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AGE-RELATED CHANGES IN DRUG ABSORPTION, DISTRIBUTION AND RESPONSE: IMPLICATIONS FOR GERIATRIC PHARMACOTHERAPY

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ABSTRACT

Aging is accompanied by physiological transformations that impact various organ systems, leading to significant alterations in drug pharmacokinetics and pharmacodynamics. Additionally, functional changes such as diminished vision, hearing, swallowing ability, motor skills, and cognitive function can interfere with proper medication adherence and administration. As a result, older adults, particularly those over the age of 75, are among the highest consumers of both prescription and over-the-counter medications, often managing multiple drug regimens simultaneously. Despite an understanding of age-related physiological changes, including shifts in body composition, declining renal function, and altered cardiovascular responses, there remains a gap in evidence-based strategies for optimizing medication prescribing in the elderly. This review highlights the clinically significant changes in drug metabolism and response in aging individuals, examines the impact on commonly prescribed medications, and explores potential adjustments in drug dosing to enhance therapeutic efficacy while minimizing adverse effects. Furthermore, recommendations are provided on how aging-related factors can be incorporated into drug development, regulatory approval processes, and prescribing guidelines to improve pharmacological care for older adults.

KEYWORDS: Aging, Body Composition, Renal Function, Pharmacokinetics, Pharmacodynamics, Geriatric Pharmacotherapy.

INTRODUCTION

Aging is a complex, multifaceted process that involves a gradual decline in physiological function and an increasing inability to maintain homeostasis under stress. It is characterized by progressive biological changes occurring at molecular, cellular, and systemic levels, which cumulatively affect an individual's ability to adapt to external and internal challenges. While the average human life expectancy has risen to approximately 85 years, with a maximum lifespan recorded at around 122 years, the aging process remains highly variable among individuals.[1,2]

Aging is not a singular, uniform process but rather the result of cumulative effects on multiple physiological systems. It is primarily associated with the gradual loss of functional units within organs, such as nephrons in the kidneys, alveoli in the lungs, and neurons in the brain.[3,4] This progressive decline in organ function reduces the body's ability to respond efficiently to physiological stressors, increasing vulnerability to disease and functional impairments.[5,6]

One of the hallmarks of aging is the dysregulation of intercellular and systemic signaling pathways that maintain homeostasis.[7,8] Disruptions in these pathways can impair adaptive responses to medications, altering both pharmacokinetics (drug absorption, distribution, metabolism, and excretion) and pharmacodynamics (the drug's effect on its target).[9,10] These physiological modifications contribute to increased drug sensitivity, a higher risk of adverse drug reactions, and the need for careful dose adjustments in elderly patients.[11,12]

In addition to functional decline, aging also involves anatomical changes that influence drug response. These include a reduction in total body water, an increase in body fat, and decreased hepatic and renal clearance, all of which affect drug metabolism and excretion.[13,14] Furthermore, cognitive decline, impaired vision and

hearing, and diminished motor coordination can impact medication adherence, making polypharmacy a significant concern in the elderly population.[15,16]

Given the rising proportion of older adults in the global population, understanding age-related changes in drug response is crucial for optimizing geriatric pharmacotherapy. This review provides an in-depth analysis of the physiological and biochemical alterations associated with aging and their impact on pharmacokinetics and pharmacodynamics. Additionally, it explores strategies for improving medication management in elderly individuals, ensuring both efficacy and safety in drug therapy.

Pharmacokinetic and Pharmacodynamic Changes in Aging

Variability in Drug Response

One of the most pronounced pharmacologic changes with aging is an increase in interindividual variability in drug response. This is attributed to a range of physiological alterations, including decreased hepatic and renal function, changes in body composition, and alterations in receptor sensitivity. These changes collectively impact drug absorption, distribution, metabolism, and excretion, leading to a need for individualized drug dosing in older adults.

Changes in Drug Metabolism and Clearance

Age-related reductions in hepatic mass, hepatic blood flow, and renal function significantly impact drug clearance. Many drugs and their metabolites rely on hepatic metabolism and renal excretion, which become less efficient with age. These alterations can result in prolonged drug half-life, increased drug accumulation, and a higher risk of adverse drug reactions.

