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CHALLENGES AND PATTERNS OF DRUG UTILISATION IN CHRONIC KIDNEY DISEASE: A REVIEW OF APPROPRIATENESS, SAFETY AND ADHERENCE

Surya S. Nair*[1], Dr. Nithin Manohar R.[2], Dr. Padmesh P.R.[3], Dr. Prasobh G.R.[4], Farhana N.[1] and Safna Faisal[1]

[1]Fifth Year Student, Doctor of Pharmacy, Sree Krishna College of Pharmacy and Research Centre, Parassala, Thiruvananthapuram, Kerala, India.

[2]Professor and HOD, Department of Pharmacy Practice, Sree Krishna College of Pharmacy and Research Centre, Parassala, Thiruvananthapuram, Kerala, India.

[3]Assistant Professor, Department of Pharmacy Practice, Sree Krishna College of Pharmacy and Research Centre, Parassala, Thiruvananthapuram, Kerala, India.

[4]Principal, Sree Krishna College of Pharmacy and Research Centre, Parassala, Thiruvananthapuram, Kerala, India.

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***Corresponding Author**
Surya S. Nair
Fifth Year Student, Doctor of Pharmacy, Sree Krishna College of Pharmacy and Research Centre, Parassala, Thiruvananthapuram, Kerala, India.

ABSTRACT

Chronic kidney disease (CKD) is a progressive condition requiring careful medication management due to altered pharmacokinetics, polypharmacy, and increased adverse drug event (ADE) risks. Patients often have multiple comorbidities necessitating complex drug regimens, making appropriate, safe, and adherent medication use essential. This review highlights key challenges in CKD drug utilisation, focusing on dosing adjustments, ADE prevention, and adherence. Antihypertensives, erythropoiesis-stimulating agents, phosphate binders, and diuretics require monitoring to prevent toxicity or therapeutic failure. Nephrotoxic drugs like NSAIDs, aminoglycosides, and contrast agents further complicate therapy. Inappropriate prescribing, drug interactions, and drug-disease interactions necessitate regular medication reviews and therapeutic monitoring. Adherence remains a major issue due to the high pill burden, complex dosing, side effects, and psychosocial barriers. Poor adherence accelerates disease progression and increases

hospitalizations. Strategies like patient education, simplified regimens, digital reminders, and pharmacist-led interventions can enhance adherence. Pharmacists play a key role in medication reconciliation, patient counselling, and therapeutic monitoring, improving treatment safety and efficacy. A multidisciplinary approach integrating evidence-based prescribing, renal-specific dose adjustments, ADE prevention, and adherence support is vital for optimal CKD management.

KEYWORDS: Chronic kidney disease (CKD), Medication adherence, Adverse drug events (ADEs), Renal dose adjustment, Nephrotoxicity.

1. INTRODUCTION

Chronic kidney disease (CKD) is a progressive and multifaceted condition characterized by a gradual decline in renal function, ultimately leading to end-stage kidney disease (ESKD) if left untreated. Given the kidneys' essential role in drug metabolism and excretion, patients with CKD face significant challenges in medication management, requiring careful selection, dosing, and monitoring of pharmacotherapy. The altered pharmacokinetics and pharmacodynamics in CKD necessitate renal-specific dose adjustments to prevent drug accumulation and toxicity while maintaining therapeutic efficacy. Patients with CKD often have multiple comorbidities such as hypertension, diabetes, cardiovascular disease, and dyslipidaemia, leading to complex polypharmacy. This high medication burden increases the risk of adverse drug events (ADEs), drug-drug interactions (DDIs), and inappropriate prescribing, which can exacerbate renal function decline and negatively impact patient outcomes. Certain medications, including non-steroidal anti-inflammatory drugs (NSAIDs), aminoglycosides, and contrast agents, are particularly nephrotoxic and must be avoided or used with extreme caution in this population. Drugs such as antihypertensives, phosphate binders, erythropoiesis-stimulating agents (ESAs), and diuretics require careful titration and frequent monitoring to ensure efficacy and safety.[1]

Beyond drug appropriateness and safety, medication adherence remains a significant challenge in CKD management. The high pill burden, complex dosing regimens, medication-related side effects, and psychosocial barriers- including depression, cognitive impairment, and financial constraints- contribute to poor adherence, leading to disease progression, increased hospitalization rates, and reduced quality of life. Addressing these barriers requires a multifaceted approach that includes patient education, medication regimen simplification,

fixed-dose combination therapies, digital adherence tools, and multidisciplinary healthcare interventions.[2]

This review aims to explore the key patterns and challenges associated with drug utilisation in CKD, focusing on appropriateness, safety, and adherence. By understanding these factors, healthcare providers- including nephrologists, pharmacists, and other multidisciplinary team members- can implement targeted strategies to optimize medication therapy and improve clinical outcomes in patients with CKD.

