29 Drug Prescription in Chronic Kidney Disease

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Before You Start: Facts You Need to Remember

- Every patient is unique and needs an individualized approach. Thus, every patient has his/her own side-effect profile with medications.
- If you do not have to prescribe a drug, you do not have to. Be conservative.
- Prefer to decrease medication pill count which helps to increase adherence and decrease drug–drug interactions.
- Kidney function tests must be reevaluated regularly to avoid medication problems related to chronic comorbid diseases.
- Primary care physicians, caregivers, and patients themselves should be careful about clinical changes that would result in new coming side effects.

29.1 Difficulties Related to Drug Prescription in CKD

Safe medication use in CKD is a complex process (Fig. 29.1). Patient and drug metabolism related differences make this complexity progress. There are two key factors influencing drug prescription in patients with CKD, multimorbidity and development and treatment of CKD-related complications. Determination of kidney function and changes in pharmacodynamics and pharmacokinetics of drugs as kidney function declines are other factors of this complexity.

29.1.1 Multimorbidity in CKD

Multimorbidity, the co-occurrence of two or more chronic diseases, is a condition that affects up to 95% of patients with CKD [1]. According to a study of Lifeline group patients (n = 2742) multimorbidity was present in 83.3% of the CKD patients [2]. The most common comorbidities are diabetes, hypertension, cardiovascular diseases, cerebrovascular diseases, painful conditions, anemia, dementia, and thyroid disorders [1]. Even hospitalization rates in CKD patients are 2–3 times higher in those with multimorbidity [3].

Multimorbidity patterns across the CKD stages are also important. Hawthorne et al. published in their study that the two most prevalent comorbidities across all stages were hypertension (55%) and musculoskeletal disorders (40%). For stages 1–2, the most prevalent comorbidity was lung conditions (33.9%). For stages 3–5 the third most prevalent comorbidity was heart problems (35.1%, 40.3%, and 26.1%, respectively) [4].

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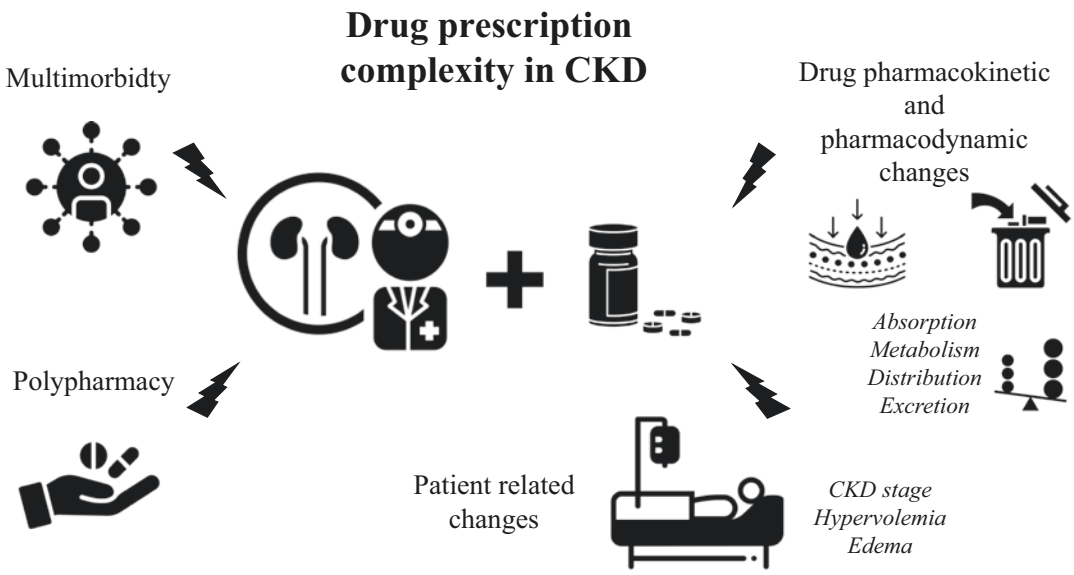

Fig. 29.1 Drug prescription complexity in Chronic Kidney Disease

Multimorbidity in CKD increases complexity with treatment medication regimens and self-management strategies. Multiple healthcare professionals are involved with these accompanying comorbidities resulting in medication accumulation and adverse medication events in CKD patients. As a result, to prevent polypharmacy shared decision-making and patient-centered approaches are necessary for this patient population [4, 5].

