24 Pain Management in Chronic Kidney Disease

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Before You Start: Facts you Need to Know

- Pain is common in patients with chronic kidney disease (50–70% of patients depending on study) and is often not recognized.
- Pain is related to comorbidities and causes and complications of chronic kidney disease.
- Pain medication should be prescribed in a logical manner using a cautious stepwise approach.
- Pain adversely affects quality of life so must not be ignored.

24.1 Pain in CKD

Pain is common—we have all experienced it. Unlike most things treated in medicine, the experience of pain is entirely subjective. We can recognize situations where we expect pain, such as fractures, tissue damage due to surgery, ischaemia, etc., but each individual perceives the pain itself differently. Pain can therefore only be diagnosed if we ask patients whether they have pain and how this is affecting them. How pain is experienced depends on many factors including culture, social support, mood, as well as the pathology causing the pain.

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Pain is particularly common in patients with advanced chronic kidney disease (CKD). The mean prevalence of chronic pain reported by patients receiving chronic haemodialysis is approximately 60.5% and the mean prevalence of moderate or severe pain is 43.6% [1]. Patients with earlier glomerular filtration rate (GFR) categories of CKD suggest similar high prevalence rates of approximately 61% as do patients with end stage kidney disease managed with conservative kidney management (i.e., without dialysis) (59.8%) [1]. Often patients will not complain about chronic pain as they feel that this is part of their illness, that the healthcare team is not interested, or that any medication they have tried has been ineffective or has had adverse side effects. However, it is important to address pain as people living with chronic pain experience psychological distress, depressive disorders, disability, lower quality of life, conflicts in close relationships, reduced participation in many social aspects of everyday life, and increased hospitalizations and emergency department visits [2–5]. For haemodialysis patients, uncontrolled pain leads to shortened or missed treatments [6].

24.1.1 Causes of Pain

It is not surprising that patients with CKD have such a high pain burden. As shown in Table 24.1, pain can be due to the underlying kidney disease,

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Table 24.1 Causes of pain related to CKD

Primary kidney disease	Some specific causes of kidney disease can be associated with significant pain, even at stages when kidney function itself is not impaired. Examples include:
	Polycystic kidneys
	Pain from bleeding into or rupture of cysts in kidney or liver
	Infection of cysts in kidney or liver
	Back pain from lumbar lordosis caused by abdominal distension from size of kidneys and/or liver
	Renal calculi—infection and obstruction
Comorbidity	Ischaemic heart disease—Angina
	Peripheral vascular disease—Claudication, ischaemic ulcers
	Diabetes—Peripheral neuropathy
	Malignancy
Complications of CKD	Renal bone disease
	Peripheral neuropathy
	Gout
	Calciphylaxis
Haemodialysis	Steal syndrome related to arteriovenous fistula access
	Cramps during dialysis
	Dialysis amyloid arthropathy
	Discitis secondary to access infection
	Femoral vein thrombosis following femoral vein access
Peritoneal dialysis	Abdominal pain related to dialysate inflow or outflow or distension
	Lower back pain related to increased intra-abdominal pressure
	Peritonitis
	Bowel obstruction secondary to encapsulating peritoneal sclerosis
Transplant	Surgery related
	Acute rejection
	Lymphocele

complications of poor kidney function, dialysis itself, and comorbidities [7–9]. Determining the cause of pain therefore requires careful history taking. Patients often have more than one cause of pain [7–9].

Increasingly, CKD is a disease of the elderly. Over 30% of people over 80 years old have impaired kidney function. The majority of patients attending a general CKD clinic is therefore elderly and will have the general features and complications of ageing. Many of these are associated with pain as shown in Table 24.2

Table 24.2 Causes of pain related to ageing

Musculoskeletal	Osteoarthritis
	Spinal stenosis
	Disc protrusion—sciatica
	Cervical spondylosis
	Vertebral fractures and collapse
Immobility	Decubitus ulcers

24.1.2 Types of Pain

It is important to differentiate between acute and chronic pain. *Acute pain* typically persists for less than 3 months and is often associated with tissue damage, e.g. after injury or surgery. Dialysis patients may also experience episodes of acute pain during dialysis, such as headaches and cramps. Acute pain can be episodic with periods without pain. It tends to last a predictable period, have no progressive pattern, and subsides as healing occurs. With acute pain it is therefore important to treat underlying causes to ensure long-term resolution.

