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PRINCIPLES OF DOSE ADJUSTMENT IN PATIENTS WITH CHRONIC KIDNEY FAILURE

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ABSTRACT
Chronic renal disease is a kidney illness marked by a progressive decline in kidney function over months or years. The usage of medications in this condition is a crucial aspect of managing kidney disease patients. When done correctly, pharmacotherapy can halt disease development and minimize morbidity and mortality. In patients with kidney illness, decreasing kidney function can drastically change the pharmacokinetics and pharmacodynamics of many medications, increase the risk of drug toxicity if not well treat. Many of these changes must be expected and mitigated by changing the medicine dosage. Complications of chronic kidney disease (CKD) that go untreated can cause significant early morbidity and mortality, as well as aggravate its progression. This literature review is based on a review of the literature and articles related to CKD to determine the principles of dose adjustment in CKD patients. Classification of drugs in CKD patients includes antifungals, anticoagulants, antidiabetics, antihypertensives, antibiotics, and analgesics. The administration of these drugs should be considered for kidney function in CKD patients. The presence of multidisciplinary interventions reduces the risk of progression of CKD severity. Adjustment of the dosage regimen in CKD patients is carried out for certain drugs that have a significant relationship between drug concentration and clinical outcomes in patients.

Keywords: chornic kidney disease; dosage; pharmacotherapy

1. INTRODUCTION

Decreased glomerular filtration rate (GFR) and structural or urinary anomalies of the renal system are the defining characteristics of chronic kidney disease (CKD). In contrast to those with good renal function, patients with renal disease generally consume over five drugs everyday (Marriott et al., 2019; Vondracek et al., 2021a). Up to 15% of people worldwide suffer from CKD, which is particularly prevalent in specific ethnic groups. In 2017, there were 697.5 million CKD cases worldwide. In 2017, Indonesia was one of the nations with over a million CKD sufferers. The incidence of chronic kidney disease (CKD) increases with age, particularly among individuals over 80 years old. Older persons with chronic kidney disease (CKD) generally consume nine drugs daily, and the interplay of CKD and aging results in cumulative changes in pharmacokinetics and pharmacodynamics. The risk of adverse drug events in older people with CKD can increase by three to tenfold compared to their counterparts without CKD. Moreover, an increased incidence of CKD may be associated with social circumstances (Bikbov et al., 2020; Vondracek et al., 2021a).

Patients with CKD are often not detected due to kidney function tests that are not routinely performed in individuals with a high risk of CKD. Untreated CKD complications can contribute to significant morbidity and premature mortality and, even worse, can exacerbate the development of CKD (Sowinski et al., 2020). Therapeutic interventions in chronic kidney disease (CKD) patients must account for pharmacological aspects to enhance treatment efficacy, mitigate risks, and address pharmacokinetics owing to impaired renal function. The absence of therapeutic medication monitoring and patient non-adherence resulting from polypharmacy might considerably complicate the treatment of CKD patients. Therapeutic management of CKD ideally involves a multidisciplinary approach to pharmacological interventions and non-pharmacological therapy. The existence of a multidisciplinary approach has shown a significant reduction in the risk of starting hemodialysis as a cause of death (Schonder, 2016). Four main points must to be monitored in CKD patients: the development of CKD stages, the risk of cardiovascular disorders, the risk of metabolic bone disease, and drug safety (Kakitapalli et al., 2020).

Patients with chronic kidney disease can alter the effects of many drugs, sometimes reducing but more often increasing or doubling them, leading to accumulation and potential toxicity. Many of these changes must be predicted and mitigated by adjusting drug doses (Kyriakopoulos & Gupta, 2025). In addition, the decline in kidney function in patients with chronic kidney disease requires dose adjustments, especially for drugs with a narrow therapeutic index, to avoid unwanted drug effects (Weking et al., 2024). This study reviewed literature and articles related to CKD to determine the principles of dose adjustment in CKD patients.

2. METHODS

2.1. Study Design

This study uses a narrative review approach with the PRISMA Flowchart approach, which aims to draw the flow of information through various phases of systematic review.

