Pain Management for Patients with Kidney Disease: 
Getting through the Conundrum

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Kidney Disease Rates Expected to Rise
126.1 million adults in the USA (~50% of the adult population) reported some form of pain

>200 million opioid prescriptions were dispensed by US retail pharmacies over the same year

25.3 million American adults suffer from daily pain

23.4 million American adults report a lot of pain

Epidemiology

Pain Prevalence in Chronic Kidney Disease (CKD)

- Pain
  - the most common symptom experienced by CKD patients
  - often undertreated

- Similar to the general population, pain prevalence in patients with CKD has been reported to be in the range of:
  - 40-60% - patients receiving renal replacement therapy (RRT)
  - 60-70% - pre-end-stage kidney disease (ESKD)
  - Up to 100% hospitalized CKD patients
Epidemiology

Pain Prevalence in CKD

• Very few studies have reported the prevalence of pain among patients with earlier stages of CKD.

• A single, small study of 130 nondialysis CKD patients with varying severity of CKD suggest that the prevalence of pain was similar among all levels of CKD patients, ~64 to 75%.

• Most studies in CKD patients show no association of chronic pain with sex, age, race, or ethnicity.
In hemodialysis (HD) patients, the prevalence of chronic pain can be up to 92%.

>60% of hemodialysis patients describe moderate or severe chronic.

A survey of HD patients found 55% reported a severe pain episode in the previous 24 hours.

~75% of HD patients report inadequate pain management.
Quality of Life (QOL)

Lower QOL scores compared to the general population.

Reduced QOL

- Restricts patients functional capacity
- Impairs their social abilities
- Greater psychosocial distress
- Insomnia and depressive symptoms
- Produce negative effects on:
  - body mass index
  - blood pressure
  - pain levels
  - medication use
Multifactorial Pain Conditions

- **Pain caused by primary disease:**
  - polycystic kidney disease
  - Gout
  - Diabetic neuropathy
  - Bone disease
  - Renal failure
  - Muscle cramps during dialysis
- **Comorbid conditions:**
  - cardiovascular disease
  - ischemic or diabetic neuropathy
  - peripheral vascular disease

**Acute, Chronic, Acute on Chronic**

- Ischemic, neuropathic, bone, and musculoskeletal
Untreated Pain
The Problem

• Limited training.
• Pain is under-recognized, the severity is underestimated, and the treatment is inadequate.
• Providers may be hesitant to prescribe analgesics to patients on HD.
• Pharmacokinetic variations of most drugs are generally well studied in “healthy” patients, while uncertain in HD patients.
• Common Assumption:
  • Estimated renal function is the main, and sometimes only, factor to consider when making dose adjustments.
The Problem

Pain Management

• Challenging in patients with renal insufficiency and on dialysis.
• We know little about drugs in general in dialysis patients and even less comparing HD and PD.
• Lack of Guidance
  • From major pain management organizations.
  • Directly attributable to the lack of evidence-based treatment guidelines.
• Published guidelines might depend on specific institutional experiences.
Special Considerations

Dialysis

• Certain characteristics impact the removal of a drug by dialysis, including molecular weight, protein binding, volume of distribution, and water solubility.

• Least likely drugs to be removed by dialysis:
  • Large molecular weights that are highly protein bound
  • High volume of distribution
  • Poor water solubility.
Dialysis patients with a history of substance abuse...

- Should not be given more abusable analgesics merely because they have ESRD and receive dialysis.
- Recommending opioids in dialysis patients requires an intimate knowledge of their pharmacology, pharmacokinetics, and pharmacodynamics in this unique population.
- ESRD and/or dialysis should not be considered a free pass to receiving opioids.
- Prescribing for ESRD requires “universal precautions.”
Special Considerations
Opioid Abuse and Misuse

Basic guidelines in prescribing opioids...

- Nonopioid preferred over opioid therapy for chronic pain whenever applicable.
- Risk Assessment
- Evaluate risks and benefits prior to opioid prescription

- Discuss:
  - treatment goals
  - use of the lowest effective dose
  - avoidance of concurrent opioids and benzodiazepines
  - regular follow-ups (3-month intervals or more frequently) for the assessment of risks and benefits of continuing opioid use.

- For patients with opioid use disorder, offer:
  - medication-assisted treatment
  - behavioral changes
  - psychosocial support.
Pain Assessment
Pain is most commonly characterized as nociceptive, neuropathic, or both.

**Mixed Type**

- **Nociceptive pain:** Nociceptors in tissues send pain signals to the CNS.
- **Neuropathic pain:** Damage to the nerve itself causes typical pain symptoms.
Nociceptive pain:
Nociceptors in tissues send pain signals to the CNS.