In contrast, *chronic pain* is often defined as pain that persists for greater than 3 months. It is usually initiated by tissue injury but is perpetuated by neurophysiological changes within the peripheral and central nervous system leading to continuation of pain once healing has occurred. The severity of the pain is often out of proportion with the extent of the originating injury. Experience of chronic pain by the patient will be affected by psychosocial factors as well as the underlying pathology causing the pain.

For the purpose of management, it is helpful to categorize pain into:

- *Nociceptive*: Pain due to tissue damage. It may be described as sharp or like a knife and felt at the site of damage, e.g. joint pain from dialysis-related arthropathy or may be experienced as a dull, aching and poorly localized with stimulation of visceral nociceptors, e.g. gut ischemia. Nociceptive pain tends to respond to analgesics.
- *Neuropathic:* Pain due to nerve damage. It may be felt at a site distant from its cause, e.g. in the distribution of a nerve. Common descriptors include burning, shooting, and electrical-like sensation. It may also be associ-

ated with episodes of spontaneous pain, hyperalgesia, and allodynia; the presence of allodynia is pathognomonic, e.g. peripheral neuropathy. Neuropathic pain responds poorly to analgesics and typically requires adjuvant therapy.
- *Mixed nociceptive and neuropathic:* For example, pain of peripheral ischaemia.
- *Incident or movement related:* Caused by bone or joint damage; pain often absent at rest but more severe on movement.
- *Other specific causes:* Such as renal colic, bowel obstruction.

24.2 Screening and Assessment of Pain (Box 24.1)

Box 24.1 Screening and assessment of Pain in CKD

Key Facts

- Pain is perceived only by the patient, so can only be described by the patient.
- Perception of pain is affected by mood and the meaning of pain for the patient.

Pain is not assessed routinely by kidney care teams and is therefore frequently not recognized. Routine and proactive assessment of pain is important [8, 9]. There are three global symptom assessment tools in regular use, which have been adapted and validated specifically for use in those with CKD. These are the Edmonton Symptom Assessment System—revised: Renal (ESAS-r:Renal), the renal version of the Integrated Palliative Care Outcome Scale (IPOS renal), and the Dialysis Symptom Index (DSI). All three tools ask the patient about the presence and severity of common physical and psychosocial symptoms in patients with CKD [10–13].

Understanding the nature, severity, and need for treatment of pain is a challenge and takes time. Many patients do not discuss their pain if they feel that the healthcare team is not interested, is rushed, or that treatment is ineffective or carries too many adverse effects. A proper assessment of pain can greatly improve the relationship between patient and their doctor or nurse. It is also important that this is ongoing with repeat assessments to assess efficacy and the need for potential changes of management.

24.2.1 Obtaining a Pain History

A pain history should determine the site of pain, duration, whether constant or intermittent, what makes it worse or better, radiation, intensity, and nature of the pain. It is also important to determine the mood of the patient, particularly whether depressed or not, and the meaning of the pain to the person [14]. A full pain assessment is shown in Table 24.3.

Table 24.3 Scheme for pain assessment

	Useful questions
Site of pain	Where is pain?
Radiation	Does the pain go anywhere else?
History of pain	When did pain start?
	Was there anything that caused pain to start such as an injury, surgical procedure, and infection?
	Has the pain got better or worse over time or does it fluctuate?
	Is the pain worse during the day or at night?
	Does the pain keep you awake?
Nature of pain	What is the pain like? Is it burning, stabbing, sharp, colicky, dull, etc.?
	Note: *Nociceptive pain* is usually described as sharp; *neuropathic pain* is commonly described as burning, shooting, and stabbing
Aggravating factors	What makes the pain worse—Movement, position, eating, etc.?
Relieving factors	What makes the pain better—Position, eating, temperature, etc.?
Severity	How severe would you say the pain is—Mild, moderate, severe?
	Can you grade the pain on a scale of 1–10, with 10 being worst?
	Does the severity vary and if so how?

