses) and reduced ability to maintain homeostasis, thus making the older adult susceptible to decompensation in stressful situations.[24,25,27] Examples of homeostatic mechanisms that may become impaired include postural or gait stability, orthostatic blood pressure responses, thermoregulation, cognitive reserve, and bowel and bladder function. An event resulting in functional impairment may involve an insult for which the body cannot compensate, and relatively small stresses may result in major morbidity and mortality.[24,25,27]

The clinical response to a medication by an individual older adult is the net result of the interaction of a number of complex processes, including PK and PD. Age-related changes in physiology can affect drug PK and PD (see Table e23-1). Concurrent medications and polypharmacy, comorbidities, and frailty also play a role. When applying general knowledge of pharmacokinetic and pharmacodynamic alterations in the older adult to the care of an individual patient in the clinical setting, it is necessary to consider the patient's overall condition, life expectancy, disease states, and concurrent medications.[28]

## Altered Pharmacokinetics

Table e23-2 and the following discussion summarize what is known about the effect of aging on each of the four major facets of PK.[24,28,29] Of interest, when multivariate population pharmacokinetic analyses are conducted, chronologic age by itself seldom is a significant predictor of individual pharmacokinetic parameters (eg, clearance). Aging-associated changes in physiology, such as reduced renal function, are more important predictors of altered pharmacokinetics than is age, per se.

TABLE e23-2

**Age-Related Changes in Drug Pharmacokinetics**

| Pharmacokinetic Phase | Pharmacokinetic Parameters |
|---|---|
| Gastrointestinal absorption | Unchanged passive diffusion and no change in bioavailability for most drugs |
| | ↓ Active transport and ↓ bioavailability for some drugs |
| | ↓ First-pass metabolism, ↑ bioavailability for some drugs, and ↓ bioavailability for some prodrugs |
| Distribution | ↓ Volume of distribution and ↑ plasma concentration of water-soluble drugs |
| | ↑ Volume of distribution and ↑ terminal disposition half-life ($t_{½}$) for lipid-soluble drugs |
| Hepatic metabolism | ↓ Clearance and ↑ $t_{½}$ for some drugs with poor hepatic extraction (capacity-limited metabolism). Phase I metabolism is affected more than Phase II. |
| | ↓ Clearance and ↑ $t_{½}$ for drugs with high hepatic extraction ratios (flow-limited metabolism) |
| Renal excretion | ↓ Clearance and ↑ $t_{½}$ for renally eliminated drugs and active metabolites |

*Data from References 24, 29, and 30.*

## Absorption

Most drugs are taken orally; thus, age-related changes in gastrointestinal physiology could affect the absorption of medications. Drug-food interactions, concurrent medication use, and comorbidities affecting gastrointestinal function must also be considered, and frailty may be a better indicator than chronologic age for potential alterations in drug absorption.[31]

Most drugs are absorbed via passive diffusion, and age-related physiologic changes appear to have little influence on drug bioavailability.[24] Nutrients absorbed by active transport, such as vitamin $B_{12}$, iron, calcium, magnesium and leucine, may have impaired absorption in older adults.[24]

There is evidence for a decreased first-pass effect on hepatic and/or gut wall metabolism that results in increased bioavailability and higher plasma concentrations of drugs such as verapamil and labetalol and reduced bioavailability of some prodrugs such as enalapril and codeine, although the clinical significance of these differences is unclear.[24,31]

Drugs that require an acidic environment for absorption may have reduced extent of absorption in a relatively small proportion of older adults with increased gastric pH due to atrophic gastritis or in those taking proton pump inhibitors and other medications that increase gastric pH.[24,31] The effects of aging on modified-release orally administered dosage forms are not known, although changes in gastrointestinal motility, pH, or gut microbiota due to age, concurrent medications, or comorbidities might affect absorption from some dosage forms in some patients.[31]

## Distribution

The distribution of medications in the body depends on factors such as blood flow, plasma protein binding, and body composition, each of which may be altered with age. For example, the volume of distribution of water-soluble drugs is decreased, whereas lipophilic drugs exhibit an increased volume

of distribution.[29] Changes in the volume of distribution can have a direct impact on the amount of medication that must be given as a loading dose.

