Review Article | Symptom Management in Palliative Medicine and Palliative Care

Pain management and the use of opioids in adults with kidney failure receiving conservative kidney management

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Abstract: Conservative kidney management (CKM) is an active treatment for kidney failure (KF) for people who will either not benefit from kidney replacement therapy (KRT), do not wish to pursue KRT, or do not have access to KRT. CKM aims to improve patients' quality-of-life through meticulous attention to symptom management. KF is associated with a high symptom burden globally that is experienced across age, sex, and race with chronic pain being one of the most severe and common symptoms. The delivery of CKM therefore requires the integration of effective pain management strategies. This review will provide a detailed insight into CKM globally and will offer an approach to pain management for people with KF who are receiving CKM. Specifically, this review will provide an overview of the clinical characteristics of people receiving CKM across both high and low resource settings and the epidemiology of pain in this population. While it will provide some high-level considerations for the non-pharmacologic management of pain, it will focus predominantly on pharmacologic approaches. This will include considerations of non-opioid analgesics and strategies for the use of opioids in people receiving CKM. Furthermore, we will explore global disparities in kidney care, CKM, and pain management resources, including access to opioids and will discuss some of the additional challenges faced in low resource settings.

Keywords: Pain management; kidney failure (KF); conservative kidney management (CKM); opioids; kidney supportive care (KSC)

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Introduction

Background

The number of people living with kidney disease worldwide is approaching one billion and currently ranks as the eighth leading cause of mortality (1). By 2040, chronic kidney disease (CKD) is projected to become the fifth-most common cause of years of life lost worldwide (2). The burden of CKD is disproportionately greater in low-income countries (LICs) and lower middle-income countries (LMICs) where there is diminished capacity for integrated kidney care (3,4). Integrated kidney care requires the provision of CKD prevention and the three treatment modalities for kidney failure (KF): conservative kidney management (CKM), kidney transplantation, and dialysis. Kidney replacement therapy (KRT), whether that be dialysis or transplantation, is a form of life support aimed at extending life and/or restoring quality-of-life for people

with KF. However, for older patients with multimorbidity and/or frailty, starting KRT may not provide a survival or a quality-of-life advantage (5-7). Furthermore, in many countries, people with KF do not have access to KRT. Even in countries such as South Africa where there has been an exponential growth of private dialysis facilities, state funded KRT remains strictly rationed and inaccessible for most people (8). The proportion of people with KF not receiving KRT is approximately 98% in LICs, 94% in LMICs, and 79% in upper-middle income countries (UMICs) compared to 30% in high-income countries (HICs) (9). KRT, therefore, is not a default care pathway and CKM should be provided for all patients unlikely to benefit from KRT, who do not wish to pursue KRT, or who do not have access to KRT (10).

CKM focuses on providing kidney supportive care (KSC) to optimize quality-of-life. KSC is anchored in the World Health Organization (WHO) definition of palliative care (11) and aims to improve the quality-of-life for people with all stages of CKD through the prevention and relief of suffering by means of early identification and impeccable assessment and treatment of pain and other problems, physical, psychosocial, and spiritual. KF is associated with a high symptom burden that is experienced across age, sex, race, and geographic location, with chronic pain being one of the most prevalent and bothersome symptoms (12). CKM therefore requires the integration of effective pain management strategies.

Rationale and knowledge gap

Inadequate clinician education and empowerment are persistent barriers to appropriate pain management. Many clinicians have limited expertise in pain management and are reluctant to prescribe and monitor analgesics (13). Survey studies from the US have reported that only 44% of 2nd year nephrology fellows were taught how to treat patients' pain (14) and only 9.4% felt very comfortable treating pain in patients with advanced CKD (15). A systematic review of prescribed analgesics for 963,269 patients with advanced CKD from 21 HICs highlighted tremendous variability within and between countries despite consistently high pain prevalence rates suggesting widespread uncertainty regarding the optimal pharmacologic management of pain in people with KF and inadequate use of analgesics, especially non-opioids and adjuvant therapy for neuropathic pain (16). In LICs and LMICs the delivery of CKM relies heavily on primary care (17) yet community palliative care and hospice services are focused primarily on care for patients with advanced cancer and HIV, with very limited expertise in KF and CKM.

