

# Chapter 9: Drug Dosing and Renal Toxicity in the Elderly Patient

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Aging is a natural process of human development and is characterized by a progressive loss of physiologic and reproductive functions.<sup>1,2</sup> Despite significant advances in the fields of human physiology, pharmacology, and pathology, as well as medical and clinical interventions, aging continues to be a significant risk factor and strong predictor of morbidity and mortality.

Geriatric patients, while accounting for 15% of the population, use 30% of all prescription drugs prescribed in the United States. By 2020, >50 million people will be over 65 yr of age and account for 25% of the US population (Figure 1). It is estimated that by 2030, the population of individuals over 65 yr of age will increase by four-fold, and this age group is the fastest growing segment of the US population. This increase will add to healthcare costs and strengthen the economic tsunami that our country is facing today.<sup>3,4</sup>

Chronic kidney disease (CKD) is a common and progressive condition that continues to rise in the United States.<sup>5–7</sup> Limited data exist regarding drug use in elderly patients with CKD. Proven therapies are often underused in the geriatric population. For example, recent data indicated that aggressive management of hypertension may be beneficial in older patients.<sup>8,9</sup> However, most physicians hesitate to treat older patients more aggressively. This is, in part, because of a high risk of drug–drug interactions, adverse drug reactions, and lack of clinical data in this population. Monitoring the medications used in older adults and identifying drug interactions and adverse events are crucial. Drug therapy management in older adults is challenging, and many factors related to normal aging, disease states, and lifestyle should be considered before initiation of pharmacotherapy (Figure 2).<sup>10,11</sup>

In a recent study, Qato *et al.*<sup>12</sup> documented that 91% of older adults regularly use one prescription drug and >50% use five or more prescriptions per

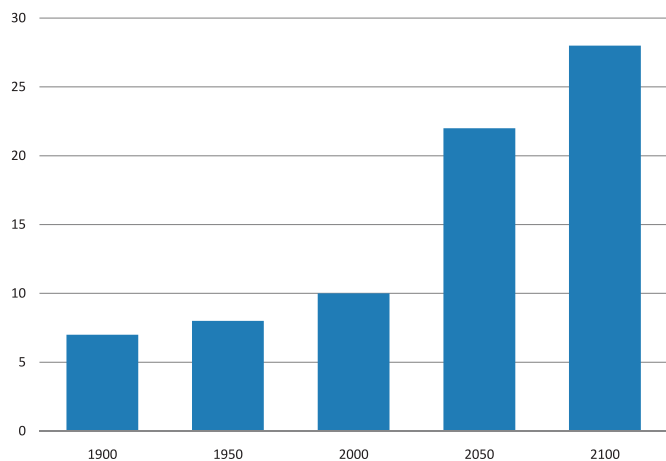
day (Figure 3). These numbers are significantly higher for patients with CKD, including those undergoing kidney dialysis. In the elderly, new-onset adverse drug reactions are commonly mistaken by healthcare providers as a new-onset disease or morbidity related to aging.<sup>13</sup> Approximately 15 to 45% of older adults develop moderate to severe forms of memory impairment from medication use.<sup>14</sup> This cognitive impairment may position older adults at a higher risk of overdose or nonadherence compared with the rest of the population.<sup>15</sup> In addition, older adults with kidney disease are cared for by a variety of healthcare providers such as nephrologists, cardiologists, general practitioners, and pharmacists and may lack good continuity of care. Medication reconciliation is still a major problem in this era of the electronic medical record. Failure to disclose a complete list of current medications taken to each provider because of cognitive impairment may have a profound impact on potential risk of drug–drug interactions or disease–drug interactions.<sup>16</sup>

The overall incidence of adverse drug reactions is three- to ten-fold higher in older adults with kidney disease compared with those without CKD.<sup>17</sup> The incidence of adverse drug reactions correlates exponentially with renal function.<sup>18</sup> Most drugs and/or their metabolites are excreted renally through glomerular filtration. The overall size, mass, and effective area of filtration decreases with increasing age.<sup>19,20</sup> These morphologic changes increase the risk for drug and/or active metabolite accumulation in older patients with kidney disease. After the age of 50, the number of nephrons progressively declines from approximately >1,000,000