29.1.2 Polypharmacy and CKD

Polypharmacy is defined as taking five or more medications regularly and can increase the risk of drug and drug interactions, high medication doses, complex medication regimens, medication costs, medication non-adherence, and lower quality of life [6]. In the German CKD study, it was published that the prevalence of polypharmacy was almost 80%, ranging from 62% in patients with CKD Stage 1–86% in those with CKD Stage 3b with a mean of eight drugs (0–27) [7]. Polypharmacy is also associated with adverse outcomes which were documented in the Fukushima CKD Cohort Study. In the study, the use of more than five medications was associated with a high risk of kidney failure, cardiovascular events, and all-cause mortality in nondialysis-dependent CKD patients [8].

The most frequently prescribed medications are antihypertensives and lipid-lowering medications which are followed by diuretics, platelet aggregation inhibitors, and urate-lowering therapy [9]. According to an Australian study, 35% of CKD patients have been prescribed at least one potentially inappropriate medication [10].

29.1.3 Screening, Monitoring, and Managing CKD

Chronic kidney disease which is defined as decreased glomerular filtration rate (GFR) is generally associated with inappropriately adjusted drug doses. In CKD patients, according to the severity of the disease drug concentrations can increase ending with adverse drug reactions or unnecessary decreases in dosage may result in undertreatment. Even nonessential changes to an alternate drug with a lower efficacy are not rare.

In CKD patients not only decreased GFR affects, but proteinuria, hypoalbuminemia, or

hypervolemia also affects medication pharmacokinetics [11]. Hypervolemia most likely affects hydrophilic drugs rather than lipophilic drugs [12].

In patients with kidney diseases, the dosing of medications must be adjusted regarding actual GFR. In the past Cockcroft–Gault equation, creatinine clearance, and modification of Diet in Renal Diseases (MDRD) formula were used by physicians for GFR assessment [13]. Recently, CKD-EPI (named after the Chronic Kidney Disease Epidemiology Collaborative) formula is used for this purpose [14]. But there is not any consensus as to which method better estimate proper GFR values. The Cockroft–Gault equation is still most often used for estimating GFR in pharmacokinetic studies and for drug dosage adjustment, although some studies have shown the MDRD Study equations to be more accurate for estimating GFR [15, 16].

29.2 Changes in Pharmacokinetics of Drugs in CKD

Pharmacokinetics examines how the drug is absorbed, distributed, metabolized, and excreted by the body. The concentration-time profile of a drug reflects the net effects of these pharmacokinetic processes after drug administration. In general, high drug exposures increase the risk of adverse drug reactions, and low drug exposures are ineffective [13]. In CKD, both have negative effects on patient outcomes including treatment failures or amplified toxic side effects, especially with narrow therapeutic index drugs [12].

In general, during the development phase of drugs, dosing regimens are determined by normal or mildly affected kidney function. This results in limited pharmacokinetic data on drugs in patients with advanced kidney diseases. Limited data guide manufacturers to declare drug contraindications in patients with eGFR<30 mL/min/1.73 m^2 in the post-marketing phase [13, 17]. As a result, this patient group has been deprived of important drug options.

The dosing principles of a drug consist of the initial dose, maintenance dose, and dose frequency. Beyond this, in CKD patients therapeutic drug monitoring (TDM) should be performed for a good safety profile [12]. TDM is also associated with clinical targets related to a prescribed drug. For antidiabetics monitoring plasma glucose levels, for antibiotics targeting minimum inhibitory concentrations with infection control, for immunosuppressives targeting the drug blood trough levels determined by clinical trials are some examples.

In patients with CKD, the initial dose or loading dose does not differ regarding achieving a target first-dose serum concentration. Because rather than changes in drug clearance, a long half-time of the drug is more important to determine the target drug concentration [18]. Conversely, a high initial dose might be necessary in case of expanded volume of distribution (Vd) in nephrotic syndrome or changes in binding patterns of drugs to plasma proteins in hypoalbuminemia [19]. For drugs with highly lipophilic properties, the actual body weight should replace the ideal body weight [20].

In contrast to the initial dose, the maintenance dose depends on clearance and affects dose frequency. In general, rather than decreasing the frequency, a dose reduction is preferred according to the toxicity profile of the drug in CKD patients [21]. Dosing reduction may provide for more constant drug levels but increases the risk of toxicity from higher plasma trough concentrations [20]. Some antibiotics are the exception to this rule where high peak serum concentrations are beneficial [12].