Effective pain management in CKM is further complicated by minimal or no access to palliative care services or essential medications (18); 83% of the world's countries have low to non-existent access to opioids (19) and even access to the simplest pain-relieving medication is often limited (20). All these factors impact how CKM, including pain management, is dealt with, especially in low resource settings.

Objectives

This review will provide a detailed insight into CKM globally and will offer an approach to pain management for people with KF who are receiving CKM. Specifically, this review will provide an overview of the clinical characteristics of people receiving CKM across both high and low resource settings and the epidemiology of pain in this population. While it will provide some high-level considerations for the non-pharmacologic management of pain it will focus predominantly on pharmacologic approaches. This will include considerations of non-opioid analgesics and strategies for the use of opioids in people receiving CKM, taking into account some of the additional challenges faced in low resource settings.

Clinical characteristics of people receiving CKM

The clinical characteristics of people receiving CKM vary across countries and resource settings, impacting both the common etiologies of pain and pain management strategies. Most of the literature on CKM comes from HICs where KRT is available and CKM is delivered following a process of shared decision-making that incorporates the individual's preferences for survival and quality-of-life. These people tend to be older, often greater than 75 years, and have considerable burden of non-communicable diseases and geriatric syndromes such as frailty. The elderly and frail tend to be more susceptible to adverse effects such as confusion, nausea, vomiting, constipation, falls, and respiratory depression when using analgesics, especially opioids (21,22). Older people may also have enhanced pharmacodynamic sensitivity to opioids with a more pronounced response to any given dose when compared to younger adults (21). Many will have been under the care of a nephrologist for years with interventions in place to slow

the progression of disease. These patients may be quite stable on a CKM pathway for several years (5-7,23).

In LICs and LMICs, there is a growing burden of non-communicable diseases, particularly hypertension, heart failure, and diabetes mellitus (DM), all of which are major contributors to KF (3,24,25). Africa is predicted to have the highest increase in DM by 2024 (129%), and currently over 1 in 2 (54%) people living with DM are undiagnosed in this region (26). The increase of communicable diseases, particularly human immunodeficiency virus (HIV), malaria, tuberculosis, and an explosion of illicit drug use are also contributing to the increased incidence of KF (3,24,25). These factors, when compounded by under resourced healthcare systems, household poverty with no or dismal national healthcare insurance, lack of awareness, poor access to preventative medicine and follow up, and lack of understanding of the impact of chronic diseases, result in people reaching KF with multiple comorbidities at a much younger age and with complex psycho-social needs. Moreover, most people in LICs and LMICs present late at the point of KF (27), often with progressive disease and a shorter life expectancy. Based on the overarching ethical principle of utilitarianism, national guidelines in LMICs mandate that only patients who are transplantable be accepted into chronic dialysis programs (28,29). Exclusion criteria include many of the common causes of KF such as DM in people over the age of 50 years due to their high cardiovascular complications with transplantation, HIV positive patients who are not virally suppressed, and illicit drug use. Where palliative care services are available, the only active treatment for KF is CKM. Issues of methamphetamine and heroin use and withdrawal contribute to the difficulties with pain management and overall CKM delivery for these people.

Epidemiology of pain in CKM

A recent systematic review of 16,558 patients from 68 studies representing 26 countries found that the estimated pooled prevalence of chronic pain was 60.5% in hemodialysis patients and the mean prevalence of moderate or severe pain was 43.6% (30). Data for those receiving CKM were much more limited involving eight studies with 1,361 patients from five HICs, the mean prevalence of all chronic pain and moderate or severe pain was similar to those on dialysis at 60.4% and 35.0%, respectively (30).