(continued)

Table 24.4 (continued)

	Useful questions
Impact of pain	How does the pain impact on daily activities, exercise, etc.?
	Does the pain stop you from sleeping?
	Do you ever feel down because of the pain?
Effect of treatment	What have you done to try and make the pain less?
	Do you take any painkillers, and if so what?
	Do you find the painkillers helpful?

24.3 Management of Pain

24.3.1 Barriers to Pain Management

A combination of clinician and patient factors contribute to poor pain recognition and management in patients. This is true for all patients, but probably happens more frequently for patients with CKD owing to the complexity of the causes of pain, the fact that many nephrologists are not trained in pain management, and the difficulty of prescribing analgesia with impaired kidney function. Table 24.4 lists potential clinician and patient factors and how these could be overcome.

Table 24.4 Potential barriers to pain management

Potential barriers	Overcoming barrier
Clinician factors	
Focus of care on management of medical problems—Kidney disease, dialysis, transplant, and comorbidity, so limited time for focus on other issues such as pain	Ensure that pain and its management in CKD is included in curriculum for all trainee kidney healthcare professionals
Lack of awareness of potential pain, so not asked about	Arrange local CPD and conferences about pain management
Not sure how to manage pain if any is reported	Make "kidney" pain-management guidelines available on wards and in clinics
Failure to monitor response to any treatment	Audit pain assessment and management as quality improvement project
Fear of drug toxicity because of impaired kidney function	
Fear of using opioids in noncancer pain	
More than one cause of pain so management complex	
Patient factors	
Underreporting of pain—Particularly if pain is chronic and thought by patient not to be related to kidney disease	Clinician should remember to ask patient about pain
Analgesia not taken because of fear of side effects	Routine symptom survey questionnaires that include pain—Though these must then be reviewed by clinical team and acted upon
Analgesia stopped because of side effects—And not reported to clinician	Availability of pamphlets about pain control in kidney disease
Anxiety about taking opioids because of fear of addiction	Availability of healthcare professional from kidney and/or palliative care team who can talk to patient about pain control and alleviate concerns
Delaying procedures that may relieve pain, e.g. amputation for ischaemic limbs	

24.3.2 Non-pharmacological Management

Pain perception and analgesic requirement vary between patients and with time in individual patients. Many factors can exacerbate pain including depression, loneliness, inactivity, fear, and anxiety about meaning of pain. Pain management therefore includes exploring psychosocial issues with patients and eliciting potential depression and anxiety which should then be appropriately managed with psychological support and/or medications such as antidepressants [7]. Other nondrug measures for pain relief may include:

- *Transcutaneous nerve stimulation* (*TENS*): The rationale for TENS is based on the gate theory for pain. TENS should only be used for chronic pain, including neuropathic pain—there is no evidence of benefit for acute pain. It should only be administered by

specialist pain clinics as how electrodes are placed makes considerable difference to efficacy.

- *Acupuncture*: Although evidence of benefit is equivocal, some patients find acupuncture beneficial for management of chronic pain. Theories for its mode of action include the production of endorphins.
- *Physiotherapy and manipulation*: Many people will try these methods, particularly for back pain, despite lack of evidence of benefit. Physiotherapy for patients with reduced mobility can also improve general well-being and mood, both of which may alleviate perception of pain.