Older adults may also exhibit differences in the distribution of drugs to their sites of action. Tissue perfusion may decrease with aging, slowing the distribution to less highly perfused tissues such as muscle and fat.[32] Small changes in protein binding (decreased albumin and increased $\alpha_1$-acid glycoprotein) have been documented with aging,[29] but these changes do not generally have a significant effect on drug distribution except for drugs that are highly extracted by the liver, extensively protein bound, or administered intravenously.[24]

Blood-brain barrier permeability may also be altered in older adults, affecting distribution of drugs into the central nervous system. A number of transporters are expressed at the blood-brain barrier endothelium, and dysfunction or reduced expression of transporters can result in greater exposure of the brain to drugs and toxins.[24,33]

## Metabolism

The liver is the major organ responsible for drug metabolism, including phase I (oxidative) and phase II (conjugative) reactions. Variations in drug metabolism and consequently drug clearance are a major source of variability in the response to medications in older adults. Hepatic metabolism of drugs depends on liver perfusion, capacity and activity of drug metabolizing enzymes, transfer of drug into the hepatocyte from the blood, and protein binding, all of which may be altered by the aging process.[24] For drugs with high intrinsic clearance (high hepatic extraction ratio) and rapid hepatic metabolism, drug clearance depends on hepatic blood flow (flow-limited metabolism). For drugs with low intrinsic clearance (low hepatic extraction ratio) and slow hepatic metabolism, drug clearance depends on hepatic enzyme activity (capacity-limited metabolism).

Age-related decreases in hepatic blood flow can significantly lower the metabolism of high extraction ratio drugs that undergo flow-limited metabolism. Hepatic blood flow may decline from 40% to 60%, and hepatic clearance of high extraction ratio drugs such as amitriptyline, fentanyl, metoprolol, and morphine may be reduced.[24] The dose of drugs with flow-limited metabolism should be reduced by 50% in older adults according to current recommendations.[24]

Interpreting the effect of age on the metabolism of drugs that undergo capacity-limited metabolism is more complex. Hepatic clearance of capacity-limited drugs depends on the fraction unbound in blood and intrinsic hepatic clearance. Most but not all studies have reported reduced liver size and enzyme content in older adults.[24] Reduced hepatic clearance is thought to be due to reduced liver mass, blood flow, drug transfer, and oxygen supply rather than to reduced function or expression of CYP450 enzymes.[24] Phenotyping may be of more value than genotyping in identifying risk for adverse drug events, and factors such as inflammation, circadian rhythm, epigenetics, and the gut microbiome may play a role in altered drug metabolism in older adults.[34]

Most research on hepatic drug metabolism and aging has focused on age differences in phase I drug metabolism pathways. Generally, phase II metabolic pathways are preserved in healthy older people.[29] Frail older adults, however, experience reduced phase II metabolism. Frailty is a risk factor for declining health status and disability. Although frailty has proven difficult to define, it is characterized by reduced lean body mass, muscle loss, malnourishment, reduced function, and reduced endurance.[35] Frailty is associated with inflammation, which may down regulate drug metabolism and transport.[29]

## Elimination

Renal excretion is the primary route of elimination for many drugs and metabolites. Age-related reductions in glomerular filtration are well documented.[35] Changes in kidney function with age may be more associated with hypertension and heart disease than with aging itself, and therefore age alone may not have as great impact on renal excretion of drugs as previously thought.[24]

The estimation of creatinine clearance, although not entirely accurate in individual patients, can serve as a useful screening approximation for the purpose of dosage adjustments. Reduced muscle mass in older adults can result in serum creatinine concentrations within a normal range even though renal function is reduced,[24] so it is essential to estimate creatinine clearance rather than relying on serum creatinine concentrations. Important to remember is that older adults can have reduced muscle mass without low body weights; sarcopenic obesity is a condition in which increased fat stores—which have become common in older adults in recent decades—mask decreased muscle mass and result in the functional disabilities of frailty

or sarcopenia (see Chapter e25, "Geriatrics: Assessing Health and Delivering Healthcare in Older Adults"). Cockcroft and Gault[36] created one of the most commonly used equations for adults with stable renal function whose actual weight is within 30% of ideal body weight:

$$\text{Creatinine clearance} = \frac{(140 - \text{Age})(\text{Actual body weight})}{72(\text{Serum creatinine concentration})}$$

where age is given in years, actual body weight in kilograms, and serum creatinine concentration in milligrams per deciliter. The resulting creatinine clearance is in units of mL/min. For women, multiply this result by 0.85.

