**Review Article:**

**Drug Prescribing to the Elderly Patients**

*Misha’l Aly A.*

**Abstract**

Age-related physiologic and anatomic changes in various body systems are accompanied by significant pharmacokinetic and pharmacodynamic alterations that make it mandatory for treating physicians to adjust types and dosages of medications for their older patients. Moreover, physicians should be always alert for adverse drug events, and consider any new symptoms as drug-related until proven otherwise. Other issues addressed include prescribing cascades, polypharmacy, drug-drug interactions, and the need to review all medications used by the elderly patients, with special attention to non-prescription and herbetic drugs. This review aims at maximizing safe medicine prescribing, and minimizing adverse drug event in caring for older subjects.

**Keywords:** Aging; pharmacokinetics; pharmacodynamics; polypharmacy; adverse drug events.

**Introduction**

Aging is characterized by heterogeneous deterioration of function of various body organs. Although the basic mechanisms underlying aging processes are not clearly understood, available evidence is consistent with accumulation of a variety of biochemical alterations that impair function of nucleic acids, proteins and lipid membranes.

The extent to which differentiated cells are affected by aging determines physiologic function, while the extent to which stem and precursor cells (reserve cells) are affected determines the capacity to replace and repair damaged cells and tissues. A twin study found that genetics accounted for about 25% of the variation in longevity among twins, and environmental factors accounted for about 50%. However, with greater longevity (to age 90 or 100 years), genetic influences become more important. Significant aging effects related to medications metabolism, therapeutic effectiveness and toxicity have been studied in various body systems.

In the stomach, several age-related physiologic changes take place, with decreased prostaglandin synthesis, decreased bicarbonate and nonparietal fluid secretion, delayed gastric emptying and impaired microcirculation. These factors are instrumental in causing increased rates of gastritis and sensitivity to gastric irritants and other insults, such as nonsteroidal anti-inflammatory drugs, and increased infection with *H. pylori*. In the small intestine, moderate villus atrophy takes place, which may induce malabsorption of several micronutrients. Vitamin D receptors, as an example, are decreased, with decreased calcium absorption.

Intestinal bacterial overgrowth and associated malabsorption can adversely affect nutritional status. Compromise of barrier function and decrease in myenteric neurons may induce painless ulcerations. In the large intestine, more prevalence of mucosal atrophy, mucosal glands abnormalities, hypertrophy of muscularis mucosa,
altered coordination of contractions with reduction of colonic propulsive motility that underly chronic constipation. Formation of colonic diverticulitis increases with age, due to decreased muscle wall strength and increased intra-abdominal pressure. In the hepatobiliary system, there is reduction of perfusion and blood flow to the liver, with decreased liver mass, up to 40% with age. Many liver functions decline, including cytochrome P450, with diminished elimination of drugs and other materials, e.g., erythromycin, galactose and reduced caffeine clearance.

LDL receptors and LDL metabolism decrease with age, and serum LDL levels increase. Synthesis of vitamin K-dependent clotting factors are decreased, due to lower amounts of vitamin K antagonists needed for anticoagulation in older people. The bile composition has higher lithogenic index, which predisposes to gallstone formation.

In the genitourinary system, renal mass decreases up to 30%, with the steepest decline after age 50. Diffuse sclerosis causes destruction of 30% of glomeruli. Fat and fibrosis replace renal parenchyma. Changes affect the renal cortex, especially nephrons responsible for maximal urine concentration. Intrarenal vascular changes, with narrowing, intimal fibrosis, shunting between afferent and efferent arterials (causing bypass of blood flow), and nephrosclerosis take place gradually.

Risks of renal injury due to certain drugs (e.g., nonsteroidal anti-inflammatory drugs-NSAIDs) are precipitated due to the above factors, and to increased vasodilating prostaglandins. Creatinine clearance decreases with age, with individual variations. Serum creatinine may remain stable despite decreases in GFR, due to decreased production of creatinine in old age. The ability to maximally dilute urine and to excrete a water load is impaired, and compromises volume regulation under stressful situations. Older kidneys have impaired ability to retain water, solute, amino acids and glucose. Older kidneys have reduction of ability to acidify urine, with impaired ability to excrete an acid load. They are more prone to:

- Nephrotoxicity due to medications, or intravenous contrast.
- Less likely to recover from acute insults.
- More vulnerable to ischemic insults.
- Tubular cells have diminished ability to regenerate and populate the tubes after acute ischemic insults.

Urge incontinence is characterized by loss of urine accompanied by sense of urgency. Stress incontinence is induced by cough, sneezing or exertion. Both disorders can be mixed. Evaluation and management should start by exclusion of reversible causes, e.g., medications-induced, infectious, metabolic and cognitive disorders. Treatment generally proceeds in a stepwise manner, starting lifestyle and behavioral measures, in the form of pelvic floor muscle training, bladder training, weight loss for obese subjects, exercise followed by medications, special devices, then surgeries.