The potential causes of pain in KF are diverse and may be caused by the underlying kidney disease, complications of poor kidney function, and comorbidities. Patients often experience pain at multiple sites and have more than one cause of pain. In HICs, where most people receiving CKM are elderly with many comorbidities, complications due to these comorbidities and general features of ageing such as immobility, osteoarthritis, and other musculoskeletal syndromes often contribute to pain. In LICs and LMICs, there is a much younger population requiring CKM. Complications due to infectious diseases such as HIV and malaria, poorly managed non-communicable diseases such as hypertension and diabetes, and general frailty and cachexia contribute to pain. Understanding the cause, intensity, and progression of the pain is essential for proper management.

General approach to pain management

Pain should be evaluated and tracked in a rigorous and systematic way so that patients and healthcare providers can assess whether treatment is working. This involves recognizing that pain is a subjective experience and self-reporting should be central to the assessment process whenever feasible. Pain is dynamic in nature and its temporal aspects should always be considered. It is also crucial to recognize that pain extends beyond the physical realm, especially when caring for patients dealing with serious illnesses like KF. Drawing upon the concept of Total Pain, as articulated by Dame Cecily Saunders, it's evident that pain is a result of a complex interplay of biological, psychological, social, and spiritual factors. Therefore, evaluating how pain impacts a patient's psychological, social, and physical wellbeing is essential. By embracing the multifaceted nature of pain, we can better shape the objectives of care. Through discussions, it becomes possible to comprehend the desired level of functionality and pain relief, apprehensions concerning treatment approaches, the threshold individuals are unwilling to surpass in pursuit of their goals, and how the family comprehends these aspects. Given the multifaceted nature of pain, it's unlikely that all chronic pain will be fully mitigated through medication or conventional treatments. This understanding is pivotal and should be communicated to patients and their families.

General pain assessment and tracking tools such as the Brief Pain Inventory (BPI) (31) and the Revised Short-Form McGill Pain Questionnaire Version-2 (SF-MPQ-2) (32) may be used. The BPI-SF captures the severity and interference of pain with daily functioning while the SF-MPQ-2 evaluates the qualities of nociceptive and neuropathic pain. Tool selection should be grounded in its practicality,

applicability, and accessibility. It's crucial to consider factors such as age, culture, gender, and language when deciding on an appropriate tool (33). For non-verbal patients or cognitively impaired patients, specialized pain assessment tools like the Abbey Pain Scale should be used (34).

Non-pharmacological management of pain

Pain is a complex biopsychosocial disease that can affect all aspects of life; treatment strategies that rely exclusively on analgesics are unlikely to be successful. Ideally, analgesics should only be used in conjunction with non-pharmacologic therapies (i.e., multimodal therapy) such as physical therapies (e.g., exercise, stretching), manual therapy (e.g., massage, acupuncture, acupressure), and psychological therapies aimed at changing emotions, thoughts or behaviors (e.g., cognitive behavioral therapy, relaxation techniques, music therapy). This multimodal approach aims to address the whole person in the unique context of their personal life. Unfortunately, vigorous evidence around optimal non-pharmacologic therapies for people with KF remains limited making solid conclusions difficult. However, what is apparent is the positive effect of exercise (35), and education to support self-management strategies (36,37). Active interventions such as exercise interventions appear most effective for addressing pain, fatigue, sleep, and overall quality-of-life. Further research is required to understand the optimal form of exercise, i.e., endurance, resistance, or stretching. More passive interventions such as relaxation techniques and listening to music had a greater positive impact on mental health such as symptoms of anxiety or depression (36,38,39).

Non-pharmacological therapies may be especially beneficial for patients known for illicit drug use, where health care workers fear the divergence of prescribed medication and family support is complicated by previous drug addiction behavior such as theft or abuse, and homelessness. These patients and their families require specific psycho-social support, which includes the realization that CKM is a palliative pathway. Treatment may require forgiveness of previous drug abuse and containing ongoing addiction.