1.1 Overview of Chronic Kidney Disease

Chronic kidney disease (CKD) is a long-term condition that involves the gradual deterioration of kidney function. This progressive disorder is typically the result of underlying health issues, including diabetes, high blood pressure, inflammation of the kidney's filtering units (glomerulonephritis), and inherited disorders like polycystic kidney disease. As kidney function declines, the body's ability to filter waste products, regulate fluid and electrolyte balances, and maintain hormonal homeostasis becomes increasingly impaired.[3]

Patients with CKD often experience a range of symptoms and complications including fatigue, edema, anaemia, bone and mineral disorders, and an increased risk of cardiovascular disease. CKD severity is classified into five stages based on the estimated glomerular filtration rate (eGFR): stage 1, mildly impaired kidney function; stage 2, mild decrease in kidney function; stage 3, moderate decrease in kidney function; stage 4, severe decrease in kidney function; stage 5, end-stage renal disease (ESRD) requiring dialysis or kidney transplantation.

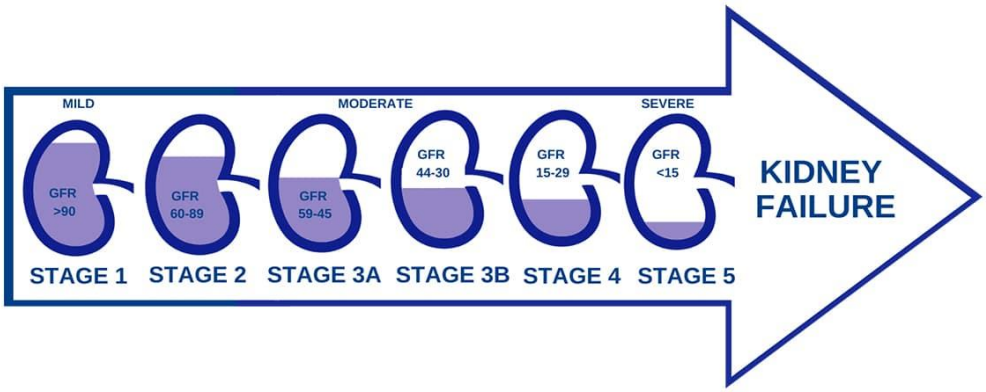

Fig. 1: Stages of Chronic Kidney Disease.

The effective management of CKD involves a multifaceted approach that includes lifestyle modifications, control of underlying conditions, and careful medication management. Optimizing drug therapy is particularly crucial in this patient population because improper medication use can lead to adverse outcomes and further exacerbate the progression of kidney disease.[4]

Table 1: Classification of CKD Based on eGFR and Management Approach.

Stage	eGFR (mL/min/1.73m^2)	Clinical Features	Management Approach
1	≥ 90	Normal kidney function, proteinuria	Risk factor control, lifestyle changes
2	60-89	Mild reduction in function	Blood pressure control, renal monitoring
3a	45-59	Moderate reduction	Medication review, CKD-specific treatment
3b	30-44	Moderate to severe reduction	Dose adjustments, nephrology referral
4	15-29	Severe reduction	ESRD preparation, dialysis discussion
5	< 15	ESRD, dialysis/transplant required	Dialysis, transplant evaluation

1.2 Commonly Used Medications in CKD

Patients with CKD are prescribed a variety of medications, often to manage comorbid conditions, such as hypertension, diabetes, and hyperphosphatemia. Common drug classes include the following.

a) Antihypertensives: ACE inhibitors, angiotensin II receptor blockers (ARBs), calcium channel blockers, and diuretics are widely used to control blood pressure and prevent progression to end-stage renal disease (ESRD).[5]

b) Erythropoiesis-Stimulating Agents (ESAs) are used to manage anaemia in patients with CKD, particularly in stages 3-5.

c) Phosphate Binders: To manage hyperphosphatemia in stages 4 and 5, medications such as calcium carbonate, sevelamer, and lanthanum carbonate are commonly prescribed.[6]

d) Diuretics: Loop and thiazide diuretics are used to control fluid overload, especially in patients with heart failure or volume overload.