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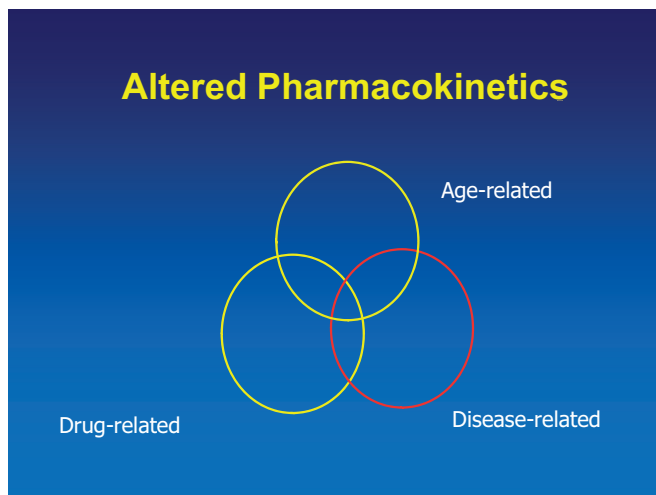


**Figure 1.** Estimated population of individuals (%) over 65 yr of age by 2100 in the United States.

to <500,000. In addition, up to 35% of nephrons show clinically important evidence of sclerosis.<sup>21</sup>

Drug dosing in CKD has been reviewed extensively in other review papers.<sup>17,18</sup> This chapter will examine how aging and physiologic changes secondary to aging effect drug elimination and provide general dosing guidelines. However, it is very important to mention that very few drugs and clinical interventions have been well studied in older adults, particularly those with CKD. Older adults are in general underrepresented in most clinical studies. Most studies exclude patients over 65 yr of age, and few studies allow the inclusion of nursing home patients.

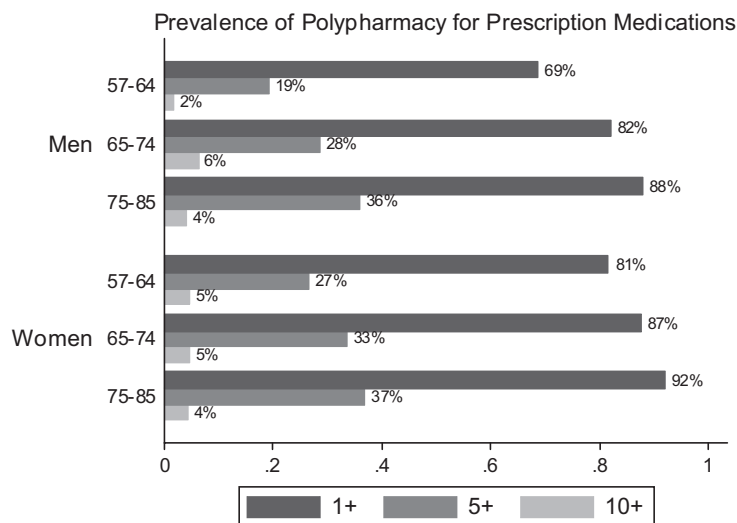
In an important study, Lindeman *et al.*<sup>22</sup> showed that a decrease in renal GFR occurs during the aging process but much less than previously perceived. These alterations in renal function are largely clinically insignificant and have a limited effect on the life of adult patients without comorbid conditions. Many investigators have discovered small artery fibrosis and decreased renal blood flow after four decades of life. Decreased renal blood flow can happen independent of cardiac output or



**Figure 3.** Altered pharmacokinetics.

cardiovascular disease as one ages. Increased renal nerve activity, increased production and release of angiotensin II, decreased local prostaglandins, and increased release of endothelin may contribute to vasoconstriction and decreased renal blood flow during later stages of life.<sup>23,24</sup> A higher incidence of vascular disease, hypertension, diabetes, and smoking and a high protein diet are common among older adults in industrialized nations and may further distress renal function. In the United States, approximately 65% of older adults have a diagnosis of hypertension.<sup>25</sup> Hypertensive nephropathy accounts for 25% of all ESRD that requires dialysis. These pathologic processes independent of aging alter drug absorption, protein binding, volume of distribution, and elimination.<sup>26</sup>

The GFR is closely correlated with renal drug elimination and is useful in determining dosage adjustments.<sup>27</sup> The age-dependent alterations to renal anatomy and physiology in older adults make the kidneys more susceptible to environmental and pathologic nephrotoxins. To avoid toxicity in older patients with kidney disease, the drug dosage should be ad-



**Figure 2.** Percent of polypharmacy at different age groups: >1 drug, >5 drugs, and >10 drugs.

**Table 1.** Agents to be avoided or used with caution in patients with CKD

Class	Examples
Antibiotics	Aminoglycosides, vancomycin, sulfamethoxazole
Antifungals	Amphotericin B
Antivirals	Foscarnet, indinavir, cidofovir
Anticoagulants	Low molecular weight heparins, warfarin
Cardiac drugs	Digoxin, sotalol, ACE-I, ARB, DRIs
Opioids	Morphine, meperidine, propoxyphene
Psychotropics/anticonvulsants	Amisulpride, gabapentin, lithium, levetiracetam, topiramate, vigabatrin
Hypoglycemic drugs	Metformin, glyburide, insulin
Drugs for gout	Allopurinol, colchicine
Others	Methotrexate, penicillamine, nonsteroidal anti-inflammatory drugs

ACE-I, angiotensin-converting enzyme; ARB, angiotensin II receptor blockers; DRI, direct renin inhibitor.

justed according to estimated creatinine clearance. There are a number of methods to estimate creatinine clearance; however, the most commonly used method is the Cockcroft-Gault method. There are a number of limitations when using the Cockcroft-Gault method in older patients. The production and elimination of creatinine decreases with age.<sup>26</sup> This may overestimate renal function and mask the early stage of renal dysfunction. In older adults, the use of Modification of Diet in Renal Disease (MDRD) may provide a better estimate of renal function. Some drugs may increase the metabolic load by increasing creatinine production and/or urea production (e.g., glucocorticoids and androgens). Some agent may also interfere with creatinine tubular secretion (e.g., cimetidine and trimethoprim). Ketosis, hyperbilirubinemia, and some cephalosporins may influence the measurement of plasma creatinine and cause renal function assessment inaccurate when serum creatinine is used.

Considering these limitations, estimating renal function is difficult in the elderly population. However, the use of the Cockcroft-Gault method is the safest and most effective approach for dosage adjustments in patients with renal impairment.

## APPROACH TO DOSAGE ADJUSTMENT IN OLDER ADULTS

Most guidelines recommend drug dosing adjustments in older adults with or without renal disease. The following recommendations provide a simple approach for healthcare providers and attempt to reduce the risk of drug toxicity and improve pharmacotherapeutic efficacy. However, patient-specific factors, comorbid condition, drug interactions, and healthcare insurance coverage should be considered and monitored during therapy.<sup>19</sup>

### Step 1: Medical History and Physical Examination

A complete medical history should be obtained, and a physical exam should be performed. The etiology and duration of renal dysfunction should be determined and defined as acute or chronic whenever possible. A review of current medications,

both prescription and nonprescription, should be obtained to identify potential nephrotoxins or interacting medications. A thorough medication history should be obtained to identify drug allergies or intolerances and previous adverse drug reactions. Body mass index (BMI) and ideal body weight (IBW) should be calculated using the following formulas: BMI = weight in kilograms divided by height in meters squared; IBW(men) = 50.0 kg + 2.3 kg for every 2.5 cm over 152 cm; and IBW(women) = 45.5 kg + 2.3 kg for every 2.5 cm over 152 cm.

Volume status, both intracellular and extracellular, should be assessed frequently. Shifts in extracellular fluid volume may change the volume of distribution of many drugs. Patients with dehydration have a higher predisposition to drug toxicity. In older adults, total body volume decreases by 10 to 15%. Muscle atrophy, reduced tissue perfusion, and increase in fat content change the volume of distribution of most hydrophilic agents. The plasma concentration of drugs with a narrow therapeutic window and small volume of distribution (aminoglycosides, lithium) may alter considerably with any change in extracellular fluids. Coexisting hepatic dysfunction may alter protein binding, volume of distribution, and intravascular volume and necessitate further dosage modification.<sup>28</sup>

### Step 2: Renal Function Assessment

The Cockcroft-Gault formula is a simple and widely used method to estimate GFR. A 24-h creatinine clearance (Cl<sub>cr</sub>) is an approximation of GFR, and it is practical and useful for estimating renal function in drug dosage modification in patients with stable renal dysfunction. In patients with acute kidney injury, rising serum creatinine, and low urine output, creatinine clearance should be assumed to be generally <10 ml/min. The Cockcroft-Gault formula includes the variables of age (yr), IBW (kg), and serum creatinine (Scr) (mg/dl) and calculates the Cl<sub>cr</sub> (ml/min):  $Cl_{cr} = (140 - \text{age}) \times IBW/72 \times Scr$  (the result should be multiplied by 0.85 for women).