Somatic Pain
Well localized
✓ Aching
✓ Throbbing
✓ Sharp
✓ Dull
✓ Sore
✓ Post-surgical pain
✓ Musculoskeletal pain
✓ Arthritis/inflammation
✓ Bone pain

Visceral Pain
Not well localized
✓ Deep pain
✓ Pressure
✓ Cramping
✓ Squeezing
✓ Left arm or jaw pain
✓ Abdominal pain
Pain Assessment
Pain Assessment

- **Location:** Is there more than one site?
- **Onset:** When did pain start?
- **Provoking or Precipitating Factors:** What makes pain better or worse? What treatments have been tried?
- **Quality:** sharp, aching, burning, sore?
- **Radiation:** does pain travel?
- **Severity:** Use validated scale
- **Timing:** Constant or intermittent
Pain Scales

Use Validated Appropriate Assessment Tool

Be consistent in tool used

Reassess and Document
Pain Management

General Overview
Pain Management

Dialysis patients

Dialysis Considerations

• In ESRD, review standard considerations for drug therapy, including metabolism and elimination of the drug
• When prescribing opioids in dialysis, determine how likely, and to what extent, they will be dialyzed.
• Characteristics impacting removal of a drug by dialysis include:
  • **Molecular weight**—Larger compounds will not pass easily through the dialysis filter.
  • **Protein binding**—Compounds that are highly protein bound are not dialyzable because the proteins are too large.
  • **Volume of distribution (Vd)**—A higher Vd indicates the drug is penetrating into bodily tissue rather than circulating within the blood and, therefore, is not available for extraction.
  • **Water solubility**—Compounds that are highly water soluble are more easily filtered through the dialysate.
Pain Management

Dialysis patients

Dialysis Considerations

• Opioids heavily extracted during dialysis may precipitate withdrawal symptoms in patients.

• Studies exploring the effect of supplemental dosing during or after dialysis are noticeably absent.
Monitoring in Dialysis Patients

• Monitoring for treatment compliance in chronic CKD pain patients is a necessary and significant challenge.

• For most, a urine drug screen is not practical.

• There are alternative options, including a serum drug screen (SDS), which by immunoassay returns a quick result for a basic panel of illicit and prescription drugs
  • This is less accurate compared to definitive testing by gas or liquid chromatography mass spectrometry.
• Renal insufficiency
  • Affects the pharmacokinetic properties of most pain medications, i.e. distribution, clearance, and excretion.
• The magnitude of the effect of renal insufficiency on drug metabolism varies…
  • depending on the agent itself
  • its metabolite
  • the extent of renal failure
Pain Management

Peri-operative Considerations

- Special attention should be placed on patients with moderate to severe impairment
  - To prevent further deterioration of renal function
  - To protect existing renal function from the effects of anesthetics and pain medications.
- Careful consideration
  - Follow-up on post-op renal function for these patients d/t susceptibility for further deterioration in kidney function.
WHO Analgesic Ladder

Stepwise approach for pain management in patient with CKD

Mild pain (1-4)
Acetaminophen (Acet)
±Adjuvants

STEP 1

Moderate pain (5-6)
Hydrocodone
Oxycodone
Tramadol
±Nonopioid analgesics
±Adjuvants

STEP 2

Severe pain (7-10)
Hydromorphone
Methadone
Fentanyl
Oxycodone
±Nonopioid analgesics
±Adjuvants

STEP 3

“Adjuvants” refers either to medications that are coadministered to manage an adverse effect of an opioid, or to so-called adjuvant analgesics that are added to enhance analgesia such as steroids for pain from bone metastases. Adjuvants also includes medication such as anticonvulsants for neuropathic pain.
Nonpharmacologic Approaches

• Low frequency of adverse reactions compared with pharmacologic approaches.

• These physical pain relief strategies focus on promoting comfort and altering physiologic responses to pain.

  Ice / Heat
  Relaxation Techniques
  Repositioning in Bed
  Reassurance
  Reike

Don’t underestimate power of touch!
Nonpharmacological Approaches

Must be considered whenever applicable.

- Topical thermal therapy
- Exercise programs
- Transcutaneous electrical stimulation (TENS)
- Cryotherapy (ice packs)
  - Thought to offer better restorative and therapeutic effects compared with topical heat therapy.
  - May reduce local metabolism and acute inflammatory response associated with nociceptive pain.
  - A reduction in local inflammatory response may also theoretically lead to shortened pain duration.
- Heat
  - Beneficial in reducing local muscle spasms and pain in the acute injury phase
- Biofeedback - for chronic pain
- Cognitive behavioral therapy (CBT) - for chronic pain

“That’s my survival kit. It has a meditation tape, aspirin, and rose-colored glasses.”
Complimentary and Alternative Medical Options

- Mind-body interventions
- Diet and lifestyle modification
- Herbal remedies
- Manual healing
- Bioelectromagnetic
- Pharmacologic-biologic treatments
Overview of Pharmacological Pain Treatments

For CKD Patients
Start Low, Go Slow
Nonopioid options

Acetaminophen (APAP)

• Does not result in platelet inhibition or gastrointestinal irritation.
• Metabolized in the liver to five inactive metabolites.
• Dialyzable compound
• Half-life is prolonged in patients with renal failure
  • Therefore, the dosing interval of APAP should be increased to 6-8 hours in renally impaired patients.
• Overall, considered one of the safest agents to use for the treatment of pain, in renal patients, including advanced CKD, stages 4–5, without increasing the disease progression rates, as long as dosing is below the minimal daily dose.
Nonopioid options

NSAIDS

Well-documented **renal toxicities** that can cause acute kidney injury and influence progression of CKD.

- Afferent vasoconstriction leading to reduced glomerular filtration
- Increase sodium retention and edema
- Worsening of preexisting HTN
- Hyperkalemia through decreased delivery of potassium to the distal tubule
- Other electrolyte imbalances including hyponatremia
- Acute renal failure through disruption of the renal hemodynamic balance
- Nephrotic syndrome by increasing lymphocyte recruitment and activation
- Acute and chronic renal papillary necrosis through direct toxicity

**Nonrenal toxicities** include:

- Increased blood pressure
- Decreased antihypertensive effects of several medications
- Increased gastrointestinal (GI) bleed risk
Nonopioid options

Ibuprofen

- Considered a safe option in patients with renal insufficiency or dialysis
- Metabolized in the liver to inactive compounds.
- It does not accumulate in renal insufficiency.

- Two of the inactive compounds are dialyzable.
Nonopioid options

Naproxen & Celecoxib

Naproxen

• Metabolized in the liver to inactive compounds.
• Not recommended in patients with moderate to severe renal impairment.
• Close monitoring of the patient's renal function is recommended.

Celecoxib (Celebrex)

• The only cyclooxygenase-2 (COX-2) inhibitor available in the U.S.
• Metabolized extensively by the liver and is unlikely to be removed by dialysis; therefore, use of COX-2 inhibitors should be avoided in severe renal impairment and in those on dialysis.
Nonopioid options

Ketorolac

- Accumulates in renal insufficiency; therefore, it is **contraindicated** in these patients and in patients at risk for renal failure, including those with volume depletion.

- Unlikely to be removed by dialysis and so **should be avoided**.
Nonopioid options

Topical analgesics

- Whenever applicable and safe, topical administration of analgesics may be preferred over oral or nontopical parenteral routes.

- Topical analgesics including diclofenac, ibuprofen and ketoprofen have been shown in small studies to be effective in relieving both soft tissue injuries and various inflammatory musculoskeletal conditions.

- Though favorable tolerability profiles, data on renal toxicities are lacking.
Adjunctive Therapeutic Options

Lidocaine patches

- Only FDA-indicated for postherpetic neuralgia
- Off label use: local pain syndromes.
- Absorption is determined by the duration of application and the surface area over which it is applied.
- There is no appreciable accumulation of lidocaine or its metabolites in renal insufficiency; therefore, dose adjustments are not required.
Adjunctive therapeutic options

Gabapentin

- FDA-indicated for partial seizures and postherpetic neuralgia
- Off-Label: used for a wide variety of neuropathic pain syndromes, including postoperative pain.\textsuperscript{24}
- Not metabolized and is excreted in the urine unchanged.
- Renal clearance of gabapentin is reduced by 40%
- Elimination half-life is increased up to 52 hours in renal insufficiency, but it is dialyzable.

**Recommendation:**

- Dose adjustments are required in patients with moderate to severe renal insufficiency
- Supplemental doses should be administered in patients after receiving dialysis.
Adjunctive therapeutic options

Pregabalin

- Structurally related to gabapentin
- Indicated for a variety of neuropathic pain conditions.
- 90% excreted unchanged in the urine
- ~50% of drug is removed after 4 hours of hemodialysis.
- **Recommendation:**
  - Dose adjustments are required in patients with moderate to severe renal insufficiency
  - Supplemental doses should be administered in patients after receiving dialysis.
Pain Management

Adjuvants

• Can cause serious side effects in patients with compromised renal function and dose adjustment must be considered.

• Gabapentin and pregabalin should be used with caution and only when they are indicated (neuropathic pain).

• Liberal administration of gabapentinoids may increase the risk of over sedation and even coma.

• These agents do not undergo hepatic metabolism and are excreted solely by the kidney.

• A reduction of 50% of the dose for each 50% decline in GFR or CCr, and increasing the time interval between the doses is advised.
Adjunctive therapeutic options

Antidepressants

Tricyclic Antidepressants (TCA’s)

- Commonly used for neuropathic pain
- Examples: Amitriptyline, nortriptyline
- Metabolized in the liver to inactive metabolites, with the exception of amitriptyline, which is metabolized to nortriptyline.
- Unlikely that the TCAs can be removed by dialysis.

Recommendation:
- Reduce dose in renal insufficiency.
- Monitor anticholinergic side effects.

Common side effects:
- Postural hypotension
- Anticholinergic SE’s:
  - Constipation
  - Urinary retention
  - Blurred vision
  - Dry mouth
  - Delirium
  - Sedation
Pain Management

The role of regional and neuraxial analgesia in chronic kidney disease

Peripheral nerve blocks or neuraxial techniques

• Can play a role in avoiding the adverse effects of both anesthetics and analgesics.

• Dialysis patients
  • Anticoagulation is a concern
  • Risk factor for developing epidural hematoma
Overview of Opioid Options

For CKD Patients
Opioids

When to initiate:
- Pain relief with other treatments has not been adequate
- Pain is moderate to severe in nature
- Quality of life and function is severely affected by pain
Opioid Options

The use of opioids in the renally impaired population is challenging, as one must balance opioid-related adverse events with adequate pain control.