Table 2: Common Medications in CKD and Their Renal Dose Adjustments.

Drug Class	Examples	Adjustment in CKD	Risks in CKD
ACE Inhibitors/ARBs	Ramipril, Losartan	Use with caution in stages 4-5	Hyperkalemia, hypotension
Diuretics	Furosemide, Hydrochlorothiazide	Loop diuretics preferred	Dehydration, electrolyte imbalance
Phosphate Binders	Sevelamer, Calcium acetate	Adjust based on serum phosphate	GI upset, hypercalcemia
ESAs	Epoetin alfa, Darbepoetin	Reduce dose in CKD stages 3-5	Hypertension, thromboembolism

Careful dosing and monitoring are required for these medications in the CKD population to ensure appropriate and safe use, as kidney function decline can significantly impact drug pharmacokinetics and pharmacodynamics.

2. CHALLENGES IN DRUG UTILISATION IN CKD

Patients with chronic kidney disease face several challenges in appropriate and safe medication management, including:

2.1 Dose Adjustments in CKD

As kidney function declines, the pharmacokinetics and pharmacodynamics of many drugs are altered, necessitating careful dose adjustments to prevent toxicity and sub-therapeutic effects. Drugs that are excreted by the kidneys, including certain antibiotics (such as aminoglycosides and vancomycin), blood thinners (like enoxaparin), diabetes medications (such as metformin and insulin), and heart-related drugs (including digoxin and beta-blockers), need dosage adjustments based on kidney function. These adjustments are calculated using either the estimated glomerular filtration rate (eGFR) or creatinine clearance (CrCl). Failure to appropriately adjust dosages can lead to drug accumulation and toxicity, particularly for drugs with narrow therapeutic windows, such as digoxin and lithium. However, excessive dose reductions may render medication ineffective, leading to poor disease control. Given these complexities, regular renal function assessment and therapeutic drug monitoring (TDM) are essential to optimize medication therapy in patients with CKD.[7]

2.2 Increased Risk of Adverse Drug Events (ADEs)

Patients with CKD are at a heightened risk of adverse drug events (ADEs) due to polypharmacy, altered drug metabolism, reduced drug clearance, and multiple comorbidities. Renal impairment affects hepatic metabolism (cytochrome P450 enzyme activity), drug-

protein binding, and electrolyte balance, further complicating drug safety. Nephrotoxic drugs such as NSAIDs, aminoglycosides, contrast agents, and some diuretics may exacerbate kidney damage if not carefully monitored. Additionally, drug-drug interactions (DDIs) are common in patients with CKD taking multiple medications, increasing the likelihood of hyperkalemia (e.g., ACE inhibitors + potassium-sparing diuretics), metabolic acidosis (e.g., metformin + iodinated contrast), or hypotension (e.g., antihypertensive combinations). To mitigate these risks, CKD management requires medication reconciliation, pharmacist-led interventions, and routine monitoring of the renal function and electrolyte levels.[8]