2.2. Inclusion and Exclusion Criteria

The literature used in this study must meet the inclusion criteria, including (1) articles written in English, (2) articles published in the last five years from 2015 to 2020, (3) accessible through electronic databases such as PubMed, ScienceDirect and Google Scholar, (4) have full text. The exclusion criteria are: (1) inconsistency between the article title and abstract, (2) not full text, (3) the journal is not relevant.

2.3. Search Strategy

The research team carried out initial strategic planning using the keywords "Dose" AND "Pharmacotherapy" "Chronic Renal Failure" AND "Therapy." The search was conducted online through journal publications such as Google Scholar, PubMed, and ScienceDirect. The article search used English with keywords.

2.4. Data Extraction

Data extraction is recorded and explained for each class of drugs, such as antifungals, anticoagulants, antidiabetics, antihypertensives, antibiotics, and analgesics. These drug classes affect the condition of patients with chronic kidney failure.

2.5. Data Synthesis

Data synthesis is carried out by analyzing the principles of dose adjustment in patients with chronic kidney failure using a narrative approach. The literature obtained is critically reviewed by researchers and discussed until a conclusion is reached.

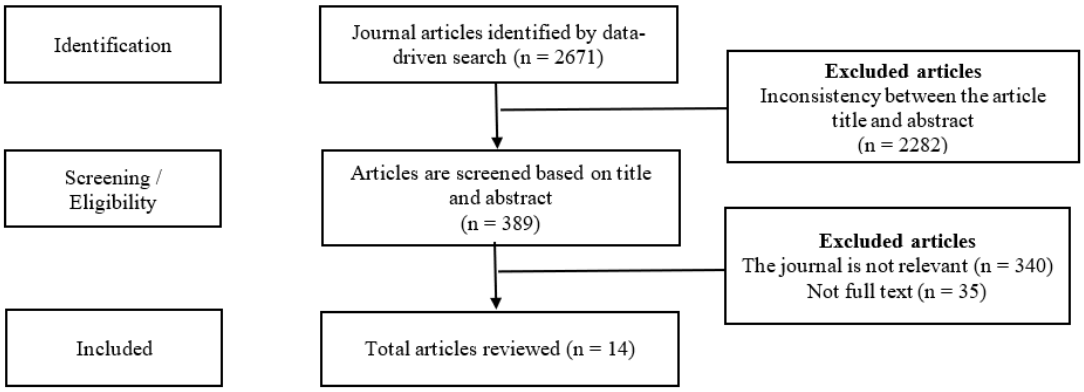

Figure 1. PRISMA flow diagram

3. RESULTS AND DISCUSSION

3.1. Fundamental Principles in Renal Pharmacotherapy

Impaired renal function can significantly alter the pharmacokinetics and pharmacodynamics of numerous drugs, increasing the risk of drug toxicity if therapy modifications are not adequately managed. The selection of drugs and dosage for individuals with compromised renal function is determined by pharmacokinetics, pharmacodynamics, and pharmacogenomics (Roberts et al., 2018). Absorption, distribution, protein binding, metabolism, and elimination exemplify pharmacokinetic parameters. Pharmacodynamics delineates drug action and the subsequent biochemical repercussions, encompassing both beneficial and adverse outcomes. The concentration-time profile of a medication can be utilized to assess its pharmacodynamic effects. The maximum plasma concentration (Cmax), the area under the concentration-time curve (AUC), and the duration over the threshold concentration can all be utilized to forecast efficacy and safety parameters (Keller, 2015; Nolin, 2015).