For medication with a narrow therapeutic index, TDM can be beneficial despite dosage adjustments according to estimated GFR. TDM generally helps clinicians to minimize toxicities. But toxicity and adverse drug reaction may occur despite appropriate plasma drug concentration. For example, despite proper plasma concentration levels, concomitant administration of vancomycin and an aminoglycoside can increase the risk for nephrotoxicity of both agents [18, 22].

The knowledge about the properties of drugs, pharmacokinetic principles, and patient-specific conditions results in a rational approach to prescribing drugs. Here are sample examples of drugs that have special considerations to be used for patients with kidney diseases and changes in their pharmacokinetics.

29.2.1 Effects of Kidney Diseases on the Absorption Process

In clinical studies absorption of a drug is generally assessed by measuring the time at which the maximum plasma concentration occurs (Tmax). Absolute bioavailability (F) is assessed by comparing the area under the plasma drug concentration-time curve (AUC) following the oral and intravascular route [22, 23]. But these parameters are disregarded in patients with kidney problems. And the extent of absorption from the gastrointestinal tract is also not studied in detail in these patients. Tmax changes may be prolonged because of reduced gastric emptying or decreased intestinal absorption. Associated comorbidities have combined effects on various aspects of drug absorption in this way. Gastroparesis, uremia-induced vomiting, and edematous gastrointestinal tract all decrease oral bioavailability. For example, for similar diuretic effects, increased dose adjustment is necessary if gut edema is prominent in congestive heart failure or cirrhosis [24]. Gastroparesis might be important for some drugs such as short-acting sulfonylureas [25].

Concomitant administration of medications in kidney diseases can alter the absorption in several ways too. Phosphate binders and histamine 2-receptor antagonists can change gastric pH, altering medication absorption [26]. The best examples are furosemide, ketoconazole, and ferrous sulfate which are best absorbed in an acidic environment [27]. On the contrary, the administration of magnesium hydroxide and sodium bicarbonate can enhance the absorption of some weakly acidic molecules (e.g., ibuprofen, glipizide, glyburide, tolbutamide) by increasing their water solubility. Also, the ingestion of cation-containing antacids (e.g., calcium, magnesium), aluminum hydroxide, sodium polystyrene sulfonate, and iron may reduce drug absorption because of chelation with other medications. Fluoroquinolones and tetracyclines are antibiotics that are highly susceptible to chelate formation in patients with CKD [21, 23, 24].

29.2.2 Effects of Kidney Diseases on the Distribution Process

In CKD patients, alterations in the protein and tissue binding are associated with problems regarding drug distribution. The plasma binding of basic drugs appears to be generally unaffected but the ones that are acidic, such as penicillins, cephalosporins, phenytoin, furosemide, and salicylates, are most severely affected by reduced protein binding [23, 25]. Hypoalbuminemia with altered protein binding leads to increased levels of free concentrations of drugs. Conversely, alkaline drugs such as propranolol, morphine, oxazepam, and vancomycin bind primarily to non-albumin plasma proteins, whose plasma concentrations are often elevated in renal dysfunction. For this reason, plasma concentrations of alkaline drugs in CKD patients may be reduced [21–23].

The Vd of several drugs is significantly increased in patients with severe renal dysfunction [14, 21, 25]. An increased Vd may be the result of fluid overload, decreased protein binding, or altered tissue binding. The Vd of a few drugs, such as digoxin, pindolol, and ethambutol, is decreased probably due to a decrease in their tissue binding. This reduction in Vd results in increased drug serum concentrations if the loading dose is not reduced especially for digoxin [14, 28]. Increased total-body water, such as edema or ascites, is expected to increase the Vd in CKD patients. Especially hydrophilic drugs like pravastatin, fluvastatin, morphine, codeine, and vancomycin are affected by this change in Vd resulting in reduced serum concentration [22–29].