When serum creatinine is expressed in μmol/L, creatinine clearance in units of mL/min can be calculated by the following equation:

$$\text{Creatinine clearance} = \frac{(140 - \text{Age})(\text{Actual body weight})}{0.814(\text{Serum creatinine concentration})}$$

The Modified Diet in Renal Disease[37] equation and the Chronic Kidney Disease Epidemiology Collaboration[38] equation have become more widely used for estimation of glomerular filtration rate (GFR). The validity of each of these equations for use in estimating GFR in older adults has been advocated and challenged.[39,40] However, dosing guidelines for medications that primarily are renally cleared are often still based on estimated creatinine clearance determined using the Cockcroft and Gault equation, and the current consensus is to continue to use the Cockcroft and Gault equation for renal drug dosing in older adults. New methods based on serum creatinine and cystatin C continue to be developed, so this recommendation may change in the future.[39]

Consensus guidelines for oral dosing of primarily renally cleared drugs in older adults have been developed.[41] Medications to avoid in older adults with creatinine clearance less than 25 to 30 mL/min (0.42-0.5 mL/s) include amiloride, apixaban, dabigatran, duloxetine, fondaparinux, probenecid, rivaroxaban, spironolactone, extended-release tramadol, and triamterene. Medications with recommended dosage adjustments for reduced renal function in older adults include cimetidine, ciprofloxacin, colchicine, dofetilide, edoxaban, enoxaparin, famotidine, gabapentin, levetiracetam, nizatidine, pregabalin, ranitidine, immediate-release tramadol, and trimethoprim-sulfamethoxazole. In making dosing decisions for older adults, it is important to consider guidelines for dosing in renal impairment for drugs with significant renal elimination along with age-related dosing recommendations.

## Altered Pharmacodynamics

Age-related changes in PK are well characterized compared to changes in PD. There is a general trend of altered drug response or increased "sensitivity" in older adults. Possible mechanisms that have been proposed include (a) changes in concentrations of the drug at the receptor, (b) changes in receptor numbers, (c) changes in receptor affinity, (d) postreceptor alterations, and (e) age-related impairment of homeostatic mechanisms.[42,43]

Understanding the effects of age on PD has proven to be complex. Differences in PD with age may be due to altered sensitivity (greater change in effect for a given change in drug concentration) but may also be due to differences between younger and older adults in baseline performance or concentrations of drug at the site of action.[42] Most studies of pharmacodynamic differences with age have focused on drugs acting on the central nervous system and cardiovascular system.

Older adults are particularly sensitive to the central nervous system effects of drugs. Changes in brain size and weight as well as changes in neurotransmitter systems have been reported with advancing age. In addition, drugs may penetrate the central nervous system more easily.[42] For example, there are multiple changes to the dopaminergic system with age, including decreased levels of the dopamine transporter, decreased number of dopaminergic neurons, and decreased density of several types of dopamine receptors. These changes are consistent with the increased sensitivity of older adults to the adverse drug effects of antipsychotics.[44] Increased sensitivity to the central nervous system effects of medications in older adults has been demonstrated for benzodiazepines, anesthetic agents, opioid analgesics, antipsychotics, lithium, and anticholinergic medications.[42,43]

Aging is associated with numerous changes in the structure and function of the cardiovascular system that can predispose the older adult to altered pharmacodynamic response to drugs acting on the cardiovascular system. Older adults are more likely to experience orthostatic hypotension as an adverse drug event.[43] Age-related changes in PD have been reported for calcium channel blockers (increased hypotensive and bradycardic effects),

beta blockers (reduced blood pressure response), diuretics (reduced effectiveness), and warfarin (increased risk of bleeding), but not with angiotensin converting enzyme inhibitors or angiotensin receptor blockers.[42,43]

## SUCCESSFUL AGING

"Successful", "positive," or "active" aging refers to the promotion of physical and mental vitality in later life. Rowe and Kahn[44,45] coined the term *successful aging* and define it as the avoidance of disease and disability, maintaining a high level of mental and physical function and having active engagement with life. Although successful aging encourages health promotion and disease prevention, it may also inadvertently perpetuate ageism by defining success as the responsibility of individual action alone.