Pharmacokinetic parameters to consider in individuals with abnormal renal function encompass alterations in absorption, distribution, protein binding, metabolism, and excretion. Numerous acidic pharmaceuticals, including as penicillins, cephalosporins, furosemide, and phenytoin, have diminished protein binding in the presence of hypoalbuminemia. The drug's Vd rises because the unbound drug is more readily transported to tissues. According to the formula Concentration at peak = (Dose×Bioavailability)/Vd, a rise in Vd means that a higher initial dose is required to achieve the target plasma concentration. For some medications, we must take into account not only the pharmacokinetics of the active ingredient but also the metabolites and stability of the excipients/diluents in the drug preparation (e.g., propylene glycol in intravenous lorazepam; cyclodextrins in intravenous voriconazole or posaconazole) (Hoff et al., 2020; Hudson & Nolin, 2018). For instance, in patients with renal impairment, meperidine's pharmacokinetics largely remain unaltered. In individuals with compromised renal function, the active metabolite normeperidine accumulates, potentially leading to seizures. Procainamide, clofibrate, allopurinol, nitrofurantoin, and certain sulfa antibiotics are more examples.

3.2. Basic Principles of Dosing Regimen in CKD Patients

3.2.1. Antifungal

Fungal infections have a mortality rate of over 65% and can worsen 4-7% of the development of chronic kidney disease (CKD) in patients in tropical nations. In addition to sporadic occurrences in healthy individuals inoculated with fungal spores, mucormycosis is an aggressive, opportunistic fungal infection that commonly affects patients with immunosuppression, uncontrolled hyperglycemia, cancer, solid organ transplantation, chronic kidney disease, malaria, and malnourishment (Shankar et al., 2021). For CKD patients, the majority of antifungals don't require dose adjustments. In patients with G3-G5 CKD (ClCr <50 mL/min), injectable formulations of some azole antifungals should be avoided or used sparingly because cyclodextrin

solvents can build up and induce renal damage. Cyclodextrins can be efficiently eliminated by hemodialysis in individuals receiving intravenous azoles.

Nephrotoxicity is a possible side effect of injecting amphotericin B for severe fungal infections. Afferent vasoconstriction with reduced GFR, renal tubular acidosis, and tubular dysfunction can all be brought on by amphotericin B. As the total cumulative dose rises, so does the risk of nephrotoxicity. The likelihood of this occurring can be decreased by using formulations based on lipids. Since glomerular filtration removes over 90% of flucytosine, patients with ClCr < 40 mL/minute need to have their dosages adjusted. Additionally, because hemodialysis can drastically lower drug levels, the drug dose should be given after hemodialysis. For individuals with a ClCr of 20–40 mL/minute, the advised flucytosine dosing interval is 37.5–50 mg/kg every 12 hours. The same amount can be taken once daily or every 24 hours to patients with ClCr 10–20 mL/min. Fluconazole prescription dose modifications are recommended for patients with chronic kidney disease (CKD) due of delayed elimination. Patients with a ClCr value of 35 mL/min showed a 50% (~10 ml/hr/kg) reduction in fluconazole clearance and a prolonged t1/2 of 96 hours. Patients with ClCr 11–50 mL/min should have their fluconazole dosage lowered by 50% (Bellmann & Smuszkiewicz, 2017; Lexi-Comp & American Pharmaceutical Association, 2019).

3.2.2. Anticoagulants

Because CKD raises the risk of thrombosis, patients with CKD are more likely to experience venous thromboembolism (VTE) and nonvalvular atrial fibrillation (NVAF). The renal function of CKD patients determines whether anticoagulants should be used. Direct-acting oral anticoagulants and warfarin are the recommended anticoagulants. Dabigatran, edoxaban, rivaroxaban, and apixaban are examples of oral anticoagulants that work directly. Direct-acting oral anticoagulants are recommended for patients with CKD stages 3–4, NVAF, and an elevated CHA2DS2-VASC score; the dosage should be decreased based on the patient's CrCl value. Patients with stage 5 CKD, with or without dialysis, are advised to take warfarin or apixaban (Aursulesei & Costache, 2019; Vondracek et al., 2021a).

Patients receiving anticoagulant drugs in the form of warfarin and direct-acting oral anticoagulants (apixaban, rivaroxaban, dabigatran, and edoxaban) with chronic renal failure comorbidities need to pay attention to dose adjustments. Adjustments to anticoagulant doses in CKD patients can be seen in Table 1.

Table 1. Adjustment of anticoagulant dosage in patients with CKD.