29.2.3 Effects of Kidney Diseases on the Drug Metabolism Process

There are Phase I and II drug metabolism processes that are affected in CKD. Slowed phase I and II metabolic reactions result in increased serum drug concentrations [26]. In general, few drugs are eliminated almost entirely unchanged by the kidneys. In many studies, it was documented that even drugs that are mostly or completely eliminated from the body by non-renal mechanisms may accumulate in patients with renal dysfunction if their dosage regimen is not adjusted [30]. Acetylation (e.g., dapsone, hydralazine, isoniazid, procainamide), glucuronidation (e.g., acetaminophen, morphine, lorazepam, oxazepam, naproxen), sulfation (e.g., acetaminophen, minoxidil, dopamine, albuterol), and methylation (e.g., dobutamine, dopamine, 6-mercaptopurine) are all slowed in patients with CKD [26, 31]. Hepatic cytochrome 450 (CYP) activity is also changed in renal function problems. For example, the plasma S/R warfarin ratio was increased by approximately 50% in ESRD patients compared to healthy controls, indicating that CYP2C9 activity in these patients was reduced more than the activity of the other enzymes contributing to the metabolism of warfarin [32].

29.2.4 Effects of Kidney Diseases on the Excretion Process

Renal excretion of medications is dependent on glomerular filtration rate, renal tubular secretion, and reabsorption. In CKD, medication elimination by glomerular filtration is decreased, resulting in a prolonged free drug elimination half-life [33]. The secretion of drugs, eliminated by the active transport system, into the proximal convoluted tubules is also reduced in CKD [34]. Some drugs eliminated in this way are ampicillin, furosemide penicillin G, phenylbutazone, probenecid, salicylic acid, cimetidine, dopamine, neostigmine, procainamide, and trimethoprim [33, 34].

In the elimination process, biologically active or toxic metabolites of parent drugs may accumulate in patients with CKD. For example, the active metabolite of midazolam, alpha-hydroxymidazolam; the active metabolite of allopurinol, oxypurinol, or morphine-3-glucuronide and morphine-6-glucuronide which are an active metabolite of morphine can accumulate in CKD patients [34, 35].

29.3 Changes in Pharmacodynamics of Drugs in CKD

Pharmacodynamics is interested in the biochemical and physiologic effects of a drug and its organ-specific mechanism of action, including effects on the cellular level. In CKD, the response to a given drug may change even though the drug's pharmacokinetics are not dramatically altered.

There are two different mechanisms in drug pharmacodynamics. The reversible and irreversible effects. The reversible effects are receptor-mediated, saturable, and observed with both increasing and decreasing concentrations. The irreversible effects are direct and proportional to rising concentrations. The reversible effects generally describe the individual drug response [36, 37]. For example, in the elderly, augmented drug response often has been explained by an impaired kidney function. But because of reversible pharmacodynamic effects, increased sensitivity and a higher drug potency at the receptor level increase drug response in the elderly [38].

In pharmacodynamics, the same concentration results in beneficial and adverse effects. Conventional drugs with a beneficial effect will also have adverse effects. The adverse drug reaction can even be used for pharmacodynamic monitoring of the therapeutic effect. As an example, mild myelosuppression with anemia, neutropenia, lymphocytopenia, and thrombocytopenia might indicate a sufficiently high dose of anticancer, anti-infective, or immunosuppressive drugs [36].

Here are sample examples of drugs that have changes in their pharmacodynamics. For reversible effect changes, an increased sensitivity has been reported for midazolam, nifedipine, morphine, phenytoin, and warfarin, where dose reduction might be necessary. But more resistance has been observed for albuterol and metoprolol which require a higher dose or a change to an alternative drug [36, 38]. For furosemide and canagliflozin, although T1/2 rises in CKD patients, a higher-than-normal dose with higher intratubular concentrations is needed. And the dose should not be reduced, but instead, be increased to obtain drug effect in the altered kidney functions. This observation related to furosemide and canagliflozin is a result of pharmacodynamic changes in kidney problems [39, 40].

Another pharmacodynamically based regimen is a time-dependent action in which drugs should be administered by continuous infusion to increase efficacy but decrease toxicity. Vancomycin, meropenem, and piperacillin are some of these drugs whose steady-state serum concentration is necessary for their target drug concentration [36, 41].

The insight into the pharmacodynamics might also affect dosing practice for direct-acting oral anticoagulants apixaban and rivaroxaban in kidney diseases. The antithrombotic efficacy and the bleeding risk were not different for apixaban and rivaroxaban even in CKD [42]. But in kidney failure, the T1/2 of apixaban rises to 17 h, whereas the rivaroxaban T1/2 increases to only 10 h. Instead of dosing 2.5 mg every 12 h, the pharmacodynamic dose adjustment of apixaban for kidney failure would suggest 5 mg once a day as per the daily dosage of rivaroxaban [43].

