Medication Management of Pain in Kidney Disease

Chronic pain is a common symptom experienced by patients with chronic kidney disease (CKD) and end-stage kidney disease (ESKD).

- Untreated pain in this population negatively impacts health-related quality of life, dialysis adherence, healthcare utilization, and mortality and may contribute to other physical and psychosocial symptoms such as depression, anxiety, and fatigue.
- There is a disproportionately high use of opioids in the CKD/ESKD population due to limited availability of non-pharmacological treatment options or safe non-opioid pharmacological options.
- In a study of over 400,000 ESKD patients, over half had received an opioid prescription and 20% were on long term opioid therapy.[1] Chronic opioid use in patients with kidney disease has been associated with increased risk of altered mental status, falls, fractures, hospitalizations, and mortality.

Causes of Pain[2,3]

- Patients with CKD are vulnerable to all the causes of pain that affect the general population. In addition, CKD patients may experience pain related to their primary kidney disease (e.g., polycystic kidney disease), comorbid conditions (e.g., diabetic neuropathy or peripheral vascular disease), or sequelae of CKD (such as calcific uremic arteriolopathy [calciphylaxis], bone pain from renal osteodystrophy, and dialysis-related amyloid arthropathy).
- Pain may also be directly or indirectly related to dialysis.
- Among patients with CKD, the pain is often mixed (i.e., nociceptive and neuropathic) in nature.

Non-opioid Medication Management in Patients with Kidney Disease[1]

Medication	Dosing in CKD	Dosing in ESKD	Comments
Acetaminophen	• CrCl 10-50 mL/min: 650 mg every 6 hours as needed • Max daily dose 3000 mg	• CrCl < 10 mL/min or dialysis: 650 mg every 8 hours as needed • Max daily dose 3000 mg	• Use scheduled doses instead of "as needed" for continuous pain control • Use with caution and lower the max daily dose to 2000 mg if liver disease or daily alcohol use
NSAIDs, preferably COX-2 selective agents such as celecoxib	• Reduce dose and increase dosing interval (i.e., administer less frequently) • Use for short term (≤5 days only) • Contraindicated in CKD stage 5	• Not significantly dialyzable • No dosage adjustment necessary with dialysis, but best to avoid usage	• Monitor for volume retention, cardiotoxicity, renal and gastrointestinal toxicity
Pregabalin	Max daily dose: • CrCl 30-60 mL/min: 300 mg daily in 2-3 divided doses • CrCl 15-30 mL/min: 150 mg daily in 1-2 divided doses • CrCl < 15 mL/min: 75 mg daily as a single dose	• Start at 25 mg once daily • Maximum dose 75 mg once daily • Well dialyzed; Additional dose required post-hemodialysis (HD)	• Start at low dose and titrate every 1-2 weeks; monitor for altered mental status and occurrence of falls

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Medication	Dosing in CKD	Dosing in ESKD	Comments
Gabapentin	Max daily dose: • CrCl 50-79 mL/min: 1800 mg daily (3 divided doses) • CrCl 30-49 mL/min: 900 mg/day (2-3 divided doses) • CrCl 15-29 mL/min: 600 mg/day (1-2 divided doses) • CrCl < 15 mL/min: 300 mg/day (single dose)	• Maximum dose 300 mg once daily • Well dialyzed; Additional dose required post-HD	• Start at low dose and up titrate every 1-2 weeks • Monitor for altered mental status and falls
Duloxetine	• Start with 20 mg daily • Max daily dose: 60 mg • CrCl 30-80 mL/min; no dose adjustment necessary • CrCl < 30 mL/min: avoid use	• Avoid use (limited data)	• Monitor for hyponatremia
Venlafaxine	• Extended release: Start at 37.5 mg once daily Max daily dose: • CrCl 30-89 mL/min: 150 mg daily • CrCl <30 mL/minute: 112.5 mg daily	• Extended release: Start at 37.5 mg once daily • Max daily dose: 112.5 mg daily • Poorly dialyzed	• Monitor for hyponatremia
Desvenlafaxine (active metabolite of venlafaxine)	Max daily dose: • CrCl 30-50 mL/min: 50 mg once daily • CrCl <30 mL/min: 25 mg once daily or 50 mg every other day	• Max daily dose: 25 mg once daily or 50 mg every other day • Poorly dialyzed	• Monitor for hyponatremia

Opioid Medication Management in Patients with Kidney Disease[1]

Medication	Dosing in CKD	Dosing in ESRD	Comments
Hydromorphone	• Start at 2.5-5 mg every 6-8 hours	• Start at 2.5-5 mg every 6-8 hours • Well dialyzed but no supplemental dose required post HD	• Use caution with high doses
Fentanyl (transdermal)	• Reduce the initial dose by 50% in mild to moderate renal impairment and titrate to desired clinical effect	• Avoid use in severe renal impairment • Poorly dialyzed	• Do not start in opioid naïve patient
Methadone	• Start 1-2 mg once or twice a day	• Start 1-2 mg once or twice a day • Poorly dialyzed	• Do not start in opioid naïve patient
Buprenorphine patch	• 5 mcg/hr per week	• 5 mcg/hr per week	• Do not start in opioid naïve patient • Lesser risk of overdose and respiratory and CNS depression as compared to other opioids
Oxycodone (short-acting) *2nd line to hydromorphone, fentanyl, methadone, and buprenorphine[2]	• Start at 2.5-5 mg every 12 hours • Recommend prolonged dosing interval in severe renal impairment	• Not recommended;[2] prolonged dosing interval in ESKD • Poorly dialyzed	• Caution should be used with long-acting formulations and when used concurrently with medications that affect CYP3A4 or CYP2D6 metabolism

Medications to Avoid in Advanced CKD[2]

- **NSAIDs**: may cause acute reduction in GFR (glomerular filtration rate-test used to check how well kidneys are working), hypertension and hyperkalemia. NSAIDs are associated with increased risk of bleeding. Avoid NSAIDs when possible for patients with a GFR < 60ml/min/1.73m^2, especially in older adults >75 years of age.
- **Morphine:** drug of choice for severe pain in hospice patients and use must be carefully considered in those with kidney disease; avoid with GFR<30 mL/min/1.73m^2 due to active metabolites accumulating that may lead to fatal respiratory depression and toxicity.
- **Codeine:** metabolized by the liver to active metabolites of morphine. In patients with a GFR< 30mL/min/1.73 m^2 many reports of narcosis (stupor, drowsiness, or unconsciousness) in patients with CKD.
- **Tramadol:** even low doses in patients with advanced CKD may cause significant side effects, including nervous system depression; serotonin syndrome is much more prevalent in patients with CKD on tramadol and antidepressants.
- **Oxycodone**: avoid use of oxycodone among patients with advanced CKD due to the risk of respiratory depression.[4] Oxycodone may be used among patients with CKD as a second-line agent after trialing the use of hydromorphone, fentanyl, methadone, or buprenorphine. Oxycodone is eliminated mainly by liver metabolism to noroxycodone and oxymorphone, both of which accumulate in patients with advanced CKD. Less than 10 percent of oxycodone is excreted unchanged in the urine.

References

1. Roy PJ, Weltman M, Dember LM. Pain management in patients with chronic kidney disease and end stage kidney disease. *Current Opinion in Nephrology and Hypertension* 29(6):p 671-680, November 2020
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