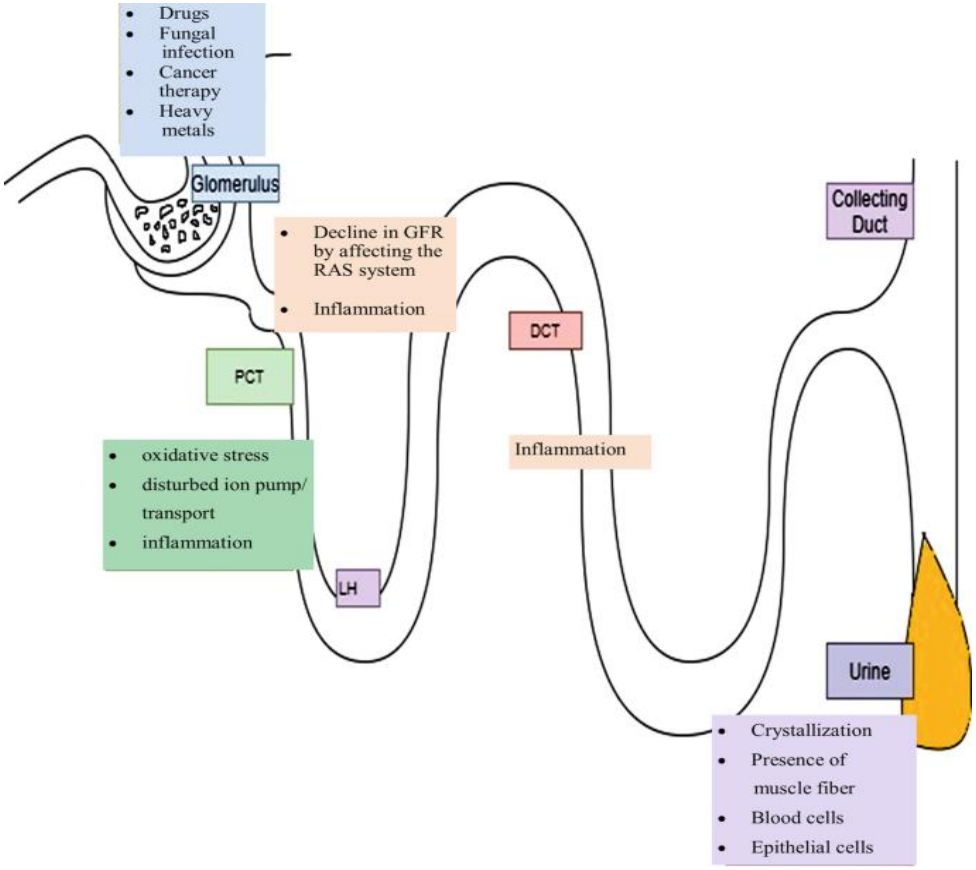

Fig. 2: Drug Induced Nephrotoxicity.

2.3 Medication Adherence Challenges

Nonadherence to prescribed medications is a major challenge in CKD management and significantly affects patient outcomes. Patients with CKD often face multiple barriers to adherence, including high pill burden, complex dosing regimens, frequent medication changes, cost issues, cognitive decline, and physical limitations (e.g., difficulty swallowing pills and vision impairment). Additionally, the asymptomatic nature of early-stage CKD may contribute to poor patient motivation, leading to missed doses or self-discontinuation of

medication. Nonadherence is particularly concerning for renoprotective agents, such as ACE inhibitors, angiotensin receptor blockers (ARBs), phosphate binders, and erythropoiesis-stimulating agents (ESAs), as their inconsistent use can accelerate renal decline, electrolyte imbalances, and anaemia progression. Strategies to improve adherence include simplified dosing schedules, fixed-dose combinations, patient education, medication counselling, and digital reminders. The involvement of clinical pharmacists and nephrologists in medication therapy management (MTM) programs can enhance adherence and improve patient outcomes.[9]

2.4 Inappropriate Prescribing in CKD

Prescribers may not always account for the unique pharmacological considerations in CKD, leading to inappropriate prescriptions, suboptimal dosing, or harmful drug combinations. Common prescription errors in CKD include failure to adjust doses based on eGFR, prescribing nephrotoxic medications without renal monitoring, and overlooking drug interactions that can worsen renal function. For instance, NSAIDs and COX-2 inhibitors are often inappropriately prescribed for pain management in CKD despite their well-documented nephrotoxicity. Similarly, proton pump inhibitors (PPIs), commonly used for acid suppression, have been linked to chronic interstitial nephritis and electrolyte imbalances; however, they are frequently overprescribed in patients with CKD.[10] Benzodiazepines and opioids, which have prolonged elimination of renal impairment, are often prescribed without proper dose modifications, increasing the risk of sedation, falls, and respiratory depression. To ensure appropriate prescribing, healthcare providers should follow evidence-based guidelines e.g., Kidney Disease: Improving Global Outcomes (KDIGO) and Kidney Disease Outcomes Quality Initiative (KDOQI), use electronic prescribing tools to flag contraindicated drugs, and conduct regular medication reviews.[11]