**Recommendation:**

- Start with lower-than-recommended doses and slowly titrate up the dose while extending the dosing interval.
- This will help limit adverse effects, such as respiratory depression and hypotension.
Opioid Options

Hydrocodone

Metabolized

hydromorphone (Dilaudid)

which is then metabolized to its major metabolite hydromorphine-3-glucuronide (H3G) and minor metabolite hydromorphine-6-hydroxy

ALL of which are excreted renally along with the parent compound.

- H3G has no analgesic properties, but it can potentially cause neuroexcitation, agitation, confusion, and hallucination.

- Hydromorphone has been used safely in patients with renal insufficiency and dialysis, as it is expected to be dialyzable.
Opioid Options

Tramadol

- Generally well-tolerated in patients with renal insufficiency and dialysis.
- Metabolized in the liver, producing one active compound.
- Approximately 30% of the tramadol dose is excreted unchanged in the urine.
- 60% of the dose is excreted as metabolites.

Recommendation:

- Reduce the dose and increase the dosing interval in patients with renal insufficiency
- Significantly removed by hemodialysis; therefore, redosing after a session may be necessary.
Opioid Options

Tapentadol (Nucynta)

- One of the least studied opioids in patients with ESRD.
- Mu-opioid receptor agonist with selective norepinephrine reuptake inhibition.
- Metabolized almost exclusively via phase II conjugation yielding inactive metabolites.
  - This results in very low risk for drug interactions.
- Excreted primarily by the kidneys (99%)
  - studies needed to verify that the accumulation of inactive metabolites will not result in toxicity.
- Extraction ratio in dialysis is unknown, but likely dialyzed to some extent due to low protein binding, low molecular weight, and average water solubility, although it is widely distributed.
Opioid Options

Oxycodone

- Metabolized by the liver with less than 10% excreted unchanged in the urine.
- Can be used in patients with mild to moderate renal insufficiency but should be used at reduced dose, with CAUTION.
- Its use is generally not recommended in dialysis patients due to lack of data.
Opioid Options

Fentanyl

• Primarily metabolized in the liver to inactive metabolites.

• Fentanyl clearance is reduced in patients with moderate to severe uremia (BUN >60 mg/dL).

• Not expected that fentanyl be dialyzable because of its pharmacokinetic properties
  • (high protein-binding, low water solubility, high molecular weight, and high volume of distribution).

• Data suggests that fentanyl can be used at usual doses in mild to moderate renal insufficiency and in dialysis patients
  • Although reduced doses may be prudent.
  • Such patients should be monitored for signs of gradual accumulation of the parent drug.
Opioid Options

Morphine

• Metabolized in the liver to morphine-6-glucuronide (M6G) and morphine-3-glucuronide (M3G)
• All are excreted renally, along with the parent compound.
• Only M6G has analgesic properties.
• When it accumulates, it can lead to CNS depression.
• M3G is associated with behavioral excitation, a side effect that is further magnified in patients with renal insufficiency.
• Although morphine is dialyzable, it should generally be avoided in patients with any level of renal insufficiency.
Opioid Options

Hydromorphone (Dilaudid)

- Morphine analogue
- Better tolerated in patients with renal insufficiency.
  - However, metabolism leads to hydromorphone-3-glucuronide (H3G), which can have similar neurotoxic effects as M3G when accumulated in the plasma.
  - (Morphine metabolite) M3G is associated with behavioral excitation, a side effect that is further magnified in patients with renal insufficiency)
- In moderate renal impairment, H3G levels in the plasma can be 100 times that of the parent drug.
- Though hydromorphone is more potent than morphine, less-drug is needed to provide similar analgesic responses.
  - Therefore, overall production and neurotoxic effects of H3G may be comparatively less than that of M3G, despite its greater potency when compared to M3G.
Opioid Options

Methadone

- Methadone and its metabolites are excreted in the urine and feces.
- Has been used safely in patients with renal insufficiency
- But poorly removed by dialysis
  - because it’s highly protein bound, with high molecular weight, high Vd, and low water solubility.
  - No specific recommendations are available regarding its dosing in dialysis.
Opioid Options

Buprenorphine

• Metabolized in the liver to active metabolites norbuprenorphine and buprenorphine-3-glucuronide.

• Excreted through the biliary system, where it is unaltered, and its metabolites are excreted by the kidneys.

• In one study, concentrations of the metabolites norbuprenorphine and buprenorphine-3-glucuronide were found to be elevated in patients with renal disease.
  • Considered far less potent analgesically, it was suggested that these metabolites may be insignificant.
Opioid Options

Codeine

• Should be avoided in CKD since it will be converted in the liver to morphine and its metabolites (M3G, M6G), ALL of which are renally excreted.
  • In those who are rapid metabolizers too much morphine can be produced leading to a higher risk of toxicity that can occur even after trivial doses.
• Lower-than-usual doses are recommended in patients with renal insufficiency
• Should be avoided altogether in dialysis patients.
Pain Management

Within Clinical Stages of CKD
Pain Management

Post-operative Considerations

Understand the clinical stages of kidney function in CKD patients undergoing surgery …

• To reduce possible adverse effects of anesthetics and analgesics
• To understand the limitations and difficulties in managing post-operative pain
• To prevent further deterioration of renal function
• To protect existing renal function
• And remember to follow-up on postoperative renal function
Pain Management

Dose adjustments

- May be necessary for patients with significant reductions in GFR
- Avoidance of certain analgesics may also be necessary due to an alteration in the pharmacokinetics and pharmacodynamics of several analgesic agents and their metabolites.
- CKD patients are at increased risk for adverse effects from:
  - associated comorbidities
  - increased drug sensitivity
  - reduction in body mass
  - small margin between analgesia and toxicity
  - drug accumulation due to impaired excretion.

Pharmacokinetic and pharmacodynamic changes depend on:
- the pharmacological agents
- the stage of renal impairment
- whether the patient is undergoing dialysis
- age
# 5 Stages of CKD

<table>
<thead>
<tr>
<th>Stage</th>
<th>GFR (ml/min/1.73m³)</th>
<th>Uremic Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage 1 – Normal function</td>
<td>≥90</td>
<td>Asymptomatic</td>
</tr>
<tr>
<td>Stage 2 - Mild</td>
<td>60-89</td>
<td>Asymptomatic</td>
</tr>
<tr>
<td>Stage 3 - Moderate</td>
<td>30-59</td>
<td>No or mild symptoms</td>
</tr>
<tr>
<td>Stage 4 - Severe</td>
<td>15-29</td>
<td>Mild to moderate symptoms</td>
</tr>
<tr>
<td>Stage 5 - (ESRD)</td>
<td>≤15</td>
<td>Moderate to severe symptoms Requires dialysis if highly uremic</td>
</tr>
</tbody>
</table>
Pain Management

Stage 1 CKD

- A structural abnormality in the kidney is present i.e. kidney cyst.
- Pain management should not differ from other patients without kidney disease.
- Post-operative, posttraumatic pain, analgesia should include consideration of neuraxial or peripheral nerve blockade when possible.
- Multimodal regimen preferred.
- Acetaminophen, NSAIDs, or specific cyclooxygenase-2 inhibitors should be considered as analgesic foundations and be used around the clock unless otherwise contraindicated.
- NSAIDs are valuable analgesic adjuncts and should not be withheld from these patients.
Pain Management

Stage 1 CKD

Other adjuvants can be used...

• to improve perioperative pain control
• reduce the dose of opioids
• minimize the possibility of progression of acute postsurgical or posttraumatic pain to chronic pain

Includes:
• Tramadol
• Anticonvulsants: gabapentin or pregabalin
Pain Management

Stage 2 CKD

Mild degree of impairment in renal function (GFR 60-89 mL/min/1.73 m²)

The level of renal function for these patients is sufficient for excretion of the drugs and their metabolites

- No need for dose adjustment of pain medications.

2 main considerations for post-op patients with Stage 2 CKD.

1. Monitor for further deterioration of renal function due to anesthetic or other perioperative events
   - bleeding
   - dehydration
   - prolonged hypotension

Readjustment of analgesic doses may be warranted.

2. Consider possible effect of NSAIDs
Pain Management

Stage 2 CKD

NSAIDs

- The risk of using NSAIDs in this group of patients should be balanced against the benefit.
- Limit to the shortest duration possible.
- Renal function should be monitored closely.
- NSAIDs should be avoided in patients with additional factors that can impair renal function such as:
  - advanced age
  - diabetes
  - use of ACE-inhibitors
  - perioperative dehydration
  - hypotension
- Cyclooxygenase-2 inhibitors (COX-2) like other NSAIDs, must also be used cautiously in these patients.
Pain Management

Stages 3 & 4 CKD

Moderate to severe impairment of renal function with GFR between 15 and 59 mL/min/1.73 m²

- The clinical utility of most analgesic drugs is altered due to:
  - altered clearance of the parent drugs and their therapeutically active or toxic metabolites.
- NSAIDs may also worsen the preexisting renal impairment in these patients.
- Regional techniques should be considered whenever possible.

- **Recommendations:**
  - Avoid NSAIDs
  - Reduce analgesic drug doses according to the GFR or CCr
  - Closely monitor drug side effects such as sedation
Pain Management

Stages 3 & 4 CKD

Moderate to severe impairment of renal function with GFR between 15 and 59 mL/min/1.73 m²

**Opioids**

A fixed algorithm for opioids in relation to GFR is not always feasible for two reasons:

1. Opioids undergo hepatic metabolism as a main route of elimination, but some opioids still have active or toxic metabolites that need to be excreted through kidney.

2. The increased sensitivity of the central nervous system in CKD patients to opioids occur in a fashion, which is not fully correlated with GFR.

- Controlled released (CR) forms carry higher risks of unwanted side effects and toxicity in patients with renal insufficiency.