Pharmacologic approach to pain management

Direct evidence to support management strategies remains limited and current recommendations are based primarily on indirect pharmacologic evidence and clinical experience. An adapted WHO analgesic ladder is recommended for the management of acute and chronic pain in patients with KF, including those receiving CKM (40-43). It involves the slow introduction and titration of analgesics, starting with non-opioids then progressing to opioids as required for pain relief. Careful selection of analgesics is essential as most analgesics and their active metabolites, including opioids, are cleared by the kidneys. Even for recommended analgesics, adverse effects are common so ongoing monitoring is critical. People with KF have a narrow therapeutic window so sustained-release preparations are generally not recommended. Oral or transdermal formulations should be used whenever possible and the adverse effects such as constipation and nausea should be explained and managed actively with anticipatory prescribing.

Treatments for neuropathic pain

Neuropathic pain should be treated with adjuvant analgesics. Pain in KF is often of mixed type i.e., both nociceptive and neuropathic such as with the pain due to ischemia. The neuropathic component should be addressed first with an adjuvant to prevent inappropriate opioid use. Only if adjuvant therapy is inadequate should opioids be added. Gabapentin, pregabalin, and carbamazepine are first line agents for the treatment of neuropathic pain in CKM (42). *Table 1* provides detailed information about dosing recommendations.

Gabapentin is cleared by the kidneys; to avoid toxicity in people with KF, substantial dose reduction is needed (48). Carbamazepine may be as effective as gabapentin with fewer adverse effects (42). It is metabolized in the liver. The metabolites are cleared by the kidneys with 20–30% excreted via the feces. Only 3–5% of the parent drug is excreted by the kidneys. The plasma half-life appears unchanged with KF, and no dose adjustment is required.

Tricyclic antidepressants (TCAs) such as amitriptyline are extensively metabolized on first pass through the liver and plasma half-life is unchanged with KF (49,50). However, they are generally considered second-line adjuvants in CKM due to anticholinergic, histaminergic and adrenergic adverse effects, which may limit their use in people who are already predisposed to these symptoms. They are especially poorly tolerated by the elderly (22). If using, it is best to start at a low, divided daily dose with slow upward titration.

Although evidence is limited, topical therapies may be beneficial for localized neuropathic pain with minimal systemic absorption. Examples include capsaicin topical cream (0.025% to 0.15%) applied 3–4 times per day or

Table 1 Recommended analgesics in CKM (42)

Analgesic	Starting dose	Maximum dose	Additional considerations	Adverse effects
Non-opioid				
Acetaminophen	325–1,000 mg daily	4,000 mg daily	For older and comorbid people, maximum of 3,000 mg daily	–
Adjuvant				
Gabapentin	100 mg nightly	eGFR 15–29 mL/min: 300 mg twice per day eGFR <15 mL/min: 300 mg once per day	For elderly or frail patients, it is reasonable to start as low as 100 mg every second night. If not effective, titrate slowly every 7 days	Sedation, dizziness, somnolence, nystagmus, edema, gait disturbance
Pregabalin	25 mg nightly	eGFR 15 to 30 mL/min: 150 mg nightly eGFR <15 mL/min: 75 mg nightly	For elderly or frail patients, it is reasonable to start as low as 25 mg every second night. If not effective, titrate slowly every 7 days	Drowsiness, dizziness, nystagmus, edema, gait disturbance
Carbamazepine	100 mg nightly	1,200 mg daily	–	Drowsiness, loss of coordination, and vertigo
Amitriptyline	10–25 mg nightly	100 mg	Although no dose reduction is required, starting at a low dose nightly is recommended given the risk of anticholinergic, adrenergic, and histaminergic adverse effects. If not effective, titrate slowly every 7 days	Blurred vision, dry mouth, constipation, orthostatic hypotension, drowsiness, urinary retention, and tachyarrhythmias
Opioids				
Hydromorphone	0.5–1.0 mg po q4h (or 0.2 mg subcutaneously)	Titrate every 3–7 days based an analgesic and adverse effects	Extensive first-pass metabolism in the liver with little parent drug excreted by the kidneys. The plasma half-life of the parent compound is not substantially changed by KF (44). Hydromorphone is metabolized predominantly to H3G, which has no analgesic activity but possibly causes neuro-excitation, agitation, confusion, and hallucination. H3G will accumulate in KF if not receiving KRT	Drowsiness, constipation, nausea and vomiting, euphoria, headaches, dizziness and confusion, which can lead to falls and fractures, respiratory depression
Fentanyl transdermal patch	12 mcg/h q72h	Titrate every 3–7 days based an analgesic and adverse effects	Hepatic metabolism with 10–20% excreted by the kidneys. The plasma half-life of the parent compound is not changed by KF. Metabolites are inactive. It is not recommended in opioid naïve patients	Drowsiness, constipation, nausea and vomiting, euphoria, headaches, dizziness and confusion, which can lead to falls and fractures, respiratory depression
Buprenorphine transdermal patch	5 mcg/h q7d	Titrate every 3–7 days based an analgesic and adverse effects	Extensive first-pass metabolism in the liver with little parent drug excreted by the kidneys (45). The plasma half-life of the parent compound is not changed by KF. Metabolites are mostly excreted in the feces with only 10–30% excreted in the urine	Drowsiness, constipation, nausea and vomiting, euphoria, headaches, dizziness and confusion, which can lead to falls and fractures, respiratory depression