Changes in Receptor Sensitivity

While pharmacokinetic changes in aging are well-documented, pharmacodynamic changes are less well understood. However, studies have shown that aging is associated with modifications in drug receptor sensitivity and physiological reserve. For example, cardiovascular and central nervous system receptors exhibit age-related changes that alter drug response:

- Cardiovascular System: A reduction in β-adrenergic receptor responsiveness in older adults results in diminished cardiac response to β-agonists, which can affect the management of conditions such as hypertension and heart failure.
- Central Nervous System (CNS): Aging is associated with a decline in dopaminergic neurons and dopamine D2 receptor density, contributing to an increased risk of extrapyramidal side effects from neuroleptic drugs. Additionally, opioid receptors undergo modifications, leading to heightened sensitivity to narcotic and anesthetic agents.

Organ-Specific Changes and Their Impact on Drug Therapy

Liver Function and Drug Metabolism

Aging is associated with structural and functional changes in the liver, which play a crucial role in drug metabolism:

- Reduction in Liver Size: Studies indicate that liver size decreases by 25-35% with age, which has been observed across various species, including humans.
- Decline in Hepatic Blood Flow: Liver blood flow decreases by approximately 40%, potentially due to structural changes in the liver sinusoidal endothelial cells, including pseudo capillarization and leukocyte accumulation.
- Alterations in Drug Metabolism: While phase I metabolism (oxidation, reduction, hydrolysis) is significantly reduced, phase II metabolism (conjugation reactions) is generally preserved. This decline in phase I metabolism affects the clearance of drugs such as benzodiazepines, leading to prolonged drug action in older adults.

Body Composition and Drug Distribution

Aging leads to marked changes in body composition, which can influence drug pharmacokinetics:

- Decrease in Lean Body Mass: By the age of 65-70, men lose an average of 12 kg of lean body mass, while women lose approximately 5 kg.
- Increase in Fat Mass: Older adults experience a relative increase in fat mass, which can affect the volume of distribution of lipophilic drugs (e.g., benzodiazepines, diazepam), leading to prolonged drug effects.
- Changes in Water Content: Extracellular fluid volume increases while intracellular water content declines, which can influence the distribution and elimination of hydrophilic drugs (e.g., aminoglycosides).

Renal Function and Drug Excretion

Renal function declines progressively with age, affecting the clearance of drugs excreted primarily by the kidneys:

- Decrease in Glomerular Filtration Rate (GFR): Cross-sectional and longitudinal studies suggest that renal function declines with age, though interindividual variability is high.
- Impact on Drug Clearance: Medications such as aminoglycosides, digoxin, and lithium require dose adjustments in older adults due to reduced renal clearance.
- Variability in Renal Function: Studies from the Baltimore Longitudinal Study on Aging have categorized older adults into different renal aging patterns, suggesting that some individuals maintain stable renal function while others experience significant declines.

Cardiovascular Function and Hemodynamic Changes

Aging is associated with multiple changes in cardiovascular physiology that influence drug response:

- Reduced Baroreceptor Sensitivity: Older adults exhibit impaired autonomic control of blood pressure, increasing the risk of orthostatic hypotension. This can impact the use of antihypertensive medications and diuretics.
- Altered Myocardial Function: Cardiac output declines with age, and there is increased arterial stiffness, leading to higher systolic blood pressure and increased left ventricular afterload. These changes affect the pharmacodynamics of cardiovascular drugs such as β-blockers and calcium channel blockers.
- Increased Susceptibility to Hypotension: A greater incidence of postural hypotension (a drop in systolic blood pressure >20 mmHg upon standing) is observed in older adults, particularly when using antihypertensive drugs.

Implications for Drug Therapy in Older Adults

Given the physiological changes that occur with aging, several strategies should be considered for optimizing drug therapy in older adults:

1. Dose Adjustment: Individualized dosing based on renal and hepatic function is critical to minimize drug accumulation and toxicity.
2. Drug Selection: Preference should be given to drugs with a lower risk of adverse effects in older adults. For example, short-acting benzodiazepines are preferred over long-acting ones to minimize sedation and fall risk.
3. Monitoring and Deprescribing: Regular medication reviews should be conducted to identify potentially inappropriate medications and deprescribe when necessary.
4. Avoiding Polypharmacy: Since older adults often take multiple medications, efforts should be made to simplify regimens and avoid unnecessary drug interactions.
5. Consideration of Non-Pharmacologic Approaches: Lifestyle modifications, physical therapy, and behavioral interventions should be prioritized whenever possible to reduce reliance on medications.