There has been much debate and little consensus on a standard definition of what comprises successful aging. Historically, the concept has been studied using either a biomedical or a psychosocial focus. However, simply using a biomedical approach ignores the eventuality of developing disease and decline that lead to mortality and inhibits research and public policy on maintaining personhood while experiencing physical disability. Conversely, simply using a psychosocial approach may provide misleading indicators that do not account for plasticity of the brain and subjective reporting of the personalized factors that constitute success for each individual.[45,46]

For these reasons, we focused our discussion of successful aging using both the perspectives of individual behavior and socio-environmental factors.

### Compression of Morbidity, Healthspan, and Optimal Longevity

In recent decades, vast improvements in preventive medicine have altered the landscape of biological aging and longevity. Not only has society experienced an unprecedented increase in longevity, the greater number of years lived is being accompanied by a longer period of activity and health and a postponement of morbidity. Known as "compression of morbidity,"[47] limiting morbidity to a shorter period closer to the natural end of life has become the dominant paradigm for healthy aging, at both individual and policy levels.

The term *healthspan* has emerged to refer to the period of life free of major chronic clinical diseases and disability.[48] Healthspan is a fluid concept that represents dynamic changes in health, the contributions of behavior, lifestyle, and policy that impact health and the role of adjustment and adaptation to changes in health.[49] Taken together, the concepts of compression of morbidity and healthspan have spawned discussion of "optimal longevity" as the general goal of living long and well.[50]

The goal of optimal longevity demands an interactive approach that examines healthy aging behaviors from biopsychosocial perspectives. From a biological standpoint, the field of physiological geroscience has emerged in an effort to increase healthspan by slowing the fundamental biological processes of aging such as inflammation, oxidative stress, mitochondrial dysfunction, impaired proteostasis, and reduced stress resistance.[51]

Of equal importance, optimal longevity is influenced by psychological and social factors that determine how people adjust to aging and whether the individual feels valued societally. Ageism—discrimination based on age—represents a widespread public health crisis, with proven damaging impacts on health and well-being. Negative attitudes about one's own aging have been correlated with adverse health outcomes, including a 7.5-year decline in longevity,[52] increased risk for chronic disease,[53] perceived ill health,[54] and reduced recovery from illness.[55] Thus, it is imperative that an integrative framework is used to educate and advocate for optimal longevity that addresses aging from biopsychosocial perspectives that incorporate healthy behaviors for both the individual and for the community as a whole.

### Primary and Secondary Strategies for Maximizing Physiological Function

Lifestyle, behavioral, and pharmacologic interventions are currently the foremost strategies for enhancing physiological functions during aging. Prevention strategies delay, reduce in magnitude, and/or prevent decline in function, thereby minimizing decreases in functional status and increasing health span. Primary prevention strategies are generally health behaviors that are applied over the course of the lifespan, while secondary prevention strategies are measures that are adopted into a lifestyle approach to maximize health once some degree of physiological dysfunction has occurred in midlife or later.[51] Primary and secondary prevention strategies both include increasing or maintaining physical activity, establishing or maintaining healthy diet and lifestyle behaviors (eg, not smoking, moderate alcohol consumption), and social engagement.

## Lifestyle—Physical Activity and Nutrition

Expected changes during biological aging include a loss of muscle mass and strength (sarcopenia), structural and functional changes to skeletal muscle, and neurological and vascular changes that may compromise muscle function. Remarkably, physical activity and exercise are well-established prevention strategies that have demonstrated positive impact on declines in muscle metabolism and function.[56] Further, engaging in physical activity can be the most effective intervention to prevent and in some cases treat chronic diseases that represent the leading causes of morbidity and mortality, such as diabetes mellitus, cardiovascular disease, and cancer.