In the musculoskeletal system, muscle mass decreases (sarcopenia) at variable rates with age. This is considered an independent risk factor for mortality. The loss of muscle mass contributes to insulin resistance, and changes in volume of distribution for water soluble drugs. Active lifestyle, with exercise, plays significant roles in minimizing age effects on muscles. Age-related hormonal changes, e.g., growth hormone and androgen, may contribute to these alterations. Bone loss proceeds, with increases in fracture rate and slower rate of repair. Bone loss is promoted by the increased proinflammatory environment. Both trabecular and cortical bone are affected, with decline in osteoblast numbers and activity. Cortical bone loss proceeds, with enlargement of marrow lumen that is infiltrated with fat. Vitamin D deficiency further accelerates bone loss. Supplementation with vitamin D, calcium, parathyroid hormone, vascular endothelial growth factor, have all shown promise to promote bone healing.

**Drug Prescribing for the Elderly**

Age-related changes in pharmacokinetics and pharmacodynamics make it mandatory for physicians to optimize drug therapy for their older patients. This should include deciding whether a drug is indicated, choosing the most appropriate drug, determining the proper doses, monitoring for effectiveness and toxicity and educating the patient and family about expected side effects and indications for seeking medical consultation. Avoidable adverse drug effects should always be borne in mind when elderly people complain of new symptoms. Any new symptom should be considered drug-related until proven otherwise. The greater risks of hospitalizations, adverse drug events and increased morbidity-mortality are significant consequences of inappropriate drug
Geriatric clinical pharmacology addresses:
- Pharmacokinetics: i.e, absorption, distribution, metabolism and excretion.
- Pharmacodynamics: i.e, the physiologic effects of drugs.
- Adverse drug reactions.
- Drug interactions.
- Rational drug therapy for older persons.

Old Age and Pharmacokinetics
Age related increase in the proportion of body fat causes increase in volume of distribution for lipid-soluble drugs: e.g: benzodiazepines. Age-related decrease in lean body mass (muscles) causes 10-15% decrease in total body water. The volume of distribution declines for hydrophilic drugs e.g, alcohol. Plasma albumen concentration decreases in the elderly malnourished subjects, especially those with advanced cancer. The plasma-binding of some drugs decreases and the unbound fraction may exceed 50%, which results in increased free drug concentrations and toxicity. Examples include: salicylates, naproxen, acetazolamide, and valproate.

Age-related decrease in liver mass reaches up to 20-50% during the age span up to 80 years. This is accompanied by decreased amounts of drug-metabolizing enzymes.

Associated with that is gradual decrease of hepatic blood flow, and decrease in clearance of drugs and decrease in elimination by conjugation of some drugs by up to 25%, e.g. theophylline. Also there is decreased first-pass metabolism of some drugs that are highly extracted by the liver, e.g. Labetalol, Propranolol, Verapamil and Morphine. This results in decreased systemic bioavailability and decreased concentration. Older smokers develop decreased hepatic metabolizing enzymes with possible increased mortality. Malnutrition, as occurs in cancer patients with anorexia, causes impairment of drug metabolism. Adjusting of dosage is important. In old frail subjects there is decreased clearance of acetaminophen up to 42%.

Warfarin
Age-related decline in liver volume results in decrease in warfarin dose requirement from the age of 50 years.

Anesthesia
There is increased brain sensitivity to I.V fentanyl and altentanil. This should be carefully taken into consideration when dealing with older subjects.

Polypharmacy
Approximately 50% of patients over age 65 years take five or more medications each week. The use of multiple medications increases the risk for inappropriate use, drug-drug interactions, duplication of therapy, adverse reactions, and medication errors. Polypharmacy is clearly associated with increased outpatient visits, increased risk for hospitalization, increased health care costs, and decrease functional status. Additionally, the risk for non-adherence increases, which can lead to treatment failure and disease progression. Polypharmacy increases the risk of “Prescribing Cascades”: When an adverse drug event (ADE) is misinterpreted as a new medical condition, and more drugs are prescribed. Certain medications have been found to particularly incur high risk for geriatric patients. The American Geriatrics Society has compiled a list of high-risk drugs that must be carefully considered in terms of risk-to-benefit ratio in the elderly.

Summary and Recommendations
- The possibility of adverse drug events (ADE) should always be borne in mind. Any new symptoms should be considered drug-related until proven otherwise.
- Physicians must always review all medications used. Special attention must be paid to non-prescription drugs, herbs and supplements.
- Various criteria sets exist in the literature that identify medications to be avoided, or prescribed with caution.
- Physicians should avoid under-utilization, as much as over-utilization of drugs.
- ADEs result in 4 times as many hospitalizations in older compared with younger adults.
- Causes of preventable ADEs include, among others: prescribing cascades, Drug-drug interactions and inappropriate drug doses.
- Follow a step-wise approach to prescribing for older adults.
- Discontinue any potentially unnecessary therapy.
- Consider non-pharmacological approaches.
Substitute with safer alternatives.

References:


