

Drug Management in the Elderly Adult With Chronic Kidney Disease: A Review for the Primary Care Physician

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Abstract

With advancing age, the functional reserve of many organs tends to decrease. In particular, the lean body mass, the levels of serum albumin, the blood flow to the liver, and the glomerular filtration rate are reduced in elderly individuals and can be further impaired by the concomitant presence of acute or chronic kidney disease. Moreover, patients with kidney disease are often affected by comorbid processes and are prescribed multiple medications. The aging process also modifies some drug interactions, including the affinity of some drugs for their receptor, the number of receptors, and the cell responses upon receptor activation. Therefore, older patients with kidney disease are particularly susceptible to the risks of adverse drug reactions. Planning a pharmacological regimen in such patients is confounded by the paucity of information available on the pharmacokinetic and pharmacodynamic profiles of a large number of drugs commonly used in this group of patients. Finally, many aged patients suffer from unintentional poor compliance. In this review, the problems physicians face in designing safe and effective medication management in elderly individuals are discussed, paying attention to those more frequently used, which may be potentially harmful in patients with kidney disease. The risks of overdosing and underdosing are outlined, and some recommendations to reduce the risk of adverse drug reactions are provided. A review of the literature covering the field of drug management in older patients with kidney disease was performed by selecting those articles published between January 1, 1990, and December 1, 2014, using PubMed as a search engine with the keywords *elderly, kidney disease, drugs, drug interaction, and renal function*.

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This review primarily addresses issues concerning the use of drugs in older and elderly adults with chronic kidney disease (CKD), the latter defined by current clinical practice guidelines.¹ Chronic kidney disease is most commonly detected in this group of patients by a sustained (>3 months) decrease of less than 60 mL/min per 1.73 m² in estimated glomerular filtration rate (eGFR) with or without abnormal urinalysis or proteinuria. In a substantial fraction of such patients, the decrease in GFR is a consequence of age-related organ senescence rather than intrinsic kidney disease. Nevertheless, a decrease in GFR can have considerable consequences on drug metabolism and excretion and can promote adverse drug reactions (ADRs), particularly in an elderly vulnerable population. Information on drug absorption metabolism and elimination in the elderly population is often lacking. Moreover, elderly patients often

have multiple comorbidities, including diabetes, hypertension, and cardiovascular disease, and are prescribed many different medications, rendering the comprehensive pharmacological assessment of any given agent difficult in these patients. The complexity of the problem is further amplified in patients with CKD and decreased GFR, hypoalbuminemia, or retention of “uremic” solutes, any one of which not only is associated with poor physical performance and frailty but can also alter the pharmacokinetic and pharmacodynamic profiles of many drugs.² Nevertheless, a number of ADRs may be preventable, and careful attention to the altered pharmacokinetic and pharmacodynamic profiles of drugs in elderly patients with CKD can help to improve overall effectiveness. To analyze the problems physicians face with the use of drugs in elderly patients with CKD, we performed an electronic search throughout the PubMed literature for

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ARTICLE HIGHLIGHTS

- The pharmacokinetic and pharmacodynamic profiles of many drugs can be altered in elderly individuals. Little information is available on such changes. Underlying kidney disease is another factor that contributes to low predictability on the effects of drugs in these patients. Because in most cases these abnormalities may result in an increased bioavailability, the initial dose of many drugs in older adults with chronic kidney disease should be set at about half the normal adult dose and then set according to the individual patient's status.
- Both the aging process and kidney diseases can modify drug-drug interactions including the affinity of some drugs for their receptor, the number of receptors, and the cell responses upon receptor activation. Older patients with kidney disease are particularly susceptible to the risks of adverse drug-drug interactions. Because this risk increases with the number of drugs concomitantly used, the number of drugs prescribed should be the lowest possible, carefully balancing their risks and benefits in such patients.
- Drugs that may exert nephrotoxicity or disquieting extrarenal adverse effects should be used with extreme caution in elderly patients with kidney disease. When prescribing drugs to such patients, the clinician should be familiar with the indications and contraindications of a finite list of drugs and try to avoid prescribing new, more unfamiliar ones to avoid running into unpredictable adverse drug reactions.
- Lack of efficacy or adverse events of drugs in older adults are often related to underdosing or overdosing, respectively. Moreover, unintentional poor adherence to prescription is frequent in elderly individuals. To prevent these problems, treatment should be as simple as possible and adherence to prescriptions should be checked frequently.

articles published from January 1, 1990, through December 1, 2014, using the keywords *elderly*, *kidney disease*, *drugs*, *drug interaction*, and *renal function*, selecting the most recent ones.

PHARMACOKINETIC PROFILES

The fraction of an administered drug that reaches the systemic circulation (bioavailability) depends on its absorption, distribution, metabolism, and elimination. These variables are highly dependent on several factors such as the ability of the gut to absorb orally taken

drugs, serum albumin levels, body fat content, and liver and kidney blood flow. Aging is accompanied by modifications in all these parameters. Moreover, with advancing age, the functional reserve of multiple organs decreases progressively. Four physiological variables tend to be reduced in elderly individuals: (1) the lean body mass; (2) the levels of serum albumin; (3) the blood flow to the liver; and (4) kidney function. All these changes can be aggravated by concomitant kidney disease.

Absorption

Drug absorption can be impaired by several conditions that are common in the elderly population, especially those presenting with CKD. These include frequent use of proton pump inhibitors, severe hypoalbuminemia, and gastrointestinal troubles.³⁻⁵ However, the net effect of changes caused by aging and kidney disease on drug absorption varies widely and is difficult to predict.

Distribution

In the elderly population, the ratio of visceral adipose tissue to muscle mass is increased. Accordingly, lipophilic drugs may have an increased volume of distribution and a prolonged half-life. In contrast, age-related decrease in GFR may reduce the elimination of hydrosoluble drugs. Thus, reduced dosages of both lipophilic and hydrophilic drugs are suggested in older patients with CKD.^{6,7} In patients with hypoalbuminemia (such as seen in nephrotic syndrome), drugs that are protein bound circulate free in the plasma at higher percentages, causing an increase in their volume of distribution.⁸ Patients with function impairment and with hypoalbuminemia are usually not affected by increased drug toxicity, and alteration of drug dosage is not required.⁹

Metabolism

The metabolism of most drugs is mainly regulated by the liver. Hepatic metabolism renders lipophilic compounds more hydrophilic so that they can be excreted by the kidneys. The liver also converts inactive drugs to active drugs, and vice versa. Liver mass and perfusion tend to decrease during aging¹⁰ together with its metabolic activity, thus contributing to the increase in the

half-life of lipophilic drugs.¹¹ Cytochrome P450 tests are available to check some gene variations, the most frequently investigated being 2D6, which processes many antidepressants and antipsychotic medications.¹² Other cytochrome P450 tests are available for other enzymes.¹³ Aiming at safe prescription if these tests are not available, the initial dosage of hepatically metabolized drugs should be reduced in older patients with CKD, particularly in those patients with a decrease of less than 30 mL/min in GFR, and then progressively titrated upward.¹⁴

Elimination

Kidneys regulate the elimination of hydrophilic drugs. The GFR decreases steadily at a rate of 0.9 to 1 mL/min per 1.73 m² annually after the age of 30 years and decreases more rapidly after the age of 65 years.^{15,16} Confounding factors such as hypertension, coronary heart disease, congestive heart failure, the use of nephrotoxic drugs, and superimposed kidney disease can contribute to the rate and magnitude of this functional decline. One of the most relevant features of CKD is the accumulation of metabolites of administered drugs, giving rise to a mixture of potentially unknown pharmacological entities whose characteristics are different from those reported for healthy patients.¹⁷

The decreased GFR does not principally affect the volume of distribution of water-soluble, non-protein-bound drugs. Therefore, their initial dose is unchanged in patients with CKD and altered GFR. However, in the case of altered GFR, the interval between dosing must be changed accordingly to maintain safe and effective blood levels. Several approaches are used for dosing interval correction in such patients. One method is based on the predicted changes in drug half-life consequent to decrements in eGFR; other methods use the change in total drug clearance by monitoring plasma drug concentrations over time. For this purpose, GFR is estimated using formulas based on values of serum creatinine, age, sex, and ancestry. At present, 2 formulas based on serum creatinine values are used to estimate GFR: Modification of Diet in Renal Disease and Chronic Kidney Disease Epidemiology Collaboration. Any

instability in serum creatinine levels renders the application of such eGFR formulas to assess the drug dosage rather useless and potentially harmful. These methods are strongly affected by malnutrition, obesity, strict vegetarian diets, concomitant drugs, muscle wasting, aging, and underlying disease.¹⁸ Moreover, these approaches do not consider age-dependent changes in bioavailability, protein binding, or the fate of active metabolites.¹⁹ Ideally, these variables should be considered when prescribing a drug to a geriatric patient. Despite this, no new strategy other than using GFR-based modulation of maintenance dosing has been proposed yet. In elderly individuals, Chronic Kidney Disease Epidemiology Collaboration—based estimates of eGFR outperformed Modification of Diet in Renal Disease—based estimates of eGFR and as a predictor of ADRs.²⁰

PHARMACODYNAMIC PROFILES

The physiological effects of a given drug depend on the interactions between the drug and its receptor. The pharmacodynamic profiles of a drug reflect the relationship between the drug concentration at the receptor site and its pharmacological response. The aging process may modify the affinity of some drugs for their receptor, the number of receptors per cell, and the cellular responses upon receptor activation. The net result of these modifications is practically impossible to anticipate, but should be taken into account when using some drugs in older patients²¹ because the risk of adverse effects is greater. For example, elderly persons have a reduced cardiovascular reserve and may be less tolerant to the introduction of a vasodilating α -adrenoceptor. Angiotensin-converting enzyme inhibitors (ACEis) do not show such age-related differences.²² Dihydropyridine calcium channel blockers (CCBs) usually show increased effects in elderly individuals, such as gingival hypertrophy and peripheral edema.²³ The reduced elimination of digoxin by the kidney may place aged patients with CKD at increased risk of adverse effects including sinoatrial block, tachycardia, and ventricular fibrillation.²⁴ The central nervous system is particularly vulnerable in elderly individuals. Agents that affect brain function

TABLE 1. Drug-to-Drug Interactions and Adverse Events in Older Patients With Renal Function Impairment

Drug-to-drug interaction	Adverse events
Two or more renin-angiotensin-aldosterone inhibitors	Hyperkalemia, hypotension, and increase in serum creatinine
Renin-angiotensin inhibitors and aldosterone antagonist	Hyperkalemia, gynecomastia, and increase in serum creatinine
Trimethoprim-sulfamethoxazole and renin-angiotensin-aldosterone inhibitor	Hyperkalemia
Trimethoprim-sulfamethoxazole and phenytoin	Phenytoin intoxication
CNI plus azoles, macrolides, calcium channel antagonists, or grapefruit juice	Increased serum levels and toxicity of CNI (nephrotoxicity, hypertension, etc)
Clarithromycin and statins	Myopathy
Clarithromycin and calcium channel blockers	Bradycardia, shock, heart block, and multiorgan failure
Clarithromycin and digoxin	Strong increase in digoxin cardiac and neurological toxicity
Trimethoprim-sulfamethoxazole or amiodarone and warfarin	Increase in warfarin effect
Oral phosphate binders	Calcium accumulation; decreased absorption of other drugs
ACEis and lithium	Acute kidney injury in 1.5/100 persons per year.
Thiazides and loop diuretics	Hyponatremia and hypokalemia
CNI plus rifampicin or anticonvulsant	Decreased serum levels of CNI

ACEi = angiotensin-converting enzyme inhibitor; CNI = calcineurin inhibitor.

(anesthetic, opioid, anticonvulsant, psychotropic, and sedative hypnotic drugs) should be used cautiously in this age group. Chronic kidney disease is another factor predisposing to adverse effects when prescribing potentially neurotoxic drugs.²⁵

DRUG INTERACTIONS

Adverse events are common in older patients treated with polypharmacy and represent a frequent cause of morbidity and hospitalization. A meta-analysis found a 4-fold increase in the rate of hospitalization related to ADRs in older adults compared with younger adults. However, most adverse events were dose related and potentially avoidable.²⁶ The incidence of ADRs correlates exponentially with renal function impairment.²⁷ However, very few drugs and clinical interventions have been well studied in older adults with CKD. Recognizing whether some symptoms are related to aging or to adverse effects of drugs

can be difficult because many drug-related adverse effects resemble symptoms of disorders common in elderly patients with CKD. This may lead to misinterpretation and useless prescription of new drugs that may cause additional adverse effects. In this regard, attempts were made to create assessment scales for the risk of drug-drug interactions and ADRs in hospitalized patients with CKD.²⁸ In addition, many hospital admissions of elderly patients for drug toxicity occur after the administration of a drug known to cause interactions. An example of pharmacodynamic additive interactions is simultaneous administration of simvastatin and amlodipine; this combination increases the blood levels of simvastatin, leading to a higher risk of hepatotoxicity and rhabdomyolysis.²⁹ Pharmacokinetic interactions are usually the most prominent. Many cytochrome P450 isoenzymes can be inhibited by macrolide antibiotics, azole antifungal agents, and CCBs, thus increasing relative drug blood concentrations and the risk of adverse reactions. Instead, rifampicin, rifabutin, and anticonvulsant drugs can induce enzymatic activity and reduce blood concentrations of other drugs. Although it is hardly possible to memorize thousands of such drug-drug interactions and their clinical significance, the practitioner should be aware of the most common and dangerous interactions, especially those that are most applicable to older patients with CKD (Table 1). Computer programs available in pharmacies can also often detect important potential drug-drug interactions in cases of polypharmacy. However, it has been pointed out that precise, up-to-date, and evidence-based information on dose adjustment regimens for drugs commonly prescribed in patients with different levels of CKD is hard to find, is often unsupported by the policymakers,³⁰ and, according to some authors, is not sufficient to prevent ADRs.³¹

INAPPROPRIATE MEDICATIONS IN ELDERLY PATIENTS

Some drug categories pose special risks for elderly patients. The Beers criteria provide a list of medications whose potential risks outweigh their benefits when used in older adults.³² These drugs are divided into 3 groups,

although some overlap exists between categories. The first group includes 110 medications to avoid in older adults because they can generate life-threatening complications and other adverse events. If a clinician cannot find an alternative, designation of the medication as potentially inappropriate can serve as a reminder for close monitoring. The drugs are divided into 8 categories: anticholinergic agents (antihistamine, antispasmodic, and antiparkinson drugs), antithrombotic drugs, antibacterial drugs, cardiovascular agents (α -blockers, antiarrhythmic drugs, digoxin, and spironolactone at inappropriate dosage), central nervous system drugs (tertiary tricyclic antidepressants, antipsychotic agents, hypnotic drugs, and benzodiazepines), endocrine agents, gastrointestinal drugs, and analgesic drugs. The second group includes medications that can exacerbate certain diseases and syndromes. In heart disease, nonsteroidal anti-inflammatory drugs (NSAIDs), non-dihydropyridine CCBs, and antidiabetic glitazones may promote fluid retention and exacerbate heart failure. Anticholinergic drugs, peripheral α -blockers, β -adrenergic blockers, and tertiary tricyclic antidepressants can increase the risk of bradycardia and orthostatic hypotension. In central nervous system diseases, antiepilepsy drugs, tricyclic antidepressants, and antipsychotic agents can worsen the behavioral problems and may increase the risk of stroke. In gastrointestinal diseases, non-dihydropyridine CCBs, anticholinergic drugs, and antihistamine drugs can worsen chronic constipation. Aspirin may favor the development of gastric or duodenal ulcers. In kidney diseases, these adverse events can be more frequent and severe. The third group consists of medications to be used with caution in older adults, including aspirin, antipsychotic vasodilators, and dabigatran in patients with CKD stages 4 and 5. Screening Tool of Older Persons' Prescriptions and Screening Tool to Alert doctors to Right Treatment are 2 further validated criterion-based instruments. Screening Tool of Older Persons' Prescriptions measures potentially inappropriate medications; it is composed of 65 clinically significant criteria for potentially inappropriate drugs to avoid in older people. Each criterion is accompanied by a concise explanation as to why the prescribing practice is

TABLE 2. Medications to Use With Extreme Caution in Elderly Patients With Kidney Disease

Medication	Adverse events
Nitrofurantoin	Pulmonary toxicity; do not use if eGFR <30 mL/min
α -Adrenergic inhibitors	Bradycardia and orthostatic hypotension
Antiarrhythmic drugs (amiodarone, propafenone, sotalol, quinidine, and dronedarone)	Thyroid disease, pulmonary disorders, and QT interval prolongation
Nifedipine (immediate release)	Risk of hypotension and cerebral or myocardial ischemia
Spironolactone and triamterene	Hyperkalemia; cautious if eGFR <30 mL/min
NSAIDs, nondihydropyridine CCBs, antidiabetic glitazones	Fluid retention
Quinolones	Tendinitis; acute kidney injury
Aminoglycosides	Nephrotoxicity; otovestibular toxicity
Metformin	Risk of lactic acidosis if eGFR <30 mL/min
Potassium-sparing diuretics	Hyperkalemia
Azathioprine	Bone marrow suppression and leukopenia
Digoxin	In patients with low eGFR, dosages >0.125 mg/d are associated with an increased risk of toxicity
Vitamin C	Organ accumulation of insoluble oxalate
Vitamin A	Increased serum levels of RBP4 and apoRBP4
PPIs	Increased risk of fractures, infections, and cognitive decline; hypomagnesemia

CCB = calcium channel blocker; NSAID = nonsteroidal anti-inflammatory drug; PPI = proton pump inhibitor; RBP4 = retinol binding protein 4.

potentially inappropriate. Screening Tool to Alert doctors to Right Treatment measures potential prescribing omission. It consists of 22 evidence-based prescribing indicators for commonly encountered diseases in older people.³³ It is unclear whether these interventions can improve appropriate polypharmacy compared with Beers criteria.³⁴

SPECIFIC ISSUES IN OLDER ADULTS WITH KIDNEY DISEASE

A number of drugs frequently used in older patients with CKD may raise specific problems (Table 2).

Renin-Angiotensin-Aldosterone Antagonists

These drugs may increase the serum level of potassium and can decrease the GFR. These effects are particularly pronounced in patients with renal artery or intraparenchymal vascular occlusive disease, 2 conditions relatively frequent in older patients. A meta-analysis

revealed that therapy with ACEis and angiotensin-receptor blockers increased the risk of hyperkalemia, hypotension, and renal failure compared with monotherapy.³⁵ The addition of an aldosterone receptor antagonist can further increase hyperkalemia and serum creatinine and cause gynecomastia in patients with cardiac failure.³⁶ Thus, these agents should be used with caution in older individuals, although they may be of significant benefit in hypertensive patients with proteinuria. In patients with hyperkalemia who need to continue treatment with renin-angiotensin antagonists, regular administration of loop diuretics may be helpful. Potassium-sodium ion-exchange resins are often suggested, although cases of gastrointestinal necrosis have been reported with their use.³⁷ To prevent constipation due to these resins, concomitant sorbitol administration may be suggested. Diphenolic laxatives that induce secretory diarrhea are more effective and may also increase the gastrointestinal excretion of K⁺.³⁸ Sodium zirconium cyclosilicate is a new effective selective cation exchanger used to treat hyperkalemia.³⁹

Aminoglycosides

Both advanced age and decreased eGFR have long been held to be important risk factors in the development of aminoglycoside-related renal and otovestibular toxicity. The loading dose of aminoglycosides does not require adjustments, but it may be prudent to reduce it by 25% because cases of toxicity have been reported after a single dose of gentamicin. These antibiotics are primarily eliminated unchanged through the kidneys, and after the first dose their administration should be modified in older patients with CKD. Dosage modification may be accomplished by dose reduction or dosing interval prolongation (the most used method). The limitations of these methods have been discussed. In clinical practice, therapeutic drug monitoring is helpful. Peak and trough levels should be checked at least twice a week or even more frequently in the case of instability of renal function. Symptoms and signs of toxicity (fullness in ears, hearing loss, and dizziness or vertigo) and kidney function should be monitored. The likelihood of toxicity increases with

increasing duration of the administration of the drug.⁴⁰

Glycopeptides

Severe ototoxicity and nephrotoxicity have been reported with the use of vancomycin. Although the newer glycopeptides seem to be better tolerated, monitoring of their serum levels should be undertaken to prevent adverse effects.⁴¹

Quinolones

Quinolones are excreted by the kidney, and their dosage should be adjusted according to eGFR. In the elderly population, quinolones may cause confusion, weakness, tremor, or depression. Quinolones may cause QT interval prolongation and should be used with caution in patients with known prolongation of the QT interval, hypokalemia, or hypomagnesemia. Tendinitis and tendon ruptures can occur during treatment or months after treatment.⁴² Last but not least, both older and newer fluoroquinolones may rarely cause acute interstitial nephritis or oliguric acute kidney injury.⁴³

Trimethoprim-Sulfamethoxazole

This antimicrobial may cause rash, fever, neutropenia, thrombocytopenia, and transaminase elevation. Moreover, trimethoprim competes with creatinine for secretion in the renal tubules. Apart from the resulting increase in serum creatinine and the artifactual decrease in eGFR, cases of true acute kidney injury have been reported.⁴⁴ In older patients treated with ACEIs, the use of trimethoprim-sulfamethoxazole increased the risk of hyperkalemia-associated hospitalization relative to other antibiotics.⁴⁵ In older patients receiving phenytoin, trimethoprim-sulfamethoxazole inhibited the hepatic metabolism of phenytoin and increased the risk of phenytoin toxicity.⁴⁶

Macrolides

Clarithromycin and erythromycin (but not azithromycin) strongly inhibit cytochrome P450 isoenzyme 3A4 and can lead to the accumulation of CCBs, which are metabolized by the same isoenzyme. Bradycardia, shock, heart block, and multiorgan failure have been reported in older patients in whom these drugs were given concomitantly.⁴⁷ The interference

with cytochrome 3A4 can also favor the development of myopathy in patients taking statins.⁴⁸ Macrolides may increase the risk of cardiac and neurological intoxication. In patients with heart failure, this risk could be as high as 55.4-fold.⁴⁹

Oral Anticoagulants

Many older adults with kidney disease require oral anticoagulation therapy. Warfarin is metabolized by cytochrome 2C9. Drugs such as trimethoprim-sulfamethoxazole and amiodarone can inhibit the cytochrome 2C9 pathway and increase the anticoagulant effect of warfarin, whereas rifampicin, carbamazepine, and barbiturates have the opposite effect. Antiplatelet agents and NSAIDs do not interfere with warfarin pharmacokinetic profiles but can increase the risk of bleeding. The association of NSAIDs and oral anticoagulants with elderly individuals increases nearly 13-fold the risk of hemorrhagic peptic ulcers.⁵⁰ Warfarin therapy may be complicated by acute kidney injury caused by obstruction of the renal tubule by red blood cell casts. Renal insufficiency and age are 2 important risk factors for this warfarin-induced nephropathy.⁵¹

Calcium Supplementation

Calcium salts are frequently used as antacids by elderly patients and are often prescribed to prevent osteopenia or to correct hyperphosphatemia in patients with advanced kidney failure. These agents may cause bowel obstruction and may reduce the absorption of other drugs. Their long-term use may also cause vascular calcifications. The calcium intake should not exceed 1 g/d.⁵²

Lithium

Lithium use can cause acute or chronic kidney failure and nephrogenic diabetes insipidus, particularly in older adults. In a systematic review of renal adverse effects of lithium in older patients, the incidence of acute kidney injury was found to be 1.5% per person-year and concurrent loop diuretic and ACEi use increased this risk. The prevalence of chronic kidney failure varied from 1.2% to 34%. Risk factors included age, previous lithium intoxication, polyuria, previously impaired renal function, and decreased maximal urine

osmolality. The prevalence of nephrogenic diabetes insipidus varied widely from 1.8% to 85%. Risk factors included lithium treatment duration, dose, level, slow-release formulation, and clinical nonresponse.⁵³ In addition to older age, the main risk factor for impaired kidney function is the duration of lithium treatment. Compared with age-matched patients who were never treated with lithium, those who received lithium had a mean decrease of 0.64 mL/min per 1.73 m² in eGFR for each year of treatment.⁵⁴ Renal cancer is also significantly higher in lithium-treated patients. In a study, the standardized incidence ratio of cancer was about 7.5 in men and about 13.7 in women treated with lithium in comparison with untreated controls.⁵⁵ Although there is no compelling evidence to suggest that lithium should be avoided in elderly patients for fear of kidney ADRs, a word of caution is needed when using loop diuretics or renin-angiotensin inhibitors in older patients treated with lithium.

Antihyperglycemic Drugs

Antihyperglycemic drugs should be titrated carefully in older diabetic adults with CKD. The risk of hypoglycemia due to sulfonylureas increases with age.⁵⁶ Also, second-generation sulfonylureas, glyburide and glipizide, are associated with a significant risk of hypoglycemia because their renal clearance is reduced.⁵⁷ Metformin is normally excreted by the kidneys. The risk of lactic acidosis, a rare but serious complication, increases proportionally with the degree of renal impairment and with patient age.⁵⁸ The current label prescribes metformin use at or above serum creatinine levels of 1.4 mg/dL in women and 1.5 mg/dL in men (to convert to mmol/L, multiply by 0.0259). However, a consensus statement of the American Diabetes Association and European Association for the Study of Diabetes reported that metformin can be considered safe unless eGFR decreases below 30 mL/min.⁵⁹ Sodium glucose cotransporter type 2 inhibitors are well tolerated by older patients and are an attractive option for patients who are not well controlled with metformin,⁶⁰ but should be used with caution in patients with low eGFR.

Antihypertensive Drugs

These medications should be started at low doses in elderly patients because their use may also be associated with an increased risk of falls.⁶¹ However, for most older hypertensive patients, multidrug therapy with standard or even high doses may be needed to obtain a satisfactory control of blood pressure. β -Blockers should be used with caution in patients older than 60 years, although they may lower the risk of cardiac events in patients with new coronary disease after myocardial infarction.⁶² A meta-analysis revealed that atenolol is associated with increased stroke in the elderly population; however, whether this extends to nonatenolol, β -blockers remains uncertain.⁶³ Although a meta-analysis supported the safety of extended-release nifedipine of mild or moderate hypertension when it was used in combination with other drugs,⁶⁴ other studies warned against the use of short-acting nifedipine in elderly hypertensive patients because it was associated with increased risk of stroke.⁶⁵ Thus, immediate-release nifedipine is on the list of drugs that should not be given to elderly patients. Benidipine, a T-type CCB, in combination with olmesartan, reduced proteinuria in elderly hypertensive patients with CKD.⁶⁶ Apart from the risk of hyperkalemia and potential interference with other drugs (see above), ACEis and angiotensin receptor blockers are well tolerated in older patients (but not both simultaneously) and may reduce the risk of cardiovascular events. Sitting and standing blood pressure should be monitored to check for orthostatic hypotension, particularly when multiple antihypertensive agents are used.

Diuretics

Low doses of thiazide can control hypertension in many elderly patients. Although at low doses the risk of hypokalemia and hyponatremia is modest, serum potassium and sodium levels should be checked regularly. It is commonly assumed that thiazides are ineffective when GFR is less than 30 mL/min; however, they may potentiate the effects of loop diuretics (eg, furosemide) even in patients with advanced renal failure.⁶⁷ Potassium-sparing diuretics should be

used with caution, particularly when the aged patient has impaired kidney function.

Statins

Statins are often used in older patients with CKD, because mixed dyslipidemic profiles are frequent in this group of patients.⁶⁸ Statins help reduce proteinuria, suppress oxidative stress, and improve endothelial function in CKD.⁶⁹ Reduction in low-density lipoprotein cholesterol with simvastatin 20 mg plus ezetimibe 10 mg daily safely reduced the incidence of major atherosclerotic events in patients with advanced CKD.⁷⁰ A systematic review reported that statins consistently lower death and major cardiovascular events by 20% in people with CKD not requiring dialysis. Statin-related effects on stroke and kidney function were found to be uncertain.⁷¹ These drugs should be used with caution in patients older than 85 years because adverse effects of statins in elderly patients are incompletely understood; a mild but significant risk of diabetes has been reported in older patients taking statins at high dose.⁷²

Nonsteroidal Anti-Inflammatory Drugs

Nonsteroidal anti-inflammatory drugs are among the most frequently inappropriately used drugs in patients with CKD who are older than 65 years.⁷³ By blocking prostaglandin synthesis, NSAIDs can lead to renal vasoconstriction and reversible reduction of kidney function.⁷⁴ This risk is increased if diuretics or ACEis are concomitantly used.⁷⁵ Nonsteroidal anti-inflammatory drugs can also cause interstitial nephritis in association with nephrotic syndrome.⁷⁶

Analgesic Drugs

Paracetamol is considered a safe and effective analgesic recommended as a drug of choice for mild and moderate pain in elderly patients.⁷⁷

Glucocorticoids

No guidelines about the use of glucocorticoids in elderly patients are currently available. Their adverse effects are numerous and mainly depend on the daily dosage and on the duration of administration. A few general recommendations may be suggested (Table 3).

TABLE 3. Precautions to Prevent or Reduce the Adverse Events of Glucocorticoids in Elderly Patients with Kidney Disease

- Use short-term acting agents (prednisone or prednisolone)
- Give the entire daily dose in a single morning administration during or after breakfast between 6 and 8 AM, or even earlier, to mimic the circadian rhythm of cortisol
- Whenever possible, use alternate-day administration regimens
- Advise low-calorie intake to prevent hyperlipidemia, diabetes, and obesity
- Advise low-salt intake to prevent hypertension and edemas
- Advise physical activity to prevent myopathy, osteopenia, and obesity
- After prolonged therapy, glucocorticoids should not be discontinued abruptly but should be tapered off gradually

Immunosuppressive Drugs

Azathioprine and mycophenolate salts are used in small-vessel vasculitis, primary or secondary glomerulonephritis, and transplantation. In elderly patients with CKD, the dosage of azathioprine should be reduced (no more than 1-2 mg/kg per day) because the bone marrow of these patients is more vulnerable to the toxic effects of the drug. Azathioprine has an oncogenic risk, particularly when patients are treated in the long term. Data on the carcinogenic effects of mycophenolate salts are conflicting. By increasing immunosuppression, these agents may favor the development of neoplasias. In a large prospective study, mycophenolate mofetil was not associated with an increased risk of neoplasms postrenal transplant.⁷⁸ However, mycophenolate salts may be associated with dose-dependent increased risk of hematological and gastrointestinal adverse effects. As a good rule, in aged patients receiving mycophenolate, the blood levels and the area under the curve of mycophenolic acid should be monitored periodically. Calcineurin inhibitors (CNIs) are used in organ transplantation and in primary glomerulonephritis, systemic lupus erythematosus, and renal vasculitis. These drugs have a narrow therapeutic index, and their use can be associated with a number of adverse events including hypertension, diabetes, hyperkalemia, and neurologic and esthetic complications, such as hypertrichosis and gingival hyperplasia. The most worrying complication of CNI is nephrotoxicity, especially in older patients.⁷⁹ Cyclosporine and tacrolimus have distinct pharmacokinetic profiles, but both are metabolized by intestinal and hepatic cytochrome P3A4/3A5 and transported across the cell membrane by

P-glycoprotein. An age-related 34% decrease in the total body clearance of cyclosporine was observed in renal transplant recipients older than 65 years compared with younger patients; older recipients also had 44% higher intracellular lymphocyte cyclosporine concentrations.⁸⁰ The concomitant use of azoles, macrolides, calcium channel antagonists, and grapefruit juice can increase the blood levels of CNI, whereas rifampicin and anticonvulsant drugs can reduce them.

Vitamins

Hydrosoluble vitamin C is normally excreted in the urine. In patients with renal failure, high doses of vitamin C should be avoided because it is retained and converted to insoluble oxalate that accumulates in multiple organs.⁸¹ The kidneys are also essential for the metabolism of vitamin A (retinol) and its transport protein retinol-binding protein 4 (RBP4) and transthyretin. Excess of retinol and RBP4 may increase the risk of cardiovascular disease in elderly patients.⁸² Even a moderate reduction of kidney function may result in an imbalance of components of vitamin A metabolism with a significant increase in retinol, RBP4, and apoRBP4 concentration in serum.⁸³ In contrast, patients with CKD have a deficiency of active vitamin D owing to the insufficient activity of α -hydroxylase enzyme, normally found in healthy renal proximal tubular cells.⁸⁴

Proton Pump Inhibitors

Proton pump inhibitors are widely prescribed in the elderly population. However, proton pump inhibitors overuse may be dangerous when they are used for long term in elderly patients with CKD. The main risks include fractures,⁸⁵ enteric infections,⁸⁶ decrement in

physical and cognitive functioning,⁸⁷ hypomagnesemia,⁸⁸ and acute kidney injury.⁸⁹

Selective Serotonin Reuptake Inhibitors

These psychotropic agents are often used in elderly patients. Apart from some psychological and gastrointestinal adverse effects, selective serotonin reuptake inhibitors (SSRIs) may cause hyponatremia associated with severe morbidity, especially in older adults with CKD.^{90,91} The current data suggest that pharmacokinetic profiles of fluoxetine and sertraline do not change in the setting of CKD, whereas the daily dose of paroxetine should be reduced by 50% in stage 5 CKD and the above-mentioned SSRIs should be used with caution in renal transplant recipients who are treated with CNIs. Furthermore, it has been shown that patients undergoing peritoneal dialysis are particularly susceptible to the adverse effects of SSRIs.⁹²

OVERDOSING

Older patients with CKD and taking multiple drugs are more susceptible to severe and even fatal adverse events.⁹³ Unfortunately, the use of eGFR to calibrate drug dosing and frequency in elderly patients is problematic because equations using serum creatinine can seriously overestimate true GFR in elderly patients because of concomitant sarcopenia. The use of Berlin Initiative Study equations,⁹⁴ GFR-cystatin C + creatinine, or measurement of true GFR by plasma iohexol disappearance may at least in part obviate this problem. The initial doses of medicaments should be lower in older adults, because starting with full doses increases the risk of overdosing and related adverse events. Moreover, deliberate drug overdose is one of the preferred and commonest methods of suicide in elderly patients.⁹⁵

UNDERDOSING

Aged patients are also susceptible to undermedication. The initial doses of many drugs are intentionally reduced in elderly persons to prevent the development of ADRs. Moreover, many older patients unintentionally use dosages that are too low, contributing to increased hospital readmissions, morbidity, and mortality.

ADHERENCE TO PRESCRIPTIONS

Poor adherence to prescriptions is a common problem in elderly individuals. A main barrier to adherence is mainly represented by

polypharmacy. A review of studies reported that compliance decreased as the number of prescribed drugs increased.⁹⁶ It has been reported that 91% of older adults regularly use 1 prescription drug and more than 50% use 5 or more prescriptions per day.⁹⁷ The number of drugs further increase in patients with CKD so that the overall incidence of ADRs is 3- to 10-fold higher in older adults with kidney disease than in those without CKD.⁹⁸ New-onset ADRs could also be mistaken by health care professionals as a new-onset disease or morbidity related to aging. Dementia is another condition that predisposes to poor adherence: older patients often forget to take medications, and the greater the number of drugs to take, the higher the risk of forgetfulness. Moreover, changes in the dosage or type of medications can often be misunderstood. These problems outline how a thorough assessment of cognitive functions should be sought in the evaluation of elderly patients. To complicate matters further, elderly patients often take over-the-counter dietary supplements and herbal medications that can produce drug interactions. Medication therapy management services provided by pharmacists and other health care professionals are tools that may be used to improve adherence.

CONCLUSION

Designing a good pharmacological regimen in aged patients with CKD is challenging because little information is available on the aging-related changes in pharmacokinetic and pharmacodynamic profiles of a number of drugs, especially of those that have a narrow therapeutic index. Another issue is represented by unintentional poor compliance to treatment regimens. Although it is difficult to provide generic recommendations for the use of drugs in older patients with CKD, some measures may be taken to reduce the risk of adverse events: (1) according to the axiom "start low, go slow," the initial dosage of many drugs should be set at about half the normal adult dose, except in life-threatening emergencies; (2) the physician should use a limited number of drugs and be familiar with the indications and contraindications in elderly patients; (3) treatment should be as simple as possible, and the number of doses per day should be as small as possible; (4) at any follow-up visit,

patients should be asked to list the drugs they are taking (including those obtained over the counter), the time of dosing, and any adverse event they may complain of; (5) serum creatinine and eGFR should be regularly checked; (6) good communication between the caregiver and the patient is crucial, and prescribers should develop an effective therapeutic partnership with the patient.

Abbreviations and Acronyms: ACEi = angiotensin-converting enzyme inhibitor; **ADR** = adverse drug reaction; **CCB** = calcium channel blocker; **CKD** = chronic kidney disease; **CNI** = calcineurin inhibitor; **eGFR** = estimated glomerular filtration rate; **GFR** = glomerular filtration rate; **NSAID** = nonsteroidal anti-inflammatory drug; **RBP4** = retinol-binding protein 4; **SSRI** = selective serotonin reuptake inhibitor

Potential Competing Interests: Dr Ponticelli was a consultant for Novartis Italy until December 2011. In the past 2 years, he received honoraria from Novartis, Janssen-Cilag, and Astellas. Dr Glasscock is a Consultant/Advisor to AbbVie, Astellas, Bristol-Myers Squibb, Chemocentryx, Eli Lilly, Genentech-Roche, Mitsubishi-Tanabe, Novartis, QuestCor (Maillinkrodt), and Sanofi-Genzyme. He also serves on the Speakers Bureau for Genentech-Roche and receives Honoraria for Editorial services to the American Society of Nephrology, UpToDate, and Karger Publishers. He owns stock in REATA, Inc.

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