Two studies examining cardiomyopathy—hypertrophy and fibrosis of the myocardium that causes heart failure—found that exercise was among the most effective interventions for preventing cardiomyopathy.[57,58] Mechanisms included improvement in inflammatory and metabolic profiles as well as exercise-induced changes intrinsic to cardiac tissue.[57] Exercise training can be a countermeasure to impaired immune function secondary to chronic disease, obesity, or advancing age. In general, physical exercise in the form of recreational, occupational, or structured activity is the lifestyle strategy for which there is strongest overall evidence of function-preserving effects, and the highest temporal association with successful aging for those with and without chronic conditions.[59]

Findings from weight loss intervention studies that have included older adults have demonstrated improvements in vascular function, glucose–insulin regulation, endothelial function, and cognition.[60,61] Studies have also observed preserved cardiac diastolic, vascular, autonomic nervous system, and glucose–insulin function, and lower markers of inflammation among older adults on calorically restricted diet,[62] and reduced functional decline among older adults who are restricting their protein and using intermittent fasting (fasting for periods during the week or day).[63] There is an abundance of support or the impact of diet composition on changes in physiological function with aging; specifically evidence that promotes diets high in vegetables, fruits, whole grains, nuts, fish, and “healthy” oils and fats.[62,64] Consumption of this type of diet composition is associated with improved maintenance of motor, vascular, cognitive, and immune function.[64] Consumption of several constituents of these broader dietary patterns including fish, vegetables, olive oils, berries, spinach, grape products and other polyphenols, nuts (walnuts), coffee, green tea, and lower-fat dairy products has been positively associated with increased physiological function during aging.[64]

## Socio-environmental Factors and Successful Aging

The importance of social factors on the capacity of individuals to age “successfully’ cannot be overstated. These include risk factors due to lifelong and systemic discrimination based on personal characteristics such as race, ethnicity, gender, sexual orientation, gender identity, and socioeconomic status; interpersonal characteristics such as family structure and living arrangement; and environmental characteristics in neighborhoods, such as access to healthy foods (eg, grocery stores) and healthcare, transportation options, housing, and urban design. A compelling body of evidence has described the powerful role of social factors in shaping health across a wide range of health indicators, populations, and settings.[65]

Formally known as social determinants of health (SDOH; see also Chapter e3, “Social Determinants of Health and Cultural Competency”), these factors have a profound influence in shaping social policy and individual impacts on health. SDOH describe how institutional factors such as income, social support, and access to education influence health and overall well-being. Successful aging and maximizing health span are directly related to the environmental factors and social factors that constitute social determinants of health. The neighborhood or “built” environment encompasses a variety of factors including safety (eg, crime, street lighting, traffic), housing quality (exposure to lead, pollution, allergens), aesthetics (eg, litter, availability of walking paths), accessibility, and amenities. Therefore, a macrolevel approach is necessary in which the view of successful aging is expanded to include contextual influences such as culture, historical time, social structure, institutional forces, and social-relational influences on health and development.[66]

A macrolevel approach is also necessary to take the necessary steps to move the conversation forward about “successful aging” as the sole responsibility of individual choice and behavior to identifying best practices for policy at community levels. The American Geriatrics Society emphasizes the importance of integration of both the health care entities and communities to promote “healthy aging.” Involvement of pharmacists and other health professionals is essential to pursuing these collaborations in the areas of advocacy, education, clinical, and research.[67] Particular attention to cultural differences in both definitions of successful aging and on environmental inequities that may support or prevent successful aging in needed.[66]

## ABBREVIATIONS

| | |
|---|---|
| PK | pharmacokinetics |
| PD | pharmacodynamics |
| NHIS | National Health Interview Survey |
| $t_{½}$ | half-life |
| pH | potential of Hydrogen |
| GFR | glomerular filtration rate |
| mL | milliliter |
| min | minute |
| s | second |
| µmol | micromolar |
| L | liter |
| SDOH | social determinants of health |

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## SELF-ASSESSMENT QUESTIONS

1. As a result of the physiologic and homeostatic alterations associated with the process of aging, older adults are more likely than younger adults to
   A. Experience adverse effects of medications
   B. Have fewer chronic disease states
   C. Be prescribed fewer medications due to pharmacokinetic changes
   D. Have decrease responsiveness to pharmacotherapy
2. Which one of the following is a physiologic change with aging?
   A. Increased total body water
   B. Decreased lean body mass
   C. Decreased body fat
   D. Increased serum albumin
3. Which of the following age-related changes contributes to alterations in absorption in older adults?
   A. Increased first pass effect
   B. Increased active transport
   C. Increased gastrointestinal pH
   D. Increased passive diffusion
4. When looking at the distribution of medications in older adults it is important to consider the _____ of the agent.
   A. Acidity
   B. Lipophilicity