Table 1 *(continued)*

Table 1 *(continued)*

Analgesic	Starting dose	Maximum dose	Additional considerations	Adverse effects
Methadone	1–2 mg/every 12–24 hours	Titrate slowly based an analgesic and adverse effects	Hepatic metabolism into inactive metabolites with ~20% excreted unchanged in the urine. In anuric patients, methadone is exclusively excreted in feces (46). The plasma half-life of the parent compound is not changed by KF	The pharmacokinetics of methadone varies greatly from person to person and the potential for drug-drug interactions high (47). Due to its interaction with the voltage-gated potassium channels of the myocardium, methadone can prolong QT intervals. It's generally recommended to limit the use of methadone to experienced prescribers. Obtain a pre-treatment ECG and a follow-up ECG 2–4 weeks after initiation to monitor for prolonged QT interval. Drowsiness, constipation, nausea and vomiting, euphoria, headaches, dizziness and confusion, which can lead to falls and fractures, respiratory depression

eGFR, estimated glomerular filtration rate; KF, kidney failure; KRT, kidney replacement therapy; H3G, hydromorphone-3-glucuronide, ECG, electrocardiogram.

lidocaine 5% topical patch with up to 3 patches applied for 12 hours/day (22). These topical therapies are not available in most public sector healthcare systems in LICs and LMICs.

While there is some evidence to support the use of selective serotonin-norepinephrine reuptake inhibitors and selective serotonin reuptake inhibitors for neuropathic pain in the general population, data and clinical experience are insufficient in patients with KF to be able to make a recommendation.

Non-opioid analgesics

Acetaminophen

Acetaminophen is the first-line analgesic for mild pain in CKM. It is metabolized by the liver. Only 2–5% of the parent drug is excreted in the urine and no dose adjustment is required for people with KF (51). The recommended maximum daily dose is 4,000 mg to avoid liver injury.

Non-steroidal anti-inflammatory drugs (NSAIDs)

Chronic use of NSAIDs should generally be avoided in CKM due to the increased risks of kidney-related complications, gastrointestinal bleeding, cardiovascular events, and psychiatric events (52). The risk and severity of kidney-related complications increase with increasing age. NSAIDs may cause a severe, irreversible reduction in kidney function, especially in the context of dehydration. Slowing progression of disease and optimizing residual kidney function to prolong life is of paramount importance for many people receiving CKM, especially younger people for whom KRT is not available. NSAIDs may also precipitate hyperkalemia causing cardiac arrhythmias and sudden death as well as sodium and water retention, aggravating peripheral and pulmonary edema. NSAIDs may be used with caution for specific indications of acute pain if used at the lowest effective dose and for less than 5–7 days. Avoiding NSAIDs may increase opioid use, therefore, the risk of NSAIDs versus low dose opioids needs to be considered for any given individual. However, in the context of CKM where preservation of kidney function and prolongation of life may still be an important goal, low dose opioids are likely a safer option. Topical NSAIDs can be effective with minimal systemic absorption and adverse effects (53).