Anticoagulant	Dosage NVAF	Dose VTE	Other
Warfarin	• People with CKD may take a dose that is twenty percent lower than people with normal renal function.		• The poorer the kidney function, a less the time in the therapy range. • Not advised in patients with severe CAD due to rising threat of arterial calcification.
Direct-acting oral anticoagulants			
Apixaban	5 mg second daily or 2.5 mg second everyday if any 2 of the following are present: Scr 1.5 mg/dL, aged eighty years, 60 kg weight of body	Ten mg twice daily for a week, then five mg 2×/every day; no dose change is indicated.	• No dose adjustment is indicated in hemodialysis patients based on PK/PD data • The direct-acting oral anticoagulant

			of option for CKD stages 4 and 5 • 14% can be dialyzed
Rivaroxaban	CLcr Fifty mL/min: twenty mg once every day with food; CLcr < Fifty mL/min: fifteen mg every day with meals; CLcr < 15 mL/min: Not advised.	CLcr Fifteen mL/min: fifteen mg twice/day with a meal for a period of 21 days, then twenty mg twice/day with meals; CLcr < Fifteen mL/min: not advised	• Minimal (< ten percent), hemodialysis amenable • There's no medical evidence in hemodialysis patients; the precise dose is yet available
Edoxaban	CLcr > 50-95 mL/minute: 60 mg 1×/every day; CLcr 15-50 mL/min: 30 mg 1×/every day; CLcr < 15 mL/min: Not advised	CLcr > 50 mL/minute: 60 mg 1×/every day; CLcr 30-50 mL/min: 30 mg 1×/day if body weight 60 kg, or therapy with verapamil or dronedarone, or quinidine	• A few (~25%) are dialyzable • For VTE, get started following 5-10 days of first treatment with injectable anticoagulant.
Dabigatran	CLcr > thirty mL/min: 150 mg twice/day; CLcr 15-30 mL/min: 75 mg 2×/day; CLcr < Fifteen mL/minute: Not advised	CLcr > thirty mL/minute: 150 mg 2x/day; CLcr thirty mL/min: Not advised.	• 40%-50% dialyzable • For VTE, get started following 5-10 days of initially medication with injectable anticoagulant.

Note: CAD = coronary artery disease; ClCr = creatinine clearance; CKD = chronic kidney disease; NVAF = nonvalvular atrial fibrillation; VTE = venous thromboembolism.

3.2.3. Antidiabetic

The hyperglycemia management approach includes medicines, nutrition planning and physical activity. The use of antidiabetics needs to be considered in terms of comorbidities such as chronic kidney failure. This is associated with adjusting the dose of antidiabetic drugs. If there is a decrease in eGFR, antidiabetic drugs, except pioglitazone and insulin, should be reduced or discontinued. Recommendations for antidiabetic therapy doses can be seen in Table 2.

Table 2. Recommended dosage in antidiabetic therapy (Abe et al., 2011; Betônico et al., 2016; Dominijanni et al., 2017).

Drugs	Dosage Adjustment Recommendations
Insulin	• Reduce dose by ~25% if ClCr 10-50 mL/min • Reduce dose by ~50% if ClCr <10 ml/min
SGLT2 inhibitors	
Empagliflozin	Not recommended if eGFR < 30mL/min/1.73 m2
Canagliflozin	• The greatest dose 100 mg orally every 24 hours if the eGFR < 30-60 mL/min/1.73 m2 • eGFR <30 mL/min/1.73 m2 with albumin levels >300 mg/d not advised initiation dose 100 mg/24 hrs • Contraindicated in hemodialysis individuals
Dapagliflozin	• Not advised when the eGFR < 25 mL/min/1.73 m2 • Contraindicated in hemodialysis individuals