Impact of Altered Human Organ Functions on Pharmacokinetics

Aging and age-related diseases can significantly influence the absorption, distribution, metabolism, and excretion of drugs. These changes affect how medications are processed in the body, making it crucial to adjust drug therapy for older individuals accordingly.

Drug Absorption in Aging

Mechanisms of Drug Absorption

Absorption refers to the movement of a drug from the site of administration into the bloodstream. For oral and some rectal medications, this process primarily occurs in the small intestine. Other routes of absorption include the skin, muscle, subcutaneous tissues, and lungs.

Changes in Absorption Due to Aging

As individuals age, several physiological changes occur in the gastrointestinal (GI) tract that may impact drug absorption, including:

- Reduced intestinal blood flow
- Decreased production of gastric acid
- Slower gut motility and delayed gastric emptying due to reduced neural control

However, studies have shown conflicting results regarding the clinical significance of these changes. In most cases, drug absorption is not significantly impaired by aging.

Absorption via Different Routes

- **Subcutaneous and Intramuscular Absorption:** Reduced tissue blood perfusion may slow the absorption rate, while decreased muscle mass can enhance the absorption of depot medications.
- **Pulmonary Absorption:** Decreased lung compliance, ventilation-perfusion mismatching, and reduced alveolar surface area may lead to impaired absorption of inhaled drugs.

First-Pass Metabolism and Drug Bioavailability

Definition and Mechanism

First-pass metabolism refers to the metabolic breakdown of a drug before it reaches systemic circulation. This primarily occurs in the liver, where the cytochrome P450 enzyme CYP3A4 plays a key role. Some drugs also undergo first-pass metabolism in the gut.

Age-Related Changes in First-Pass Metabolism

With aging, first-pass metabolism decreases due to factors such as:

- Reduced liver mass and hepatic blood flow
- Declining activity of metabolizing enzymes (e.g., CYP enzymes, flavin monooxygenases, and UDP-glucuronosyl transferases)

As a result, drugs that undergo extensive first-pass metabolism (e.g., opioids, metoclopramide) may have increased bioavailability, requiring lower starting doses.

Impact on Prodrugs

Some medications, such as angiotensin-converting enzyme (ACE) inhibitors (e.g., enalapril, perindopril), require first-pass metabolism to become active. Reduced first-pass metabolism may lead to lower systemic concentrations of these active drug forms. However, this effect is generally not clinically significant for drugs with a broad therapeutic index.

Drug Distribution in the Aging Body

Volume of Distribution

The volume of distribution (Vd) refers to the ratio of the total amount of drug in the body to its plasma concentration. Several patient- and drug-related factors influence Vd, including:

- Drug solubility (lipophilic vs. hydrophilic)

- Protein and tissue binding properties
- Changes in body composition with aging

Changes in Body Composition
Aging alters drug distribution due to:
- **Reduced Total Body Water:** Hydrophilic drugs (e.g., gentamicin, digoxin, lithium, theophylline) distribute into a smaller volume, leading to higher plasma concentrations and necessitating lower doses.
- **Increased Body Fat:** Lipophilic drugs (e.g., benzodiazepines, morphine, amiodarone) accumulate in fat stores, prolonging their elimination half-life and effects.

Clinical Implications
Drugs with an increased volume of distribution (e.g., diazepam, thiopental, lidocaine) may have prolonged effects even after discontinuation, raising the risk of drug accumulation and toxicity in older adults.

Drug Metabolism and Aging
Role of the Liver in Drug Metabolism
The liver is the primary organ responsible for metabolizing drugs, converting lipid-soluble compounds into more water-soluble forms for elimination. Metabolism occurs in two phases:
- **Phase I (Oxidation, Reduction, Hydrolysis):** Primarily mediated by cytochrome P450 enzymes (e.g., CYP3A4)
- **Phase II (Conjugation Reactions):** Includes glucuronidation, sulfation, and acetylation

Age-Related Changes in Hepatic Metabolism
Several factors contribute to reduced hepatic drug clearance in older adults:
- Decreased liver size and blood flow
- Reduced uptake of drugs into hepatocytes
- Declining enzyme activity (especially CYP-mediated metabolism)

Clinical Considerations
Drugs primarily metabolized by phase I reactions (e.g., benzodiazepines) may exhibit prolonged effects in older adults due to decreased metabolism. In contrast, drugs that undergo phase II metabolism (e.g., lorazepam, oxazepam) are less affected by aging.