24.3.3 Drug Management

The World Health Organization (WHO) analgesic ladder uses a stepwise approach to prescribing analgesics that selects initial analgesia according to the severity of the pain, starting at the lowest appropriate level and titrating as required to alleviate pain. This approach has been found to be useful and efficacious for cancer pain. It is now advocated for use in patients with non-malignant chronic pain and has been adapted for use for patients with advanced CKD and those on dialysis [15, 16]. An example of such an approach adapted for patients with advanced CKD is shown in Fig. 24.1 [4]. Table 24.5 out-

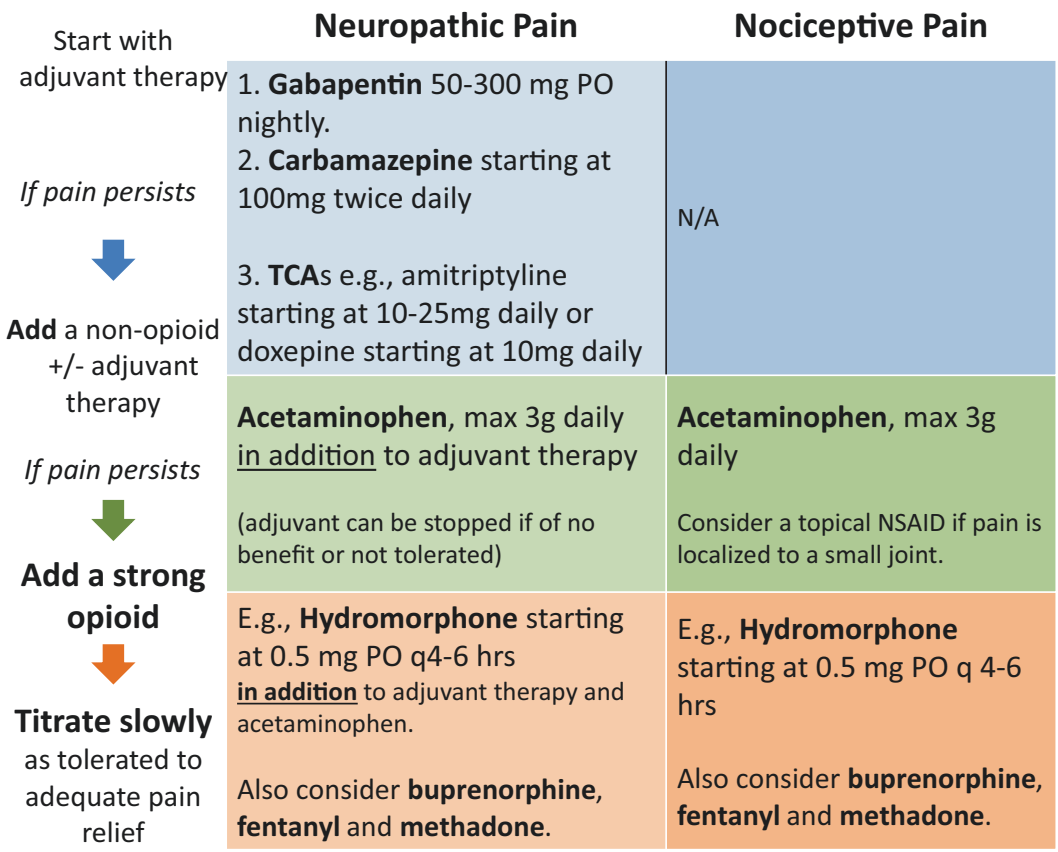

Fig. 24.1 Adapted analgesic ladder for patients with advanced chronic kidney disease

Table 24.5 Principles of pain management

By mouth	Use the oral or transdermal route whenever possible
By the clock	Where pain is continuous or predictable, analgesics should be given regularly. Additional breakthrough medication should be available on an "as needed" basis
By the ladder	Cautious stepwise approach using the modified WHO ladder starting with non-opioids and progressing to low-dose opioids. The analgesic should be used to its full-tolerated dose before stepping up to the next level. Adjuvant drugs can be added to all steps of the ladder. Non-opioid analgesics can be added to opioids
For the individual	There is no standard dose of strong opiates. The "right dose" is that which relieves pain without causing unacceptable adverse effects. Sensitivity to adverse effects varies between patients and must be monitored for closely. The impact on overall symptom burden, physical function, emotional state, cognition, and quality of life should be assessed
Attention to detail	Pain changes over time; thus, there is a need for ongoing reassessment. Side effects of opioids should be explained and managed actively, e.g. constipation and nausea, with anticipatory prescribing.