Opioids

All opioids can cause significant toxicity in people with KF

due to reduced clearance and accumulation of the parent analgesic and/or active metabolites, but some are less problematic than others (see *Table 1* for detailed dosing recommendations for recommended opioids). Weak opioids such as codeine or tramadol are not less risky than strong opioids at their lowest effective dose and in fact may be associated with a higher risk of adverse effects (42,54). In patients with KF, strong opioids at a low dose with careful titration is recommended when opioid therapy is required (42). Morphine should also be avoided due to the risk of profound toxicity in people with KF (42).

Current recommendations for opioid use in KF are based on very little clinical research and tend to focus on patients receiving dialysis. Many of the opioids and their metabolites can be removed by dialysis due to their low molecular weight, low protein binding, water solubility and low volume of distribution. However, patients receiving CKM do not have this ability to remove accumulated drug. The greater multimorbidity, disability, and cognitive deficits of many people receiving CKM also predispose them to increased adverse effects from analgesics, and in particular opioids. All opioids should be used cautiously. Vigilant monitoring of dosing and adverse events is critical. Initiating opioids at low doses with increased dosing intervals while titrating slowly is essential. Breakthrough doses can generally be prescribed at 10% of the total 24-hour opioid dose every 2–6 hours as needed.

There are tremendous differences between these international recommendations for pain management in CKM and what is available in low resource settings, leaving healthcare providers uncertain. Despite the greatest need for CKM in LICs and LMICs, these countries account for only 7% of global opioid use and opioids are often legally restricted (55,56). The WHO lists acetaminophen, codeine, morphine, transdermal fentanyl, and amitriptyline as essential medications; methadone is on the complementary list but only for the management of cancer pain (57). This list is not fully aligned with the recommended analgesics for people with KF. Furthermore, the essential opioids are rarely available; across Africa and India typically only codeine and morphine are on formulary (20,55,56). Other regions and organizations such as the African Palliative Care Association recommend that only morphine be available as part of the essential palliative care package for moderate to severe pain (58). In multiple African countries, access to even the simplest pain-relieving medication is limited (20). Although prevailing literature, primarily stemming from HICs, discourage the use of morphine for CKM patients or advocate for its use only in single doses, there is an ethical imperative not to withhold effective pain relief from suffering patients (59). The potential risks associated with accumulation of morphine in CKM patients can be mitigated through education on morphine usage, close patient monitoring, and gradual dosage adjustments. Providing a rational strategy for morphine use in LICs and LMICs has the potential to alleviate the profound anguish experienced by these individuals.

Conclusions

This review explores the need for CKM globally, and in particular in LICs and LMICs where there is limited or no access to KRT. CKM is a core component of integrated kidney care and requires the provision of effective pain management strategies in order to improve the quality-of-life for people who will either not benefit from KRT, do not wish to pursue KRT, or do not have access to KRT. This review has described an approach to pain management for people receiving CKM while considering the global disparities in pain management resources, including access to opioids, and the additional challenges this poses. We have provided high-level considerations for the non-pharmacologic management of pain. Analgesics, including opioids, are an important component of pain management and can be used safely and effectively in people receiving CKM to relieve suffering. We have discussed the pharmacologic recommendations and strategies for these complex patients, including considerations of non-opioid analgesic and opioid use. Given the increasing global burden of KF, the extremely high prevalence of chronic pain in this population, and the lack of knowledge and capacity of many clinicians and health systems to address pain, a coordinated approach involving policies will be needed to support education, essential medicines, research, and community support to optimize the care for these complex and vulnerable patients.

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