- CR preferably avoided especially for patients with Stage 4-CKD (GFR <30 mL/min/1.73 m²).
Pain Management

Stages 3 & 4 CKD

Gabapentin & pregabalin

- Use with caution and only when they are indicated (neuropathic pain).
- Liberal administration of gabapentinoids may increase the risk of over sedation and even coma.
- These agents do not undergo hepatic metabolism and are excreted solely by the kidney.
  - A reduction of 50% of the dose for each 50% decline in GFR or CCr, and increasing the time interval between the doses is advised.
Fentanyl

- Dose adjustments depend on possible active metabolites that are dependent on the kidney for excretion.
- **Safe** pharmacological profile for patients with renal impairment.
- Metabolized by the liver producing **no active or toxic metabolites**.
- Less than 10% of the parent drug is excreted unchanged in the urine.
- There is no dose modification required for boluses,
  - but **caution** is advised with repeated boluses or continuous infusion, as there may be a slight plasma accumulation during advanced stages of renal impairment.
Pain Management

Morphine

• For patients with GFR of 50 mL/min/1.73 m² or less, morphine dose reduction should be considered by more than 50% and is even best avoided when possible.

• The risk of toxicity is much higher with GFR <30 mL/min/1.73 m² and morphine avoidance becomes highly recommended.
Hydromorphone (Dilaudid)

- Accumulation of both H3G and M3G in ESRD patients between hemodialysis sessions associated with increase hyperalgesia
  - but the effect of H3G is deemed less than that of M3G.
- Unlike morphine, hydromorphone does not have an analgesically active 6-glucuronide metabolite,
  - which may decrease the risk of developing respiratory depression in this population.

**Recommendations:**

- Although hydromorphone is relatively safer than morphine in renal insufficiency, dose adjustment depending on GFR may be necessary.
Pain Management

Opioids in Advanced, Nondialysis Dependent Chronic Kidney Disease

Codeine & Oxycodone

Codeine

• Should be avoided in this patient population since it will be converted in the liver to morphine and its metabolites (M3G, M6G).

Oxycodone

• There is little evidence regarding the use of oxycodone for acute postoperative pain as it is more commonly used for chronic pain.

• Associated with significant sedation with usual doses in renal failure patients.

• Its use is generally not recommended in dialysis patients due to lack of data.
Tramadol

- Analgesic efficacy requires metabolism to its active metabolite, O-desmethyltramadol (M1), by the liver.
  - Failure of excretion of this metabolite through the kidney can lead to accumulation causing serious side effects i.e. sedation and seizure activity
- **Caution** use with serotonin re-uptake inhibitors (SSRI’s/SNRI’s) and other serotonergic agents
  - may increase the possibility of developing seizures, serotonin syndrome

**Recommendation:**

- Lower the maximum daily dose.
- Increase the interval between doses in patients with renal insufficiency.
Ketamine

- Commonly used as an adjunct for acute postoperative or posttraumatic pain.
- Certain patients seem to benefit more from the addition of ketamine:
  - chronic neuropathic pain
  - opioid dependence or tolerance
  - acute hyperalgesia.
- 8% of administered ketamine is metabolized by the liver, which possess only 20-30% of the potency of ketamine.
- The metabolite, Norketamine is excreted by the kidney.

- Dose modification for ketamine is not required for patients with decreased renal function.
- Administration:
  - Additionally to opioids
  - Use in patient controlled analgesia (PCA) pumps
  - Continuous infusions
  - Oral divided doses
Pain Management

Stage 5 CKD

Postoperative pain management in the Nondialysis ESRD

• Follow the same rules as delineated for CKD-Stage4.

For dialysis dependent patients

• Acute-on-chronic pain may also influence the quality of patient care and pain management.

• Approximately 50% of dialysis patients experience chronic pain that is rated as severe.

• Cyclical changes in the plasma concentration of most analgesics before and after dialysis increases the need for dose adjustments.
Acetaminophen

• Considered the safest analgesic agent in ESRD.
• Should be used routinely as an analgesic foundation.
• With chronic use, however, acetaminophen itself may cause nephrotoxicity.
• In addition to renal failure, the presence of malnutrition, underlying liver impairment, or excessive alcohol consumption are risk factors for serious complications of acetaminophen related toxicity for these patients.
Pain Management
Stage 5 CKD

NSAIDS

• There is no role for NSAIDS in postoperative pain management in ESRD due to the high risk of serious side effects in this population.

• Some exceptions may be accepted for short-term NSAID usage in ESRD such as for those patients with acute, painful gout.
Dialysis Patients

- The use of **fentanyl** and **hydromorphone** are relatively safe in dialysis patients
  - but doses should be adjusted to minimize the risk of respiratory depression.
- Consider lingering anesthetic agents and the accumulation of other analgesic adjuvants before dialysis, in the postoperative patients.
- The general condition of dialysis patients with comorbid illnesses may also aggravate the risk of opioid complications.
- **Morphine** should be avoided, due to the accumulation of toxic metabolite M3G.
- **Codeine**, which will be converted to morphine, **should also be avoided** for the same reasons.
Pain Management