lines the five key principles to keep in mind when prescribing analgesics. Sustained-release preparations are generally not recommended in patients with advanced CKD.

Most analgesics, including opioids and their active metabolites, are cleared renally. The selection of analgesics for patients with advanced CKD is therefore challenging and must take into account the altered pharmacokinetics and pharmacodynamics, especially when eGFR is <30 mL/min. Table 24.6 outlines recommended analgesics in CKD [16]. Even for recommended analgesics, adverse effects are common so ongoing monitoring is important [17–20].

Acetaminophen is considered the non-narcotic analgesic of choice for mild to moderate pain in CKD patients. All of the opioids can cause sig-

Table 24.6 Analgesic use in advanced chronic kidney disease based on an adapted analgesic ladder

Recommended but use with caution	
Non-opioids	
Acetaminophen	Metabolized by the liver with only 2–5% excreted in the urine and does not require dose adjustment in CKD. Recommended maximum daily dose of 3.2 g/day. In high-risk patients (chronic stable liver disease, alcoholics, and malnourished patients), limit the maximal dose to 2.6 g/day
Opioids	
Oxycodone	Limited pharmacokinetic evidence for safety in advanced CKD with conflicting case reports. Although less than 10% is excreted unchanged in the urine, both the parent drug and the active metabolites appear to accumulate in CKD. The potential for drug interaction and unpredictable pharmacodynamic response is also relatively high. While not contraindicated, use with extreme caution and never use slow-release formulations. Consider a starting dose of 2.5 mg by mouth every 8–12 h
Hydromorphone	Extensively metabolized by the liver. Metabolites removed by dialysis, and if followed carefully, patients can tolerate well if doses started low and titrated slowly. Consider a starting dose of 0.5–1 mg by mouth every 6 h. active metabolites accumulate without dialysis therefore may not be an appropriate analgesic for patients with stage 5 CKD not on dialysis
Fentanyl patch	Rapidly metabolized in the liver, with only 5–10% excreted unchanged in the urine. Its metabolites are considered to be inactive. There does not appear to be clinically significant accumulation in advanced CKD and transdermal preparations have been used successfully. Not appropriate for opioid-naïve patients

Table 24.6 (continued)

Recommended but use with caution	
Methadone	Extensively distributed in the tissues where it accumulates. Slow release from the tissues can result in prolonged pharmacological action of up to 60 h. in advanced CKD it is excreted mainly in the faeces and does not appear to accumulate appreciably in plasma. It may be more effective for neuropathic pain than other strong opioids because of its N-methyl-D-aspartate receptor antagonism
Buprenorphine patch	Limited experience in advanced CKD, but the liver metabolizes it with little parent drug found in the urine. Pharmacokinetics appears minimally altered in CKD. Metabolites, however, accumulate in CKD but appear relatively inactive. It can be administered via a transdermal patch but might be difficult to antagonize with opioid antagonists. Additional care should be taken when used with benzodiazepines
Adjuvants	
Gabapentin	First-line therapy for neuropathic pain in advanced CKD. Titrate slowly. Doses up to 300 mg/day are generally safe but monitor for side effects (nystagmus, ataxia, tremor, somnolence, and reduced level of consciousness)
Carbamazepine	It requires no dose adjustment for patients with CKD and may have fewer adverse effects than gabapentin. Start at 100 mg twice daily and titrate slowly to a maximum of 1200 mg daily
TCA antidepressants (e.g. nortriptyline, desipramine)	Use may be limited due to anticholinergic, histaminergic, and adrenergic side effects resulting in symptoms such as dry mouth, orthostatic hypotension, and somnolence. Tachyarrhythmias are also a concern. Considered second-line therapy for neuropathic pain in CKD. Initiate at low dose, give in divided daily doses and titrate slowly

