Management of chronic pain in Advanced chronic Kidney disease

By:

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INTRODUCTION:

- Pain is one of the most common and distressing symptoms among patients with CKD.
- pain, in particular chronic pain, is associated with psychologic distress; insomnia, depressive disorders; limitations in work, family, and social life; decreased life satisfaction and quality of life (QOL); and increased hospitalizations and emergency department visits .
- For patients receiving hemodialysis (HD), uncontrolled pain leads to shortened or missed HD treatments .

- Many analgesics that are typically used in the non-CKD population should not be used among patients with advanced CKD (ie, eGFR <30 mL/min/1.73 m^2; including those on dialysis).

- Evaluation of pain requires a comprehensive patient assessment and physical examination that includes understanding the patient's diagnosis and medical history in addition to determining the effects Of the pain on the patient's psychologic status, social functioning, functional status, and QOL.

- Four aspects of the evaluation essential to determining a pharmacologic approach Include: (1)pain intensity(2) Chronicity and possible reversible causes for the pain (3)the type of pain—nociceptive, neuropathic, or combined (4) treatment goals.

Pain Intensity:

- Determining pain intensity helps establish the need for treatment.
- The experience of pain is unique to each individual and can only be measured by that individual.
- Several global symptom assessment tools have been validated for use in patients with CKD.

Chronicity of Pain:

Acute pain :

- Typically persists for <3 mo.
- Associated with tissue damage.
- Usually episodic with periods without pain.
- Tends to respond well to pharmacologic therapy

Chronic pain :

- Often defined as any painful condition that persists for >3mo.
- Usually initiated by tissue injury but is perpetuated by neurophysiologic changes.
- More likely to result in functional impairment and disability, psychologic distress, sleep deprivation, and poor QOL than acute pain.
- May not respond well to analgesics, including opioids, except early in the course of treatment.

- Determining the chronicity of pain is important in determining appropriate management strategies .

- Patients with chronic pain often do not have a treatable underlying cause for their pain and the somatosensory component of the pain assumes greater prominence than in acute pain.

- For patients with chronic pain, non pharmacologic assessment and support is essential.

Type of pain:

Nociceptive pain:

- Results from tissue damage in the skin, muscle, and other tissues, causing stimulation of sensory receptors.
- May be described as sharp or like a knife and often felt at the site of damage .
- With stimulation of visceral nociceptors, may be experienced as dull, aching, and poorly localized (e.g., gut ischemia).
- Tends to respond to analgesics.

- Causes of nociceptive pain common among advanced CKD patients include : osteoarthritis, renal osteodystrophy, dialysis-related amyloid arthropathy, and kidney or liver capsule distension from autosomal dominant polycystic kidney disease (ADPKD). All can cause mild, moderate, or severe pain.

Neuropathic pain

- Neuropathic pain arises from abnormal neural activity secondary to disease, injury, or dysfunction of the nervous system. Common examples of neuropathic pain among patients with CKD include : diabetic neuropathy and carpel tunnel syndrome and other peripheral neuropathy.
- 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.
- Responds poorly to analgesics and typically requires adjuvant therapy .

- Among CKD patients, the pain is often mixed nociceptive/neuropathic in nature.
- It is important to target the neuropathic component first with adjuvant therapy to prevent inappropriate use of opioids.
- The choice of initial analgesic is dependent upon the type of pain.

Treatment Goals:

- The World Health Organization (WHO) analgesic ladder has been advocated for the management of pain, including chronic pain in patients with CKD .

- It involves the slow introduction and upward titration of analgesics, starting with nonopioids then progressing to weak then strong opioids as required for pain relief.

TREATMENT :

- In the general adult population, treatment options for chronic pain :

- ✓ pharmacologic
- ✓ physical medicine such as aerobic exercise, stretching, massage, acupressure, and acupuncture
- ✓ behavioral medicine such as cognitive behavioral therapy, biofeedback, relaxation techniques, counseling and …
- ✓ Neuromodulation
- ✓ Interventional
- ✓ surgical approaches.

Non pharmacologic treatment:

- Nonpharmacologic modalities are generally the same among CKD patients as in the general population .
- However, frailty or general disability may prevent some patients from benefiting fully from physical interventions.
- In addition, behavioral approaches such as cognitive-behavioral therapy (CBT) may be challenging and possibly less effective for some CKD patients, especially those already on dialysis, because of the time and cognitive ability required. Regardless, where available, these modalities should be tried as first-line therapy.

Pharmacologic treatment of mild to moderate CKD (eGFR ≥30 mL/min/1.73 m2

- With the exception of NSAIDs, the pharmacologic treatment of chronic pain in patients with mild to moderate CKD is similar to the general population without CKD. However, NSAIDs should typically be avoided.

- Occasionally, NSAIDs provide greater pain control and potentially fewer side effects than other medications, particularly among patients with mild reductions in eGFR (ie, >45 mL/min/1.73 m^2).

- NSAIDs are best reserved for specific indications of acute, rather than chronic pain, limiting their use to the lowest effective dose and shortest duration.

- All CKD patients who are being chronically treated with NSAIDs should have close monitoring of eGFR (ie, every three months), with discontinuation of NSAIDs if the eGFR declines faster than expected.

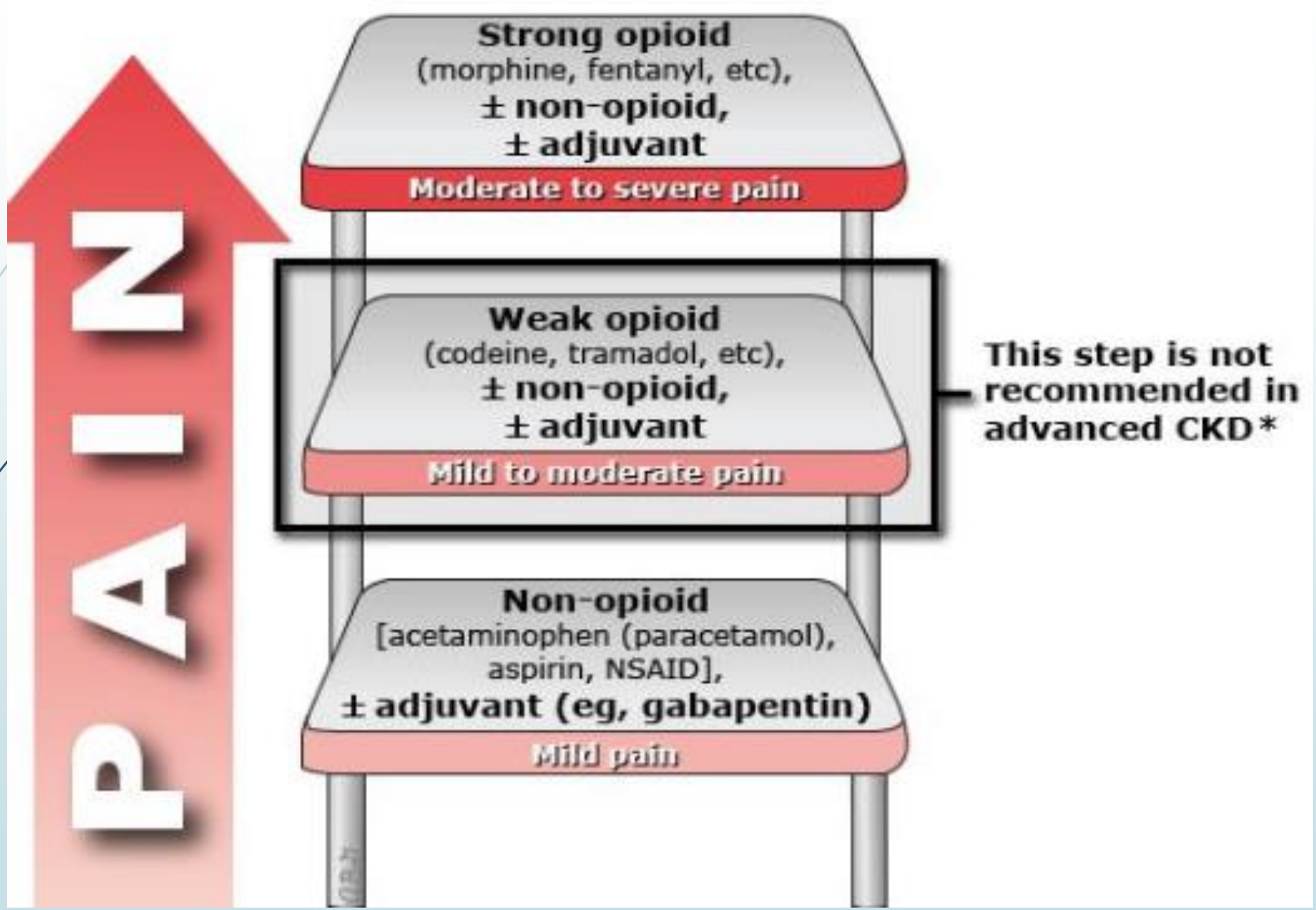
- However, there is no dose of NSAID that is considered "safe" for individuals with reduced eGFR.