2.5 Navigating Drug-Disease Interactions

The complex interplay between medications and CKD pathophysiology presents additional challenges in drug utilisation. Some drugs may worsen fluid retention and electrolyte imbalances, or accelerate kidney function decline, necessitating close monitoring. For example:

a) Diuretics (loop and thiazide)- While essential for managing volume overload in CKD, excessive use can lead to dehydration, electrolyte imbalances (hypokalemia, hyponatremia), and acute kidney injury (AKI)

b) Renin Angiotensin Aldosterone System (RAAS) inhibitors (ACE inhibitors, ARBs)- These drugs provide renoprotective effects but can cause hyperkalemia and a temporary rise in serum creatinine. This requires careful dose titration and potassium monitoring.[12]

c) Phosphate binders and vitamin D analogs- Used to manage CKD-associated mineral and bone disorders (CKD-MBD), these medications must be adjusted to prevent hypercalcemia, vascular calcification, and secondary hyperparathyroidism.[13]

d) Sodium-glucose cotransporter-2 (SGLT2) inhibitors- These newer antidiabetic agents offer cardiorenal benefits but may cause volume depletion and AKI in patients with advanced CKD.

3. MEDICATION ADHERENCE IN CHRONIC KIDNEY DISEASE

Medication adherence is a critical component of chronic kidney disease (CKD) management; however, it remains a significant challenge owing to multiple patient-related, treatment-related, and healthcare system-related factors.[14] Non-adherence to prescribed medications can lead to disease progression, increased hospitalization rates, and poor overall outcomes. Despite the availability of effective pharmacological interventions for CKD and its complications, many patients struggle to maintain consistent medication use. Key barriers to adherence include the complexity of the regimen, medication side effects, and psychosocial factors, all of which impact a patient's ability to follow prescribed treatment plans.[15][16]

3.1 Complexity of the Medication Regimen

Patients with CKD often require multiple medications to manage renal function, blood pressure, electrolyte balance, anaemia, bone mineral disorders, and comorbid conditions such as diabetes and cardiovascular disease. Polypharmacy, defined as the use of five or more medications, contributes to confusion, dosing errors, and pill burden, making adherence difficult. Additionally, medications for CKD often have strict dosing schedules (e.g., phosphate binders must be taken with meals, diuretics in the morning to avoid nocturia, and erythropoiesis-stimulating agents at specific intervals), which further complicates adherence.[17] Patients may struggle to remember the correct timing, frequency, and administration instructions, leading to missed doses or improper use of medication. To improve adherence, simplified regimens, fixed-dose combinations, and clear patient education can help to reduce the burden of complex medication schedules.[18]

3.2 Side Effects and Their Impact on Adherence

Medication-related side effects play a major role in nonadherence among patients with CKD. Many commonly used CKD medications are associated with unpleasant or distressing adverse effects that may discourage patients from continuing treatment. For example:

a) Phosphate binders (e.g., calcium acetate, sevelamer) can cause gastrointestinal disturbances such as bloating, nausea, constipation, and diarrhea, which makes it difficult for patients to tolerate.
b) Erythropoiesis-stimulating agents (ESAs), used for anaemia management, may lead to fatigue, hypertension, and flu-like symptoms, causing some patients to skip the doses.
c) Diuretics, prescribed for fluid overload, can result in frequent urination, dehydration, or electrolyte imbalances, leading patients to reduce their use without consulting with healthcare providers.
d) RAAS inhibitors (ACE inhibitors, ARBs) may cause dizziness, cough, and hyperkalemia. This leads some patients to discontinue therapy prematurely.