Drug Excretion and Aging
Role of the Kidneys in Drug Elimination
Renal excretion is the primary route of elimination for many drugs. Age-related structural changes in the kidneys include:
- A 20–30% reduction in kidney size between ages 30 and 80
- Increased fibrosis and tubular atrophy
- Decreased glomerular filtration rate (GFR)

Impact on Drug Clearance
Reduced renal function affects the clearance of several drugs, including:
- Water-soluble antibiotics
- Diuretics
- Digoxin
- Water-soluble β-blockers
- Lithium
- Nonsteroidal anti-inflammatory drugs (NSAIDs)
- Newer anticoagulants (e.g., dabigatran, rivaroxaban)

Risk of Drug Accumulation
Drugs with a narrow therapeutic index (e.g., aminoglycosides, digoxin, lithium) pose a higher risk of toxicity when renal clearance declines. Furthermore, in older adults with reduced muscle mass, serum creatinine levels may remain within normal limits despite significant renal impairment, necessitating alternative measures of kidney function, such as creatinine clearance estimation.

Age-Related Pharmacodynamic Changes
Mechanisms of Pharmacodynamic Alterations
Pharmacodynamics refers to how drugs exert their effects on the body. Several age-related changes may influence drug sensitivity, including:
- Altered drug-receptor interactions (e.g., changes in receptor number, affinity, and second messenger responses)
- Impaired homeostatic regulation
- Increased drug sensitivity in the central nervous and cardiovascular systems

Clinical Implications of Altered Pharmacodynamics
- **Increased Sensitivity to Sedatives and CNS Depressants:** Older adults are more susceptible to the effects of benzodiazepines, opioids, and anaesthetics.
- **Reduced β-Adrenergic Responsiveness:** β-blockers may be less effective in aging individuals due to decreased receptor sensitivity.
- **Heightened Risk of Orthostatic Hypotension:** Older adults have impaired autonomic responses, increasing their susceptibility to blood pressure-lowering drugs.

What an altered human organ functions affect pharmacokinetics
The processes of drug absorption, distribution, metabolism, and excretion are influenced by both aging and diseases commonly associated with aging. These changes can affect drug efficacy and safety, necessitating careful consideration in clinical practice.

Absorption
Absorption refers to the movement of a drug from its administration site into the bloodstream. For orally and rectally administered drugs, absorption primarily occurs

in the small intestine. Other routes include the skin, muscle, subcutaneous layer, and lungs.

Bioavailability represents the fraction of an administered dose that enters systemic circulation. With age, physiological changes such as reduced intestinal blood flow, decreased gastric acid production, slowed gut motility, and delayed gastric emptying can impact drug absorption. However, studies suggest that while these changes occur, they rarely have significant clinical consequences. The absorption of subcutaneous or intramuscular drugs may be slower due to reduced tissue perfusion, while decreased muscle mass can enhance absorption of depot formulations. Additionally, reduced lung compliance and alveolar surface area can impair the absorption of inhaled medications.

First-Pass Metabolism and Bioavailability

First-pass metabolism refers to the breakdown of drugs before they reach systemic circulation, occurring primarily in the liver (e.g., propranolol, lidocaine) and intestines (e.g., benzylpenicillin, insulin). Aging reduces first-pass metabolism due to decreased liver mass, hepatic blood flow, and enzyme activity. Consequently, drugs with extensive first-pass metabolism, such as opioids and metoclopramide, exhibit increased bioavailability, requiring lower initial doses.

Conversely, the activation of prodrugs, such as enalapril and perindopril, may be diminished. However, for drugs with a broad therapeutic index, these changes are often not clinically significant.

Distribution

The volume of distribution (Vd) describes how a drug disperses throughout the body. Aging-related changes in body composition, such as reduced total body water and increased fat, influence drug distribution. Water-soluble drugs (e.g., gentamicin, digoxin, lithium) have a smaller Vd, leading to higher plasma concentrations and requiring dose adjustments. Conversely, lipid-soluble drugs (e.g., benzodiazepines, morphine, amiodarone) exhibit increased Vd, prolonging their half-life and potentially leading to prolonged drug effects.