In contrast to the reversible effects, irreversible pharmacodynamic effects rarely have been published in the literature. Some drug examples for irreversible effects are ibrutinib, cisplatin, clopidogrel, and pantoprazole [36].

29.4 Concluding Remarks

Altered kidney functions affect more than just the renal clearance of drugs and/or active drug metabolites. Even when the dosage adjustments recommended for patients with CKD are carefully followed, adverse drug reactions remain common. Safe drug prescribing for patients with CKD can be complex, but with the application of a following algorithmic approach, the difficulties can be minimized [23, 25, 26, 44]. Additionally, clinicians should also be aware of what clinical guidelines say for drug dosing considering patients with kidney problems. A Clinical Update from Kidney Disease, Improving Global Outcomes (KDIGO) is summarized in Table 29.1 [45].

Table 29.1 Stepwise approach to adjust drug dosage regimens for patients with CKD and AKI

Step 1	Clinical history	Assess demographic information, past medical history including history of renal disease, and current clinical and laboratory information, including DNA polymorphisms to ascertain drug therapy needs
Step 2	Relevant GFR estimation	Use most appropriate tool to assess eGFR or CLcr for the patient based on age, body size, ethnicity, and concomitant disease states
Step 3	Current medications	Identify drugs for which individualization of the treatment regimen will be necessary
Step 4	Personalized treatment regimen	Calculate dosage regimen based on pharmacokinetic characteristics of the drug and the patient's volume status and eGFR or CLcr
Step 5	Monitor	Monitor parameters of drug response and toxicity; monitor drug levels if available/applicable
Step 6	Revise regimen	Adjust regimen based on drug response or change in patient status (including renal function) as warranted

Adapted from [45]

Before You Finish: Practice Pearls for the Clinicians

- Assess the degree of kidney function severity and GFR, be sure of the stage according to universal methods, and determine a clinical action plan according to stages.
- Take the medical history, examine the patient, and specify the comorbidities the patient has.
- Review the medication list. Check the complete medication list including all prescriptions, over-the-counter and dietary supplements (including herbal, nonherbal, and vitamin supplements). Collect history of drug allergies/sensitivities, adjustment, or discontinuation of medication due to impaired kidney function or toxicity.
- Plan the medication list. Ensure that all drugs patients use are still required and that new medications have specific indications. Evaluate for potential drug interactions.
- Choose less nephrotoxic medications. Review the indication for the agent to determine whether the potential for harm outweighs the evidence for efficacy. For example, RAAS blockers, which can lead to hyperkalemia and AKI, should undergo harm versus benefit evaluation, especially in patients where the benefits of treatment targets are unknown or equivocal. Also, consider patient preferences.
- Calculate/adjust the dose based on the patient's GFR, drug characteristics, and literature recommendations.
- When in doubt, appropriate information for dosing guidelines should be sought in recently published monographs or texts. Decision-support platforms such as Micromedex and Lexicomp offer easily accessible monographs. The Natural Medicine Comprehensive Database is also a useful resource to consider the safety of herbals, dietary supplements, vitamins, and other nutraceuticals in CKD.
- Loading dose is important, not avoid. For maintenance doses, the most common recommendations are often to reduce the drug dose rather than expand the dosing interval.
- Monitor the treatment you have started. Document the signs of efficacy, toxicity, and change in symptoms of the patient. Monitor drug levels if monitoring is available to guide further therapy.
- Reassess the patient to evaluate drug effectiveness and the need for ongoing therapy.
- Follow recommended online sources.
  - FDA: Pharmacokinetics in Patients with Impaired Renal Function—Study Design, Data Analysis, and Impact on Dosing and Labeling, 2020 Available at: http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm
  - KDIGO Drug Prescribing in Kidney Disease: Initiative for Improved Dosing. Available from: https://kdigo.org/wp-content/uploads/2017/02/201005_Grabe_Stevens.pdf
  - European Medicines Agency. Evaluation of medicines for human use. Available from: www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003123.pdf
  - Dosing – Tool for drug application and security. Department of Clinical Pharmacology and Pharmacoepidemiology, University Hospital Heidelberg. Available from: www.dosing.de

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