Table 24.6 (continued)

Recommended but use with caution	
Do not use	
Non-opioids	
NSAIDs	Risks include irreversible reduction in GFR for those with residual renal function, an increased risk of gastrointestinal bleeding and possible increased risk of myocardial infarction. Use is best reserved for specific indications of acute pain such as gout or renal colic. Use at the lowest effective dose and for the shortest duration, typically < 5 days.
Opioids	
Codeine	Metabolized by the enzyme CYP2D6 in the liver to its active metabolite morphine, which accumulates and can cause prolonged narcosis and respiratory depression. There is tremendous genetic polymorphism of the CYP2D6 gene and an individual's response is highly variable and can result in unpredictable toxicity with trivial doses or poor analgesic response with standard doses
Morphine, propoxyphene, meperidine (pethidine)	Neurotoxic metabolites are excreted renally and accumulate in patients with CKD. Patients are at high risk of neurotoxicity, including seizures

nificant toxicity, but some are less problematic than others (see Table 24.6). They should all be used cautiously, with both dose reduction, increase in the dosing interval, and regular monitoring. Patients requiring opioids can be managed effectively with short-acting hydromorphone that can be switched to transdermal fentanyl if the daily hydromorphone dose exceeds 12 mg.

24.3.4 Neuropathic (Nerve) Pain

Neuropathic pain is unlikely to respond to analgesics, including opioids alone. Adjuvants such as anticonvulsants and antidepressants have

proven successful in this regard, though studies specific to patients with advanced CKD are lacking. Opioids may be required in addition to adjuvant therapy. Methadone may be more useful than opioids for treating neuropathic pain. There are insufficient data or clinical experience with selective serotonin reuptake inhibitors (SSRI) and selective serotonin-norepinephrine reuptake inhibitors (SSNRI) for neuropathic pain in patients with advanced CKD to make a recommendation.

24.3.5 Other

Opioids can be abused so safe prescribing requires consideration of the risks associated with drug abuse and addiction. These issues need to be separated from physiological physical dependence, which is defined as the occurrence of withdrawal symptoms if the dose is abruptly reduced or after administration of an opiate antagonist. Experience suggests that less than 10% of patients have the biological characteristics that put them at risk of becoming addicted. Risk is highest in patients who have a personal or family history of alcohol or drug abuse. Such patients will benefit from careful monitoring by a specialist pain team.

24.4 Conclusion

Pain is common in patients with chronic kidney disease and can be caused by the kidney disease itself, complications related to kidney disease and comorbidities. It is therefore important that all patients should be asked about the existence and nature of any pain, that the cause of the pain is identified and that patients are given adequate and appropriate pain control. Management of pain also includes addressing psychosocial issues as pain can adversely affect quality of life, and this in turn can impact negatively on the perception of pain severity by the patient. Renal clinicians should be aware of the complex manner in which analgesic dosing is affected by kidney function and therefore become familiar with a few analgesics for each stage of the WHO pain-control ladder. Referral to palliative care or specialist pain services should be considered for management of complex pain or when drug abuse or addiction is suspected.

Before You Finish: Practice Pearls for the Clinician

- Regularly ask all patients with kidney disease about the existence of pain.
- Take a full pain history to determine nature, cause, and severity of pain and its psychosocial impact.
- Ask patients about existing analgesia to determine whether this is sufficient and/or appropriate for level of kidney function.
- Become familiar with one or two drugs in each analgesic class regarding dosage related to kidney function and likely side effects.
- Collaborate with your local specialist pain service and refer patients.
- Monitor for impact on overall symptom burden, physical function, emotional state, cognition, and quality of life.

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