Metabolism

Metabolism converts drugs into more water-soluble compounds for excretion, primarily occurring in the liver. This process involves Phase I reactions (oxidation, reduction, hydrolysis via cytochrome P450 enzymes, particularly CYP3A4) and Phase II reactions (conjugation, glucuronidation, sulfation).

With aging, reductions in liver volume, hepatic blood flow, and enzyme activity can impair drug metabolism, leading to prolonged drug effects and increased toxicity risks.

Excretion

Excretion is the removal of drugs and their metabolites via urine, feces, bile, or lungs, with the kidneys being the primary route. Renal function declines with age, reducing the clearance of many drugs (e.g., water-soluble antibiotics, diuretics, digoxin, lithium, NSAIDs, and newer anticoagulants like dabigatran).

Because serum creatinine levels may remain normal despite reduced renal function due to lower muscle mass, alternative methods such as creatinine clearance calculations should be used to assess kidney function in older adults.

Age-Related Changes in Pharmacodynamics

Pharmacodynamics refers to the effects of drugs on the body, including drug-receptor interactions and homeostatic regulation. Older adults often exhibit increased sensitivity to certain drugs due to changes in receptor function and reduced compensatory mechanisms.

Anticoagulants

Aging increases sensitivity to anticoagulants, particularly warfarin, due to enhanced inhibition of vitamin K-dependent clotting factors. While age is not a contraindication for anticoagulant therapy, careful monitoring is essential. Newer anticoagulants (dabigatran, rivaroxaban, apixaban) require cautious dosing in older adults due to increased risk of adverse drug events.

Cardiovascular Drugs

Calcium Channel Blockers

Older adults experience a greater drop in blood pressure and heart rate with calcium channel blockers like verapamil due to increased sensitivity to their vasodilatory effects. Diltiazem also undergoes age-related metabolic changes, but its effects on blood pressure and heart rate remain consistent across age groups.

Central Nervous System (CNS) Drugs

Older adults are more sensitive to CNS drugs, increasing the risk of adverse effects such as sedation, cognitive impairment, and motor disturbances.

- **Antipsychotics**: Increased risk of extrapyramidal symptoms, arrhythmias, and postural hypotension.
- **Benzodiazepines**: Greater sedative effects and postural instability, increasing fall risk.
- **Opioids**: Heightened sensitivity, requiring lower doses.
- **Anaesthetics**: Enhanced effects, necessitating dose adjustments.

Age Considerations in Drug Development

To ensure drug safety and efficacy in older populations, clinical trials should include older adults. The International Council for Harmonization (ICH) E7 guideline recommends geriatric inclusion in drug studies. However, many trials exclude older patients, limiting available data on age-related pharmacokinetic and pharmacodynamic changes. Organizations like the

Expertise Centre Pharmacotherapy in Old Persons (Ephor) work to optimize drug use in older adults through evidence-based recommendations.

Adverse Drug Reactions (ADRs) and Drug Interactions

ADRs are more common in older adults due to altered drug sensitivity, polypharmacy, and inadequate monitoring. Drug interactions are also more frequent, increasing exponentially with the number of medications taken.

Polypharmacy

Older adults often take multiple medications for various conditions, increasing ADR risks. Issues such as inappropriate prescribing, lack of monitoring, and patient non-adherence contribute to adverse outcomes. A careful approach to drug selection, dosing, and monitoring is crucial.

Strategies to Prevent ADRs in Older Adults

Reducing unnecessary medication use is one of the most effective strategies to lower ADR risks. **Deprescribing**, or systematically discontinuing inappropriate drugs, can improve patient outcomes. A five-step deprescribing protocol includes:

1. Reviewing all medications
2. Assessing medication necessity
3. Prioritizing drugs for discontinuation
4. Implementing a withdrawal plan
5. Monitoring for withdrawal symptoms or improvements

Careful documentation of patient conditions, medication history, and treatment goals is essential. Newly introduced drugs should be titrated slowly, and new symptoms should be evaluated for potential ADRs to avoid the prescribing cascade. By prioritizing appropriate prescribing and deprescribing strategies, healthcare providers can improve medication safety and enhance the quality of life for older adults.