C. Bioavailability

D. High extraction ratio

5. Which of the following agents would be expected to have reduced hepatic clearance in older adults?

A. Lisinopril

B. Oxazepam

C. Digoxin

D. Metoprolol

6. Which of the following should be used for renal drug dosing in older adults?

A. The Modified Diet in Renal Disease equation

B. Bedside Schwarz Equation

C. Cockcroft and Gault equation

D. Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI)

7. Which one of following agents has *not* shown increased central nervous system effects in older adults?

A. Benzodiazepines

B. Opioid analgesics

C. Angiotensin converting enzyme inhibitors (ACE inhibitors)

D. Antipsychotics

8. The avoidance of disease and disability, maintaining a high level of mental and physical function and having active engagement with life is referred to as

A. Desired aging

B. Successful aging

C. Delayed aging

D. Ideal aging

9. All of the following are expected to change during biological aging *except*:

A. Skeletal muscle

B. Neurological function

C. Endocrine system

D. Vascular system

10. _____ describe how institutional factors such as race, income, social support, and education influence physical health and overall well-being.

A. Social determinants of health

B. Lifestyle factors

C. Personal characteristics

D. Genetics

11. Women aged 65 years or older have a higher prevalence of which of the following conditions compared with men?

A. Heart disease

B. Arthritis

C. Cancer

D. Diabetes

## SELF-ASSESSMENT QUESTION-ANSWERS

1. **A.** Older adults are more likely than younger adults to suffer from medication associated adverse events including: hypotension, hypoglycemia, constipation, delirium, bleeds, cognitive decline, urinary retention, functional decline, and falls. This is related to the physiologic and homeostatic alterations that are associated with aging.

2. **B.** The body composition of an older adult includes a decrease in total body water, a decrease in lean body mass, an increase in body fat, and a decrease or no change in serum albumin. These are important to recognize as they affect the pharmacokinetics of medications in the older adult.

3. **C.** Contributing factors to age-related changes in gastrointestinal absorption include decrease in active transport, decrease in first pass metabolism, and an increase in gastric pH. This will impact the drugs bioavailability of some agents in older adults.

4. **B.** Distribution of medications depends on blood flow, plasma protein binding, and body composition. Therefore in older adults lipophilic drugs have an increased volume of distribution, which will impact dosing in this population.

5. **D.** Throughout the aging process alterations in hepatic metabolism occur. One example of this is a decrease in hepatic blood flow. Metoprolol, a high extraction ratio drug is greatly affected by this decline in hepatic blood flow. The clearance of metoprolol is reduced from ~34% to 50% or more in older adults.

6. **C.** The Modified Diet in Renal Disease equation and the Chronic Kidney Disease Epidemiology Collaboration equation have been used to estimate GFR in older adult. However, the Cockcroft and Gault equation is currently the preferred equation to provide renal dose adjustment in older adults.

7. **C.** Angiotensin converting enzyme inhibitors do not affect the central nervous system. In older adults drugs may penetrate the central nervous system more readily and an increased sensitivity may result. Agents that have demonstrated increased central nervous system effects in older adults include: benzodiazepines, anesthetic agents, opioid analgesics, antipsychotics, lithium, and anticholinergic medications.

8. **B.** Successful aging is defined as the avoidance of disease and disability, maintaining a high level of mental and physical function and having active engagement with life. Additionally terminology includes successful, positive, or active aging.

9. **C.** Loss of muscle mass and strength are expected changes during biological aging. As a result structural and functional changes to skeletal muscle as well as neurological and vascular changes can compromise the ability of the muscle to function.

10. **A.** Social determinants of health (SDH) describe how institutional factors such as race, income, social support, and education influence physical health and overall well-being.

11. **B.** Women have a higher prevalence of arthritis and asthma, while men have higher rates of heart disease, cancer, and diabetes.