Stage 5 CKD

Dialysis Patients

• **Tramadol** - Lower the maximum daily dose and increase the interval between doses,
  • to avoid the risks of sedation, respiratory depression and seizure from accumulation of its metabolite.
<table>
<thead>
<tr>
<th>Opioids in ESRD</th>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fentanyl</td>
<td>Safe</td>
</tr>
<tr>
<td>Hydromorphone (Dilaudid)</td>
<td>Safe, dose adjustments may be required</td>
</tr>
<tr>
<td>Morphine</td>
<td>Preferably to be avoided</td>
</tr>
<tr>
<td>Codeine</td>
<td>AVOID</td>
</tr>
<tr>
<td>Oxycodone</td>
<td>Not enough Evidence</td>
</tr>
</tbody>
</table>

(Tawfic, 2015)
Pain Management
Stage 5 CKD

Dialysis Patients

- Adjuvant medications:
  - Help improve pain scores
  - Reduce opioid doses
  - Treat neuropathic components of pain in dialysis patients.
  - Ketamine
    - Well established treatment for dialysis and palliative care patients with chronic pain
Pain Management

Stage 5 CKD

Dialysis Patients

• Anticonvulsant analgesics
  • may be required for the treatment of neuropathic pain.
• Assess for increased risk of sedation in dialysis patients with accumulation between dialysis sessions.
• Withdrawal and escalation of pain can occur after dialysis.
• A small daily dose can be used on a non-dialysis day with an additional loading dose immediately after dialysis.
# Pain Management in CKD Stage 1

<table>
<thead>
<tr>
<th>Pain Level</th>
<th>Recommended Treatments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neuraxial or Peripheral Nerve Block whenever possible</td>
<td>acetaminophen ± NSAIDS ± tramadol</td>
</tr>
<tr>
<td>Mild pain</td>
<td>Acetaminophen ± NSAIDS ± Tramadol</td>
</tr>
<tr>
<td>Moderate to Severe pain</td>
<td>Acetaminophen ± NSAIDS ± Tramadol ± Opioids</td>
</tr>
<tr>
<td>Perioperative gabapentin or pregabalin as adjuvants in select cases like trauma or neuropathic pain</td>
<td></td>
</tr>
</tbody>
</table>
### Pain Management in CKD Stage 2

<table>
<thead>
<tr>
<th>Pain Intensity</th>
<th>Treatment Options</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mild pain</strong>:</td>
<td>Acetaminophen + NSAIDS + Tramadol</td>
</tr>
<tr>
<td><strong>Moderate to Severe pain</strong>:</td>
<td>Acetaminophen + NSAIDS + Tramadol + Opioids</td>
</tr>
<tr>
<td></td>
<td>Perioperative gabapentin or pregabalin as adjuvants in select cases like trauma or neuropathic pain</td>
</tr>
</tbody>
</table>

Neuraxial or Peripheral Nerve Block whenever possible
# Pain Management in CKD Stage 3 & 4

<table>
<thead>
<tr>
<th>Pain Intensity</th>
<th>Treatment Options</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Neuraxial or Peripheral Nerve Block</strong></td>
<td>Whenever possible</td>
</tr>
<tr>
<td><strong>AVOID NSAIDS</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Mild pain:</strong> Acetaminophen ± Tramadol</td>
<td></td>
</tr>
<tr>
<td><strong>Moderate to Severe pain:</strong> Acetaminophen ± Tramadol  ± Opioids (fentanyl or hydromorphone) ± ketamine</td>
<td></td>
</tr>
<tr>
<td><strong>Antiepileptics in neuropathic pain only</strong></td>
<td></td>
</tr>
</tbody>
</table>

- Adjust opioid doses
- Avoid morphine
- Avoid Long Acting opioids
# Pain Management in the Dialysis Patient

<table>
<thead>
<tr>
<th>Pain Management</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neuraxial or Peripheral Nerve Block whenever possible</td>
<td></td>
</tr>
<tr>
<td>AVOID NSAIDS</td>
<td></td>
</tr>
<tr>
<td><strong>Mild pain:</strong> Acetaminophen ± Tramadol</td>
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</tr>
<tr>
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<td></td>
</tr>
</tbody>
</table>