CONCLUSION

The ageing process brings about structural and functional changes in all organ systems, leading to a decline in the body's ability to maintain homeostasis. While the function of various systems may remain stable under normal conditions, the reduced physiological reserve makes older adults more vulnerable to stress. Alterations in body composition, along with diminished liver and kidney function, contribute to an increased volume of distribution for lipid-soluble drugs and a reduced clearance of both lipid- and water-soluble drugs. These changes result in a prolonged plasma elimination half-life of many medications. Additionally, significant pharmacodynamic shifts occur, often increasing drug sensitivity. The decline in physiological reserves further heightens this sensitivity by weakening the body's ability to compensate for disruptions. Gaining a deeper understanding of how ageing affects drug metabolism and response can help improve the safety and effectiveness of medication use in older adults.

REFERENCES

1. World Health Organization (2020). Depression and other common mental disorders: Global health estimates. Geneva: WHO.
2. Kessler, Ronald C., & Bromet, Evelyn J. The global burden of depression: A systematic analysis. The Lancet Psychiatry, 2018; 5(2): 113-122.
3. Friedrich, Matthew J. Depression is the leading cause of disability worldwide. JAMA, 2017; 317(15): 1517.
4. Malhi, Gin S., & Mann, John J. Depression. The Lancet, 2018; 392(10161): 2299-2312.
5. Delgado, Pedro L. Depression: The case for a monoamine deficiency. Journal of Clinical Psychiatry, 2000; 61(6): 7-11.
6. Rush, A. John, Trivedi, Madhukar H., & Wisniewski, Stephen R. STAR*D: Lessons learned and future directions. American Journal of Psychiatry, 2006; 163(11): 1905-1917.
7. Andrade, Chittaranjan Pharmacotherapy for major depressive disorder: Efficacy and tolerability of antidepressants. Journal of Clinical Psychiatry, 2020; 81(3): 19f13153.
8. Cipriani, Andrea, Furukawa, Toshi A., & Salanti, Georgia Comparative efficacy and acceptability of 21 antidepressant drugs. The Lancet, 2018; 391(10128): 1357-1366.
9. Hyman, Steven E. Revitalizing psychiatric therapeutics. Neuropsychopharmacology, 2014; 39(1): 220-229.
10. Krishnan, Vaishnav, & Nestler, Eric J. The molecular neurobiology of depression. Nature, 2008; 455(7215): 894-902.
11. Sanacora, Gerard, Zarate, Carlos A., & Krystal, John H. Beyond monoamines in antidepressant action: The role of glutamate and GABA. Biological Psychiatry, 2012; 71(11): 1171-1180.
12. Duman, Ronald S., & Aghajanian, George K. Synaptic dysfunction in depression: Potential therapeutic targets. Science, 2012; 338(6103): 68-72.
13. Autry, Anita E., & Monteggia, Lisa M. Brain-derived neurotrophic factor and neuropsychiatric disorders. Pharmacological Reviews, 2012; 64(2): 238-258.
14. Castrén, Eero Neuronal network plasticity and recovery from depression. JAMA Psychiatry, 2013; 70(9): 983-989.
15. Hillhouse, Todd M., & Porter, James H. A brief history of the development of antidepressant drugs: From monoamines to glutamate. Experimental and Clinical Psychopharmacology, 2015; 23(1): 1-21.
16. Hasler, Gregor Pathophysiology of depression: Do we have any solid evidence of interest to clinicians? World Psychiatry, 2010; 9(3): 155-161.