Biguanid	
Metformin	• If eGFR 30-44 mL/min/1.73 m2, commence treatment at half the usual dose (250 mg) and may titrate to 1 g/day if no active renal disease and situations contributing to inadequate perfusion and a lack of oxygen (acute heart failure and dehydration) • If eGFR ≤ 30-44 mL/min/1.73 m2 during therapy, assess the risks and benefits, reduce the dose by 50%, and the maximum dose is one g/day • Contraindicated in eGFR <30 mL/min/1.73 m^2
GLP-1 agonies	
Liraglutide	No amount modifications is necessary.
Semaglutide	No amount modifications is necessary.
Albiglutide	No amount modifications is necessary.
Dulaglutide	No amount modifications is necessary.
Exenatide	• Immediate delivery not proposed if ClCr <30 mL/min • Extended release is not advised if eGFR < fifteen mL/min/1,73 m^2
Lixisenatide	Not advised if an eGFR <15 mL/min/1,73 m^2
DPP-4 inhibitor	
Alogliptin	• ClCr 30-59 mL/min: 12.5 milligrams orally/day • ClCr 15-29 mL/min and hemodialysis 6.25 milligrams/day
Saxagliptin	an eGFR <45 mL/min/1.73 m^2 and dialysis 2.5 mg/day
Sitagliptin	• an eGFR 30-44 mL/min/1.73 m^2 50 mg/day • an eGFR < thirty mL/min/1.73 m^2 and dialysis 25 mg/day
Linagliptin	No amount modifications is necessary.
Sulfonylureas	
Glimepiride	• No number changes is indicated; Conservative dose is advised while starting therapy. • Consider change treatment if an eGFR <15 mL/min/1.73 m^2
Glipizide	• No number changes is indicated; Conservative dose is indicated while starting therapy. • Avoid if possible if an eGFR < 10 mL/min/1.73 m^2
Glyburide	ClCr < Fifty mL/min due to the probability of hypoglycemic raises
Meglitinides	
Repaglinide	• ClCr 20-40 mL/min initiation dose 0.5 mg with food • ClCr < 20 mL/min, and hemodialysis is not recommended
Nateglinide	• eGFR <30 mL/min/1.73 m^2 conservative dose starting 60 mg 3x daily with food • eGFR < 15 mL/min/1.73 m^2 use needs to be closely monitored
Thiazolidinedione	
Pioglitazone	No dose adjustment is required.

Note: ClCr = creatinine clearance; CKD = chronic kidney disease; DPP-IV = Dipeptidyl peptidase-IV; GFR = glomerular filtration rate; GLP-1 = glucagon like peptide-1; SGLT2 = sodium glucose cotransporter-2.

3.2.4. Antihypertensive

According to most guidelines, ACE inhibitors as well as ARBs are the first-line antihypertensive drugs in CKD patients, especially when accompanied by albuminuria. Both ARBs and ACE inhibitors stimulate efferent arteriolar vasodilation, which causes a drop in intraglomerular pressure and hence reduces proteinuria. However, combining an ACE inhibitor with an ARB is unsuccessful in slowing CKD progression or lowering CV events in individuals with CKD (with or without diabetes). This combination may predispose to hyperkalemia, acute renal damage, and dual blockage with ACE inhibitors and ARBs. More than fifty percent all CKD patients take at least three medicines to manage their hypertension. Some studies show that uncontrolled blood pressure is connected with a rapid reduction in GFR and a poorer risk of renal and cardiovascular growth at all ages. Managed hypertension in CKD patients has a reduced likelihood of cardiovascular events (myocardial infarction, other acute coronary syndromes,

stroke, heart failure, or death from CV causes) and all-cause mortality. However, there was no change in the development of CKD (Ku et al., 2019; Pugh et al., 2019; Sinha & Agarwal, 2019).

3.2.5. Antibiotics

When taking antibiotics to patients with reduced kidney function, practitioners should be careful of a number of variables. The condition of the kidneys should be given account when altering the pharmacodynamic aspects of antibiotics that alter medicine shipment. The pharmacodynamic properties of antibiotics vary according to time or concentration. To optimize the delivery of antibiotics, dosage modifications should be done. Maintaining medication concentrations above the minimum inhibitory concentration (MIC) for as long as feasible is crucial for antibiotics whose pharmacodynamics are time-dependent, such as penicillins, cephalosporins, and carbapenems. Increasing MIC to administer antibiotics in smaller dosages while keeping regular dosing intervals. With the exception of cephalosporins like ceftazidime and cefazolin. Due to HD patients' extended half-lives, antibiotics can be given three times a week following dialysis, which improves compliance and comfort. Frequent dosing at longer intervals will enhance peak concentrations above the minimal inhibition concentration (Cmax/MIC) for medications with concentration-dependent pharmacodynamics, such as aminoglycoside antibiotics and fluoroquinolones. while reducing adverse effects. Some antimicrobials do not have considerable renal excretion and do not require dose adjustment in patients with impaired renal function, even though the majority of them do (Eyler & Shvets, 2019; Vondracek et al., 2021a).

Given the possible elevated risk of antibiotic-related side effects, individuals with impaired kidney function should be evaluated for antibiotic therapy (Etebu & Arikekpar, 2016; Vondracek et al., 2021a).

a. Confusion, myoclonus, and seizures are examples of central nervous system adverse effects that can happen if beta-lactam medicines are not properly regulated.
b. Patients with uremic platelet dysfunction may experience the uncommon adverse effect of impaired platelet aggregation, which is brought on by penicillins.
c. Using carbapenems may make seizures more likely.
d. Nephrotoxicity, which is more prevalent in cases of high rates, obesity, prolonged therapy, and the use of high daily dosages, can be brought on by aminoglycosides and vancomycin, particularly when combined with piperacillin. Plasma creatine kinase concentrations must be examined at least every week, or more often, in patients with poor renal function as daptomycin in may elevate the probability of damage to muscles (myopathy).
e. Fluoroquinolones can result in a multitude of toxicities, including glycemic effects, peripheral neuropathy, tendon rupture, QT prolongation, and brain effects. Ions and fluoroquinolones may chelate. They should therefore remain free of binders of phosphate and other divalent/trivalent cations that are when administered orally.
f. Patients with weakened kidney function should use trimethrim/sulfamethoxazole with precaution. By inhibiting amiloride-sensitive sodium channels that reside in the distal kidney, the the antibiotic component of Bactrim can result in high potassium levels. Antibiotic administration may result in complications for patients with G4–G5 CKD. Due to a decrease in its tubular secretion, trimethoprim can also raise Scr. It can deteriorate renal function but does not alter GFR. Sulfamethoxazole, like other sulfonamides, can result in acute tubular necrosis, crystal nephropathy, and interstitial nephritis, which can lead to renal failure.

3.2.6. Analgesic

Acetaminophen, topical capsaicin cream, nonsteroidal painkillers (NSAIDs), topical lidocaine patches, anticonvulsant and pregabalin, tricyclic antidepressant drugs, and norepinephrine and serotonin inhibitors of reuptake are examples of non-opioid painkillers for persistent pain. NSAIDs raise the risk of bleeding in uremia patients by impairing platelet function and irritating the stomach mucosa. Hyperkalemia, hyponatremia, hypervolemia (edema), and hypertension are among the nephrotoxic side effects of NSAIDs. Reduced GFR due to a

prostaglandin-dependent decrease in renal blood flow is one of the nephrotoxic products. Patients with stage 5 CKD should not take NSAIDs, and those with stage 4 CKD should be closely monitored (Baker & Perazella, 2020; Vondracek et al., 2021a).

A non-opioid medication called acetaminophen is used to relieve mild to moderate pain in CKD patients. Use up to 4 grams per day; there is no need to modify the dosage (Davison et al., 2020). Patients with chronic kidney disease do not need to change their dosage of tricyclic antidepressants. The QT interval and anticholinergic adverse effects (such as orthostasis, drowsiness, constipation, urine retention, disorientation, and dry mouth) may worsen with this use. If necessary, lower dosages of desipramine and nortriptyline are safer since they have fewer anticholinergic effects (Vondracek et al., 2021a).

To lower the danger of accumulation, dosage adjustments are necessary for pregabalin and gabapentin. Patients on hemodialysis should use gabapentin carefully. A selective serotonin and norepinephrine reuptake inhibitor, duloxetine is used to treat neuropathic pain, anxiety disorders, and depression. Patients with stages 4 and 5 of CKD are not treated with this therapy (Vondracek et al., 2021a). Table 3 shows the dosage of non-opioid analgesics.

Table 3. Non-opioid analgesics

Non-Opioids	Dosing Issues	Comments
Acetaminophen	500-1000 mg oral each six times	• For sensory pain • Maximum dose of 4 g/day
Topical Capsaicin Cream	Administer lightly topical 3-4x each day	• For localized inflammation
Topical 5% Lidocaine Patch	Apply up to 3 patches 12 hr daily	• For localized inflammation
Topical NSAID (diclofenac gel)	Administer 2-4 g into the affected spot four times everyday	• For localized inflammation
NSAIDs oral	The eGFR 30 to 60 mL/min/1.73 m^2: The eGFR 15 to 29 as well mL/min/1.73 m^2: case by case with careful observation. The eGFR < fifteen mL/min/1.73 m^2: inappropriate.	• For nociceptive pain relief • Side impacts: ↑ potential for Gastrointestinal bleeding, ↑ incidence of cardiovascular disease, ↑ fluid retention, ↑ high potassium levels, ↓ GFR
Tricyclic antidepressants	Nortriptyline: No modification required Desipramine: Begin at twenty-five milligrams every day and adjust carefully	• For nerve pain. • To decrease seizures • An anticholinergic adverse reaction.
Gabapentin	100-300 milligrams taken orally every day is adjusted to an appropriate dosage given the ClCr	• For nerve pain.
Pregabalin	25 milligrams orally once or twice each day adjusted up to suggested dosage given ClCr	• For nerve pain.
Duloxetine	30 milligrams once daily. Not advised if ClCr < 30 mL per minute .	• For nerve pain. • ClCr < thirty mL/min: indicate at 40 milligrams everyday adjusted with precaution • The starting dose was 30 milligrams everyday
Venlafaxine	37,5 milligrams taken every day.	• For nerve pain.

Note: ClCr = creatinine clearance; CKD = chronic kidney disease; CV = cardiocascular; GFR = glomerular filtration rate; GI = gastrointestinal; NSAIDs = nonsteroidal anti-inflammatory drugs.

Opioids should absolutely be employed by precaution for individuals with chronic kidney disease, also called CKD, who have moderate to severe pain that cannot be treated with non-opioid treatments. Hydromorphone, fentanyl, methadone, and buprenorphine are among the

opioids given to individuals who have chronic renal failure. Among those who have chronic kidney dysfunction, oral or injection hydromorphone, which is a short-term opioid that reduces intense acute discomfort. Through persons with CKD stages 4 and 5, hydromorphone is largely metabolized in the liver to hydromorphone-3-glucuronide, which is excreted in the form of urine. This metabolite is linked to myoclonus and delirium but has no analgesic effect. It is important to take hydromorphone with caution, titrating based on response and beginning at 25% to 50% of the initial dose.

A strong opioid with a brief half-life is fentanyl. The liver quickly breaks down fentanyl into inactive metabolites. Injectable administration is safe for people with chronic kidney disease (CKD), although numerous dosages and short half-life make it unpleasant for managing acute pain. Transdermal fentanyl is used to treat chronic pain in CKD patients. Methadone functions as both an agonist and an antagonist of NMDA receptors. Patients with CKD stages 4 and 5 can safely use methadone for chronic pain since it is converted in the liver to inactive metabolites. By lengthening the QTc interval, methadone raises the risk of torsades de pointes. Consequently, QTc electrocardiography monitoring is required for CKD patients (Coluzzi et al., 2020; Davison et al., 2020; Vondracek et al., 2021a).