- Adjust opioid doses
- Avoid morphine
- Avoid Long acting opioids
<table>
<thead>
<tr>
<th>Agent</th>
<th>Dose adjustment based on calculated CRCL or GFR based on labeling</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetaminophen</td>
<td>GFR ≥50 mL/minute: No dosage adjustment necessary.</td>
</tr>
<tr>
<td></td>
<td>GFR 10 to 50 mL/minute: Administer every 6 hours.</td>
</tr>
<tr>
<td></td>
<td>GFR &lt;10 mL/minute: Administer every 8 hours.</td>
</tr>
<tr>
<td>Morphine</td>
<td>Active metabolite accumulates in renal impairment. GFR &lt;50 redose dose by 50% or avoid and use alternative.</td>
</tr>
<tr>
<td>Oxycodone</td>
<td>CrCl &gt; 60 no dose adjustment needed</td>
</tr>
<tr>
<td></td>
<td>CrCl &lt;60 decrease dose by 50%. Start at low dose and titrate as needed/tolerated</td>
</tr>
<tr>
<td>Hydromorphone</td>
<td>CRCl &gt; 60 no dose adjustment</td>
</tr>
<tr>
<td></td>
<td>CRCL 40-60, start at 50 % of normal starting dose.</td>
</tr>
<tr>
<td></td>
<td>CrCl &lt;30 Initiate at 25% of normal starting dose</td>
</tr>
<tr>
<td>Buprenorphine</td>
<td>CRCl &lt;30: Consider reducing initial and titration incremental dose by 50%.</td>
</tr>
<tr>
<td>Fentanyl</td>
<td>No dosage adjustment in labeling. Geriatrics use caution with dose selection and titrate slowly.</td>
</tr>
<tr>
<td>Tramadol</td>
<td>CrCl &gt;30 no dosage adjustment</td>
</tr>
<tr>
<td></td>
<td>CRCL &lt;30 increase dosing frequency to q12hours Max: 200 mg/day</td>
</tr>
<tr>
<td></td>
<td>Age &gt; 75 max dose 300 mg</td>
</tr>
<tr>
<td>Gabapentin</td>
<td>CrCl ≥60 mL/minute: 300 to 1,200 mg 3 times daily.</td>
</tr>
<tr>
<td></td>
<td>CrCl &gt;30 to 59 mL/minute: 200 to 700 mg twice daily</td>
</tr>
<tr>
<td></td>
<td>CrCl &gt;15 to 29 mL/minute: 200 to 700 mg once daily</td>
</tr>
<tr>
<td></td>
<td>CrCl 15 mL/minute: 100 to 300 mg once daily</td>
</tr>
<tr>
<td>Pregabalin</td>
<td>CrCl &gt;60 Max daily dose 600 mg</td>
</tr>
<tr>
<td></td>
<td>CrCl 30-60 Max daily dose 300 mg</td>
</tr>
<tr>
<td></td>
<td>CrCL 15-30 Max daily dose 150 mg</td>
</tr>
<tr>
<td></td>
<td>CrCL &lt;15 Max daily dose 75 mg</td>
</tr>
<tr>
<td>Nortriptyline</td>
<td>No renal dose adjustment needed</td>
</tr>
</tbody>
</table>
Case

HPI: This is a 34 y.o. male with a PMH of heroin abuse, poly-substance abuse, ulcerative colitis, chronic pancreatitis, viral Hepatitis C, anxiety/depression, who presents with left leg pain after falling down.

Patient reports watching TV 2 nights ago and waking up yesterday morning at 3 am on the ground in the kitchen after fainting. He states that he has had fainting spells every couple of months, over the past 2 years with no follow-up. Upon waking, he had significant pain 10/10 in his left thigh and leg as well as numbness. The patient admits to snorting heroin two times that morning in attempt to self-medicate symptoms related to colitis and pancreatitis (not for pain in the legs as reported initially during this hospitalization). He called EMS when pain persisted and was brought in by ambulance to ED. He was found to have significant edema in left thigh consistent with compartment syndrome. Patient underwent urgent fasciotomy, was intubated overnight and extubated this morning.

Our service was consulted to assist in pain management for this very complicated patient with long history of polysubstance abuse with multiple hospitalizations for SUD issues, chronic pancreatitis/abdominal pain, depression and anxiety.
Dx: Acute kidney injury. Due to ATN/rhabdo. Nonoliguric but urine output not improving much and creatinine continues to rise. Will check urine sodium to assess avidity and inform role of additional fluids. Tentative plan to obtain HD access tomorrow unless urine output picks up. Discussed with nephrology.

**Recommendations:**

1. For pain control, since patient will be hospitalized for several days, makes sense to start dilaudid PCA. Ok to start at 0.2mg/6 minute lockout/ 2 mg hourly limit and titrate as necessary. Will reassess on Monday as our service is not here on the weekend.

2. Patient has h/o Hep C and LFT's are elevated. D/c acetaminophen.

3. Restart home dose lyrica 100mg TID…changed to renal dose 50mg.

4. Patient has h/o severe anxiety with hospitalizations in the past for depression/anxiety. Please restart klonopin at half the usual dose (1mg TID at home), 0.5mg TID and monitor for sedation with opioid use.

5. Restart abilify.

6. Patient normally on duloxetine 120mg daily. Due to renal function, will discuss options with pharmacy to avoid withdrawal from SNRI. May need to increase klonopin to home dose to avoid withdrawal.

7. Due to colitis and h/o GIB, unable to use NSAIDS.
Take Home…

• Similar to the general population, pain is a common problem among patients with CKD.

• Suboptimal pain control is associated with poor quality of life and depression.

• There needs to be a basic understanding of both condition-specific and stepwise pain management and the pharmacokinetics of commonly prescribed analgesics/opioids to avoid severe adverse complications and abuse and dependence.
Take Home…

• Pain management strategies for patients with CKD change as kidney function becomes progressively impaired.

• When devising a strategy:
  • strive to protect the kidney from further damage
  • avoid developing serious side effects due to accumulations of analgesic agents or their metabolites.
  • understand the pharmacokinetics of analgesic agents to predict their tolerability in patients with CKD.
Thank You!

Questions????