17. Monteggia, Lisa M., Luikart, Bryan W., & Parada, Luis F. BDNF signaling in psychiatric disorders. Molecular Psychiatry, 2013; 18(8): 834-839.
18. Berton, Olivier, & Nestler, Eric J. New approaches to antidepressant drug discovery: Beyond monoamines. Nature Reviews Neuroscience, 2006; 7(2): 137-151.
19. Hasler, Gregor Pathophysiology of depression: Do we have any solid evidence of interest to clinicians? World Psychiatry, 2010; 9(3): 155-161.
20. Hillhouse, Todd M., & Porter, James H. A brief history of the development of antidepressant drugs: From monoamines to glutamate. Experimental and Clinical Psychopharmacology, 2015; 23(1): 1-21.
21. Nestler, Eric J., & Carlezon, William A. The mesolimbic dopamine reward circuit in depression. Biological Psychiatry, 2006; 59(12): 1151-1159.
22. Fava, Maurizio, & Davidson, Karl G. Definition and epidemiology of treatment-resistant depression. Psychiatric Clinics, 2016; 39(2): 145-162.
23. Zhou, Xiang, Michael, Nora, & Smith, Evan M. High-throughput screening in antidepressant drug discovery. Journal of Neuroscience Methods, 2015; 241: 76-82.
24. Jaffe, Jerome H., & Klein, Donald F. Drug discovery and antidepressant research. Biological Psychiatry, 2012; 72(10): 671-674.
25. Zanos, Panos, Moaddel, Ruin, & Morris, Peter J. Ketamine and its metabolite, hydroxynorketamine, sustain antidepressant effects via AMPA receptor activation. Nature, 2016; 533(7604): 481-486.
26. Ramya P, Vasanth P M, Prasad P V, Babu S V Qualitative phytochemical screening tests of Alpinia galanga L. World Journal of Pharmaceutical Research, 2019; 8(5): 1064-1077.
27. Deepthi V, Rao PK, Vasanth PM Evaluation of therapeutic response of methotrexate and calcipotriol combination compared with methotrexate alone in plaque psoriasis. Our Dermatol Online, 2014; 5(2): 118-123.
28. Prasanthi, R. M., Vasanth, P. M., & Ramesh, T. Assays for oxidative stress and antioxidant status. Research Journal of Pharmaceutical, Biological and Chemical Sciences, 2013; 4(1): 846-856.
29. Lipsitz, Lewis A. Physiological complexity, aging, and the path to frailty. Science of Aging Knowledge Environment, 2004; 16: 16.
30. Kirkwood, Thomas B. Understanding the odd science of aging. Cell, 2005; 120(4): 437-447.
31. López-Otín, Carlos, Blasco, Maria A., Partridge, Linda, Serrano, Manuel, & Kroemer, Guido. The hallmarks of aging. Cell, 2013; 153(6): 1194-1217.
32. Ferrucci, Luigi, & Fabbri, Elisa. Inflammageing: Chronic inflammation in ageing, cardiovascular disease, and frailty. Nature Reviews Cardiology, 2018; 15(9): 505-522.
33. Franceschi, Claudio, & Campisi, Judith. Chronic inflammation (inflammaging) and its potential contribution to age-associated diseases. Journals of Gerontology Series A: Biological Sciences and Medical Sciences, 2014; 69(S1): S4-S9.
34. Harman, Denham. Aging: Overview. Annals of the New York Academy of Sciences, 2001; 928(1): 1-21.
35. Kennedy, Brian K., Berger, Shelley L., Brunet, Anne, et al. Geroscience: Linking aging to chronic disease. Cell, 2014; 159(4): 709-713.
36. Niccoli, Teresa, & Partridge, Linda. Ageing as a risk factor for disease. Current Biology, 2012; 22(17): R741-R752.
37. Barzilai, Nir, Cuervo, Ana M., & Austad, Steven. Aging as a biological target for prevention and therapy. JAMA, 2018; 320(13): 1321-1322.
38. Reeve, Emily, Wiese, Michael D., & Mangoni, Arduino A. Alterations in drug disposition in older adults. Expert Opinion on Drug Metabolism & Toxicology, 2015; 11(4): 491-508.
39. Mangoni, Arduino A., & Jackson, Stephen H. Age-related changes in pharmacokinetics and pharmacodynamics: Basic principles and practical applications. British Journal of Clinical Pharmacology, 2004; 57(1): 6-14.
40. Hilmer, Sarah N., & McLachlan, Andrew J. Pharmacokinetics and pharmacodynamics in older adults: A review. British Journal of Clinical Pharmacology, 2007; 65(1): 49-63.
41. Shah, Rishi R. Drug development and use in the elderly: Search for the right dose and dosing regimen. British Journal of Clinical Pharmacology, 2015; 80(1): 4-7.
42. Ziere, Guido, Dieleman, Jeannette P., Hofman, Albert, Pols, Hein A., van der Cammen, Tischa J., & Stricker, Bruno H. Polypharmacy and falls in the middle age and elderly population. British Journal of Clinical Pharmacology, 2006; 61(2): 218-223.
43. Gudmundsson, Adalsteinn, & Höglund, Peter. Pharmacokinetics in the elderly. Clinical Pharmacokinetics, 2007; 46(6): 467-485.
44. Davies, E. Anne, & O'Mahony, M. S. Adverse drug reactions in special populations—The elderly. British Journal of Clinical Pharmacology, 2015; 80(4): 796-807.