Use of Iohexol is a new method to estimate GFR but is currently being used only in the clinical research setting. Iohexol provides a more accurate measurement of renal function without exposing the patient to radiolabeled material. Finally, the MDRD study recently reported a new formula to estimate renal function. This method provides a more accurate estima-

**Table 2.** Therapeutic drug monitoring

Drug Name	Therapeutic Range	When to Draw Sample	How Often to Draw Levels
Aminoglycosides (conventional dosing)	Gentamicin and tobramycin: Trough: 0.5–2 mg/L	Trough: immediately before dose Peak: 30 min after a 30- to 45-min infusion	Check peak and trough with third dose  For therapy less than 72 h, levels not necessary. Repeat drug levels weekly or if renal function changes
Gentamicin, tobramycin, amikacin	Peak: 5–8 mg/L Amikacin: Peak: 20–30 mg/L Trough: <10 mg/L		
Aminoglycosides (24-h dosing) gentamicin, tobramycin, amikacin	0.5–3 mg/L	Obtain random drug level 12 h after dose	After initial dose. Repeat drug level in 1 wk or if renal function changes
Carbamazepine	4–12 µg/ml	Trough: immediately before dosing	Check 2–4 days after first dose or change in dose
Cyclosporin	150–400 ng/ml	Trough: immediately before dosing	Daily for first week and then weekly.
Digoxin	0.8–2.0 ng/ml	12 h after maintenance dose	5–7 d after first dose for patients with normal renal and hepatic function; 15–20 d in anephric patients
Lidocaine	1–5 µg/ml	8 h after intravenous infusion started or changed	
Lithium	Acute: 0.8–1.2 mmol/L  Chronic: 0.6–0.8 mmol/L	Trough: before a.m. dose at least 12 h since last dose	
Phenobarbital	15–40 µg/ml	Trough: immediately before dosing	Check 2 wk after first dose or change in dose. Follow-up level in 1–2 mo
Phenytoin	10–20 µg/ml	Trough: immediately before dosing	5–7 d after first dose or after change in dose
Free phenytoin	1–2 µg/ml		
Procainamide NAPA (n-acetyl procainamide) a procainamide metabolite	4–10 µg/ml  Trough: 4 µg/ml  Peak: 8 µg/ml 10–30 µg/ml	Trough: immediately before next dose or 12–18 h after starting or changing an infusion  Draw with procainamide sample	
Quinidine	1–5 µg/ml	Trough: immediately before next dose	
Sirolimus	10–20 ng/dl	Trough: immediately before next dose	
Tacrolimus (FK-506)	10–15 ng/ml	Trough: immediately before next dose	Daily for first week and then weekly.
Theophylline p.o. or Aminophylline i.v.	15–20 µg/ml	Trough: immediately before next dose	
Valproic acid (divalproex sodium)	40–100 µg/ml	Trough: immediately before next dose	Check 2–4 d after first dose or change in dose
Vancomycin	Trough: 5–15 mg/L  Peak: 25–40 mg/L	Trough: immediately before dose  Peak: 60 min after a 60-min infusion	With third dose (when initially starting therapy, or after each dosage adjustment). For therapy <72 h, levels not necessary. Repeat drug levels if renal function changes

tion of renal function in patients with low muscle mass, high protein intake, or geriatric populations and is subject to less artifact interference. In dialysis patients, with a residual renal function, the residual renal function may to a large extent contribute to the elimination of drugs and their active metabolites. The effect of residual renal function on drug elimination in dialysis patients with urine output <500 ml/d is very difficult to estimate. Residual renal function decreases over time and is usually <5 ml/min after 1 yr on hemodialysis.

### Step 3: Loading Dose Determination

For most drugs, the loading dose should not be adjusted. In patients with normal renal function, steady-state drug concentration is reached after approximately five half-lives. The half-life of drugs that are excreted renally may be significantly prolonged in patients with CKD. To rapidly achieve a therapeutic plasma concentration, a loading dose should be administered. However, when the volume of distribution is altered secondary to CKD, a smaller loading dose may be required for some agents. For example, in dialysis patients, the loading dose of digoxin should be reduced by 25 to 50% to avoid toxicity. Although routine plasma concentration monitoring of digoxin is not necessary in patients with normal renal function, in dialysis patients and patients with a history of hypokalemia, the plasma concentration should be monitored very closely.<sup>29</sup> The loading dose can be calculated as follows to achieve a desirable plasma concentration:  $LD = Vd (L/kg) \times IBW (kg) \times [C_p]$ , where  $C_p$  is the desired plasma concentration (mg/L).

### Step 4: Maintenance Dose Determination

The maintenance of drugs that are primarily eliminated unchanged through the kidneys should be modified in patients with CKD. Dosage modification in older adults with kidney disease can be accomplished by dose reduction, dosing interval prolongation, or both methods. For drugs whose clinical efficacy correlates with adequate peak concentrations (aminoglycosides, cephalosporins), the dosing interval should be adjusted. For agents whose efficacy correlates with area under of the curve or a rapid rise in plasma concentration correlate with toxicity, the dosage interval should be prolonged. In general, for most drugs, a combined approach using both the dose reduction and interval prolongation methods is often used. This method provides a constant plasma drug concentration without increasing the risk of toxicity from high peak or trough levels.<sup>30</sup> Finally some medications should be avoided or be used with caution in patients with CKD (Table 1).

### Step 5: Drug Level Monitoring

Despite dosage adjustments and prolongation dosage interval, drug toxicity is a common problem in older adults with CKD. Because of inter- and intraindividual pharmacokinetic variabilities, comorbid conditions, and drug interactions, therapeutic drug monitoring (TDM) is important in older patients with renal impairment. The diagnostic value of TDM relies on correct interpretation of plasma drug concentrations. It is im-

portant to know the exact dose given, the route of administration, time of administration, and time since the last dose. Peak levels are meaningful for only few drugs. Peak drug levels represent the highest drug concentration achieved after initial rapid distribution. For most drugs, trough levels are obtained immediately before the next dose, represent the lowest serum concentration, and predict drug toxicity. For most drugs, TDM is not available and could be very costly. TDM should be used only for drugs in which plasma concentrations correlate with toxicity or efficacy. It is important to mention that, even with TDM, drug toxicities can not always be avoided. For example, aminoglycoside antibiotics can accumulate in tissues such as the inner ear and renal tubules. Aminoglycoside toxicity can occur after a single dose or in some cases without associated high plasma concentrations. Clinical practitioners must incorporate ongoing clinical assessment and TDM simultaneously. Assessment of adverse drug reactions is important even when drug levels are within the established therapeutic range. Finally, in older adults with kidney disease, protein binding is altered significantly. For highly protein-bound drugs, the free fraction can be elevated significantly, whereas the total plasma concentration is within therapeutic range. Most assays do not distinguish between free and protein-bound drug in the plasma. An increase in unbound drug is common in patients with renal failure. For example, a dialysis patient with albumin of <2 g/dl and phenytoin level of 6 mg/L could experience phenytoin toxicities while phenytoin levels are within the therapeutic range (therapeutic level: 10 to 20 mg/L). Free phenytoin levels provide better therapeutic drug monitoring in older patients with renal impairment.<sup>31,32</sup> Table 2 summarizes the therapeutic drug monitoring parameters in renal insufficiency for drugs in which monitoring of levels is routinely recommended.

### TAKE HOME POINTS

- Review patients past medical history and medication profiles for any possible drug–drug interactions
- For GFR <50 ml/min, renally excreted drugs should be adjusted according to the renal function
- Dosage modification can be accomplished by dose reduction, dosing interval prolongation, or both methods
- If needed, consider therapeutic drug monitoring (TDM) in older patients with renal impairment

### DISCLOSURES

None.

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**REVIEW QUESTIONS: DRUG DOSING AND RENAL TOXICITY IN THE ELDERLY PATIENT**

1. Of the following, which would be of important consideration in assessing renal function in older patients?
  - a. Serum creatinine
  - b. Weight and muscle mass
  - c. Urine output
  - d. All of the above
2. Drug–drug interaction occurs as a result of:
  - a. Pharmacokinetic and pharmacodynamic properties of the drugs
  - b. Intended therapeutic indication
  - c. Both a and b
  - d. Neither a nor b
3. The elderly are subject to a greater risk of ADR and DDIs because:
  - a. Comorbidity
  - b. Alter pharmacokinetics
  - c. Seen by a number of health care providers
  - d. All of the above