An opioid agonist-antagonist combination is buprenorphine. The liver breaks down buprenorphine into its active metabolites, that are higher than the original chemicals and can only be faintly eliminated by the kidneys. In CKD patients, transdermal buprenorphine seems to be safe. For CKD patients, oral oxycodone is a short-term opiate. The liver transforms oxycodone to oxymorphone, an active metabolite that can build up in stages four and five of chronic renal disease. Rarely used for mild to moderate pain, codeine is a mild opiate that can serve as an antitussive. The liver converts codeine into an active metabolite that the kidneys then eliminate (Davison et al., 2020; Vondracek et al., 2021a). Table 4 shows the opioid analgesic dosages.

Table 4. Opioid analgesics.

Opioids	Dosing Issues	Comments
Hydromophone	Creatinine clearance of less than 60 mL/minute: Decrease dosage (25%-50% of the initial dosage) or prolong the recommended dosing interval.	• Short-acting opiates: indicated for severe discomfort in patients with chronic kidney failure • The buildup of the active substance hydromorphone-3-glucuronide may induce neuroexcitatory effects, such as confusion, myoclonus, and convulsions. • Active metabolites eliminated with dialysis
Fentanyl	• Injection: Not dose change is advised for mild to moderate chronic kidney failure (CKD). • Patches: If creatinine clearance (ClCr) is less than 50 mL/minute, decrease the dose to 75% of the standard dosage; if ClCr is less than 10 mL/minute, decrease it to fifty percent of the typical dosage.	• The metabolites exhibit inactivity; • the half-life remains unchanged in chronic kidney failure. • Not eliminated by continuous dialysis
Methadone	Not dosage modification required for chronic kidney disease.	• Not alleviated by continuous dialysis
Buprenorphine transdermal patch	Not dosage modification required for chronic kidney disease.	• Eliminated by continuous dialysis
Hydrocodone	• Converted in the liver to hydromorphone	• Frequently taken in conjunction with paracetamol

	• Refrain from utilizing extended-release formulas.	• Exercise caution around penguins.
Oxycodone	• When creatinine clearance is less than 60 mL/minute, administer 50%-75% of the standard dosage and contemplate prolonging the treatment frequency to every 6 to 8 hours. • Refrain from utilizing extended-release formulas.	• Oxycodone and oxymorphone compounds are primarily eliminated renally and can build up. • Exercise caution in usage if alternative solutions are unavailable. • Eliminated by continuous dialysis
Morfin	• IV use and oral immediate release with caution: - ClCr 30-59 mL/minute: 50-75% of the initial dose (consider extending the dosing interval); Titrate carefully. - ClCr 15-29 mL/minute: 25-50% of the initial dose (consider extending the dosing interval). - ClCr < 15 mL/minute: avoid use. • Avoid using extended-release formulations.	• Accumulation of active metabolites (morphine-6-glucuronide, morphine-3-glucuronide) • It would help of you were careful in use. • Morphine and its metabolites are removed by intermittent hemodialysis.
Tramadol	• ClCr over 30 mL/minute: raise the time between doses every twelve hours, with an appropriate daily dosage of 200 mg • Max dosage on hemodialysis: fifty milligrams each twelve hours; dose after hemodialysis • Avoid utilizing extended-release formulas	• Not advised for use during CKD stages four and five. • Be cautious as this can lessen the likelihood of epilepsy • Incidence of the syndrome of serotonin • Effects will be influenced by slow, quick, or swift metabolic Eliminate by continuous dialysis

Note: ClCr = creatinine clearance; CKD = chronic kidney disease.

4. CONCLUSION

The number of people with CKD is rapidly rising worldwide, necessitating particular consideration of the treatment that CKD patients get. Numerous comorbidities and problems can arise in CKD patients, leading to a significant treatment burden. Patients with CKD are susceptible to drug buildup and toxicity if the dosage is not appropriately adjusted because the majority of medications used in therapy are removed by the kidneys. For CKD patients, measuring kidney function is crucial to figuring out the right dosage. In CKD patients, treatment plans and dosages can optimize the advantages of therapy by lowering the severity of CKD consequences, the risk of patient damage, and the financial burden of therapy.

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6. CONFLICT OF INTEREST

All authors declare no conflict of interest

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