Healthcare providers must proactively address side effects by modifying doses, switching to better-tolerated alternatives, and educating patients about the importance of medication adherence despite the mild side effects. Counselling patients about the expected side effects and potential management strategies can improve their willingness to continue therapy.[20]

3.3 Psychosocial Barriers to Adherence

Beyond pharmacological challenges, psychosocial factors significantly influence medication adherence in CKD patients. Many patients with CKD experience depression, cognitive impairment, financial constraints, and low health literacy, all of which contribute to poor compliance with prescribed regimens.

a) Depression and Anxiety: Psychological distress is common in CKD due to the chronic nature of the disease, lifestyle restrictions, and fear of progression to end-stage renal disease (ESRD). Depression can lead to low motivation, forgetfulness, and intentional nonadherence, particularly in patients who do not perceive immediate benefits from their medication. Routine mental health screenings and counselling can help to address this issue.[19]
b) Cognitive Impairment: CKD is associated with mild cognitive decline, especially in advanced stages, affecting memory, decision-making, and executive function. Patients

with cognitive impairment may struggle to remember doses, understand instructions, or recognize the importance of adherence.[21]

c) Caregiver involvement, pill organizers, and digital medication reminders can help support such patients.[20]

d) Financial Constraints: Many CKD medications, such as ESA therapy, phosphate binders, and potassium binders, are costly, and patients with limited financial resources may prioritize basic needs over medication purchases. Nonadherence due to financial barriers can be mitigated by generic alternatives, financial assistance programs, and medication insurance coverage support.

e) Low Health Literacy: Some patients may have difficulty understanding medical terminology, dosage instructions, or the rationale behind specific treatments, leading to poor adherence.[22]

Patient education programs, simplified language, and visual aids can improve their comprehension and adherence.

3.4 Strategies to Improve Medication Adherence

To enhance adherence in CKD patients, a multidisciplinary approach involving nephrologists, pharmacists, nurses, and caregivers is essential. Effective strategies include the following.

a) Medication counselling and shared decision-making to empower patients in their treatment plans.[9]

b) Pill organizers, mobile health apps, and automated reminders to improve the medication tracking.

c) Fixed-dose combination therapies to reduce the pill burden and simplify regimens.[9]

d) Routine follow-ups and adherence monitoring using pharmacy refill data or self-reported adherence tools.[23]

e) Addressing psychosocial factors through mental health support, financial assistance, and caregiver involvement.[23]

4. OPTIMIZING DRUG UTILISATION IN CHRONIC KIDNEY DISEASE

Optimizing drug utilisation in patients with chronic kidney disease (CKD) is essential to ensure appropriate medication, safety, and adherence, while minimizing drug-related complications. Given the complexities of CKD pharmacotherapy, a multidisciplinary approach is required with pharmacists playing a critical role in medication management. Pharmacists contribute significantly to improving patient outcomes by conducting medication

reviews, educating patients, and monitoring drug levels to optimize dosing and prevent adverse events.[24]

4.1 Medication Review and Reconciliation

Pharmacists play a key role in medication reconciliation, ensuring that each prescribed drug is appropriate, effective, and safe, based on the patient's renal function, comorbid conditions, and overall treatment goals. CKD patients often receive multiple medications for blood pressure control, anaemia management, electrolyte balance, and metabolic complications, increasing the risk of drug-drug interactions and nephrotoxicity.

a) Adjusting Medication Doses: Many drugs require renal dose adjustments to prevent accumulation and toxicity. Pharmacists assess renal function (e.g., using eGFR or creatinine clearance) and recommend dose modifications for drugs such as digoxin, metformin, aminoglycosides, and opioids.[25]

b) Identifying Nephrotoxic Medications: Some commonly used drugs, including non-steroidal anti-inflammatory drugs (NSAIDs), contrast agents, and certain antibiotics, pose a high risk of kidney damage and must be avoided or used with caution. Pharmacists help identify these risks and suggest safer alternatives.[20]

Table 3: Nephrotoxic Drugs to Avoid or Use with Caution in CKD.

Drug Class	Examples	Nephrotoxic Mechanism	Alternative options
NSAIDs	Ibuprofen, Naproxen	↓ Renal blood flow, interstitial nephritis	Acetaminophen (for pain)
Aminoglycosides	Gentamicin, Amikacin	Tubular toxicity	Beta-lactam antibiotics
Contrast Agents	Iodinated contrast	Acute kidney injury	Non-contrast imaging

c) Managing Polypharmacy and Drug Interactions: Given the high prevalence of polypharmacy in CKD, pharmacists review prescriptions to minimize unnecessary medications and to avoid harmful interactions. For example, RAAS inhibitors (ACE inhibitors, ARBs) combined with potassium-sparing diuretics can increase the risk of hyperkalemia, while NSAIDs can worsen renal function when taken alongside diuretics.[24]

Through medication reconciliation, pharmacists reduce the risk of inappropriate prescriptions, adverse effects, and preventable hospitalizations, thereby improving overall CKD care.

4.2 Patient Education and Medication Adherence

Education is a fundamental aspect in optimizing drug therapies for CKD. Many patients struggle with medication adherence due to the pill burden, cost, side effects, and lack of understanding of their condition.[26] Pharmacists play a key role in educating patients on medication use, adherence strategies, and side-effect management.

a) Explaining the Purpose of Medications: Patients may be more likely to adhere to therapy when they understand the importance of each medication. Pharmacists educate patients on how drugs help manage CKD progression, control symptoms, and prevent complications.[9]
b) Providing Adherence Strategies: Simple interventions like pill organizers, mobile reminders, and simplified dosing schedules Help patients stay on track. Pharmacists can recommend combination medications to reduce the pill burden where possible.[27]
c) Addressing Side Effects and Alternative Options: Some patients stop taking medications due to side effects without consulting with healthcare providers. Pharmacists can discuss alternative medications or dose adjustments to improve tolerance and maintain therapeutic efficacy.[28]
d) Encouraging Self-Monitoring: Patients with CKD benefit from tracking blood pressure, glucose levels (in diabetics), and symptoms like swelling or fatigue. Pharmacists educate patients on warning signs of worsening kidney function and seeking medical help. Improving patient understanding and engagement leads to better adherence, fewer complications, and improved quality of life in patients with CKD.[29]

4.3 Monitoring Drug Levels and Therapeutic Drug Monitoring (TDM)

Therapeutic drug monitoring (TDM) is essential for medications with narrow therapeutic windows, where small changes in dose can result in toxicity or sub-therapeutic effects. In CKD, altered drug metabolism and excretion necessitate the close monitoring of serum drug levels for several high-risk medications.

a) Tacrolimus and Cyclosporine (Immunosuppressants): CKD patients undergoing kidney transplantation require immunosuppressive therapy to prevent organ rejection. TDM

ensures adequate drug levels while minimizing the risk of nephrotoxicity and systemic toxicity.[30]

b) Digoxin (Cardiac Glycoside): Reduced renal clearance in CKD can lead to digoxin accumulation, increasing the risk of arrhythmias, nausea, and visual disturbances. Monitoring serum digoxin levels and kidney function prevents toxicity.

c) Vancomycin and Aminoglycosides (Antibiotics): These antibiotics are renally excreted and have a high risk of nephrotoxicity and ototoxicity. TDM helps adjust doses based on renal function to ensure effective bacterial clearance while preventing toxicity.

d) Phosphate Binders and Electrolyte Management: CKD patients often require phosphate binders (sevelamer, calcium acetate) and potassium binders to manage electrolyte imbalance. Monitoring serum phosphate and potassium levels helps prevent hyperphosphatemia and hyperkalemia-related complications.[1]

5. CONCLUSION

Drug utilisation in chronic kidney disease (CKD) is complex and fraught with challenges, including nephrotoxicity, drug accumulation, polypharmacy, and medication nonadherence. The altered pharmacokinetics and pharmacodynamics of CKD necessitate careful drug selection, dose adjustment, and therapeutic monitoring to prevent adverse outcomes. Medication adherence is another critical issue that is often hindered by the pill burden, side effects, financial constraints, and cognitive or physical limitations. Addressing these challenges requires a multidisciplinary approach, with pharmacists playing a key role in optimizing drug therapy by conducting medication reviews, patient counselling, and therapeutic drug monitoring.[31] Ensuring appropriate prescriptions, improving adherence strategies, and minimizing drug-related complications can significantly enhance patient outcomes and slow CKD progression. Future research should focus on developing precision medicine approaches, personalized dosing strategies, and innovative adherence interventions tailored to CKD patients. Additionally, the safety and efficacy of newer drug therapies should be further explored to enhance treatment options while reducing the risk of nephrotoxicity. By integrating these strategies, healthcare professionals can improve the appropriateness, safety, and adherence to medication use in CKD, ultimately leading to better disease management and quality of life for patients.[32]

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