Pharmacologic treatment of advanced CKD (eGFR <30 mL/min/1.73 m2)

- Our pharmacologic approach is adapted from the World Health Organization (WHO) analgesic ladder, which involves a cautious, stepwise approach to prescribing analgesic agents according to pain severity .

- According to the WHO analgesic ladder, mild pain is treated with nonopioid analgesic agents (tier 1), moderate pain is treated with a weak opioid with or without a nonopioid agent (tier 2), and severe pain is treated with a strong opioid (tier 3).

- The WHO ladder is modified for patients with CKD since many specific agents (such as codeine) should not be used for individuals with a severely reduced eGFR .


PAIN
Strong opioid
(morphine, fentanyl, etc),
± non-opioid,
± adjuvant
Moderate to severe pain
Weak opioid
(codeine, tramadol, etc),
± non-opioid,
± adjuvant
Mild to moderate pain
This step is not recommended in advanced CKD*
Non-opioid
[acetaminophen (paracetamol), aspirin, NSAID],
± adjuvant (eg, gabapentin)
Mild pain

- We deviate some what from the recommendations of the WHO; specifically, we do not use a weaker opioid prior to a stronger opioid, due to lack of clear advantages with this approach.

- Weaker opioids have a variable response among patients with advanced CKD, with an unpredictable risk of fatal overdosing with trivial doses or a poor analgesic effect after administration of standard doses .

- In addition, weaker opioids have a similar rate of dose-dependent adverse effects as low-dose strong opioids.

- Instead, we favor treatment with a strong opioid initiated at a low dose with slow titration to desired effect, especially among patients with an estimated glomerular filtration rate of <30 mL/min/1.73 m^2 .

Preferred analgesic medications for chronic pain management in CKD stages 4 and 5

WHO step	Recommended	Use with caution	Do not use
1	Acetaminophen		NSAIDs
2			Codeine Tramadol
3	Hydromorphone Fentanyl, Alfentanil Methadone Buprenorphine	Oxycodone	Morphine Meperidine Propoxyphene
Adjuvant	Gabapentin Pregabalin	Carbamazepine TCAs	

Principles for dosing and administration:

- The general principles of the pharmacologic treatment of pain are the same for patients with advanced CKD as for the general population.

- These include the following principles:

1. By mouth :

- Oral administration is the safest and therefore usually preferred.
- However, consideration should also be given to effectiveness, patient comfort, and patient control. For example, if ingestion or absorption of the medication is uncertain, analgesia needs to be given by an alternative route such as transdermal, subcutaneous, or rectal routes.
- Although hemodialysis patients have easy IV access, IV administration should be avoided as the route of administration of analgesic agents for chronic pain in order to optimize safety and minimize the risk of addiction and abuse.

2.By the clock

- Analgesics given for moderate to severe pain are given on a fixed-dose schedule around the clock and not only on an "as needed" or "prn" basis.
- This allows for more consistent pain relief.
- Some patients with mild pain may achieve adequate pain relief with analgesic dosing post-hemodialysis only.
- An example is CKD patients with mild neuropathic pain, which may be adequately controlled with gabapentin postdialysis.

3.By the ladder:

- A stepwise approach is recommended, in which medications are added sequentially.
- For CKD patients, it is important to select analgesic agents carefully, depending on the eGFR.
- The drug should be used at its full tolerated dose before moving to the next level.
- Sustained-release preparations are generally not recommended, at least until the individual patient's response to the medication has been observed, due to the narrow therapeutic window in patients with advanced CKD.

4.For the individual:

- There is a great deal of interpatient variability in the response to analgesic agents.
- Since there are no studies on the long-term use of analgesics in patients with CKD, careful attention must be paid to issues of efficacy and safety, and close monitoring is essential.
- The“correct”dose for strong opioids is the amount needed to relieve the pain without producing intolerable side effects. Evaluation of benefit and toxicity is essential.

5. Attention to detail:

- Pain changes over time; therefore, there is the need for ongoing reassessment.
- Side effects of opioids should be explained and managed actively ;e.g., constipation and nausea.
- Careful attention must be paid to efficacy and safety.

Drug selection:

- The analgesic choice for individual patients with advanced CKD depends on at least three variables:

- ✓ Nature of the pain
- ✓ Severity of pain
- ✓ Severity of kidney dysfunction

1. The nature of the pain:

- Pain is generally classified as either nociceptive or neuropathic.
- Among patients with advanced CKD, the pain is often mixed nociceptive/neuropathic in nature.

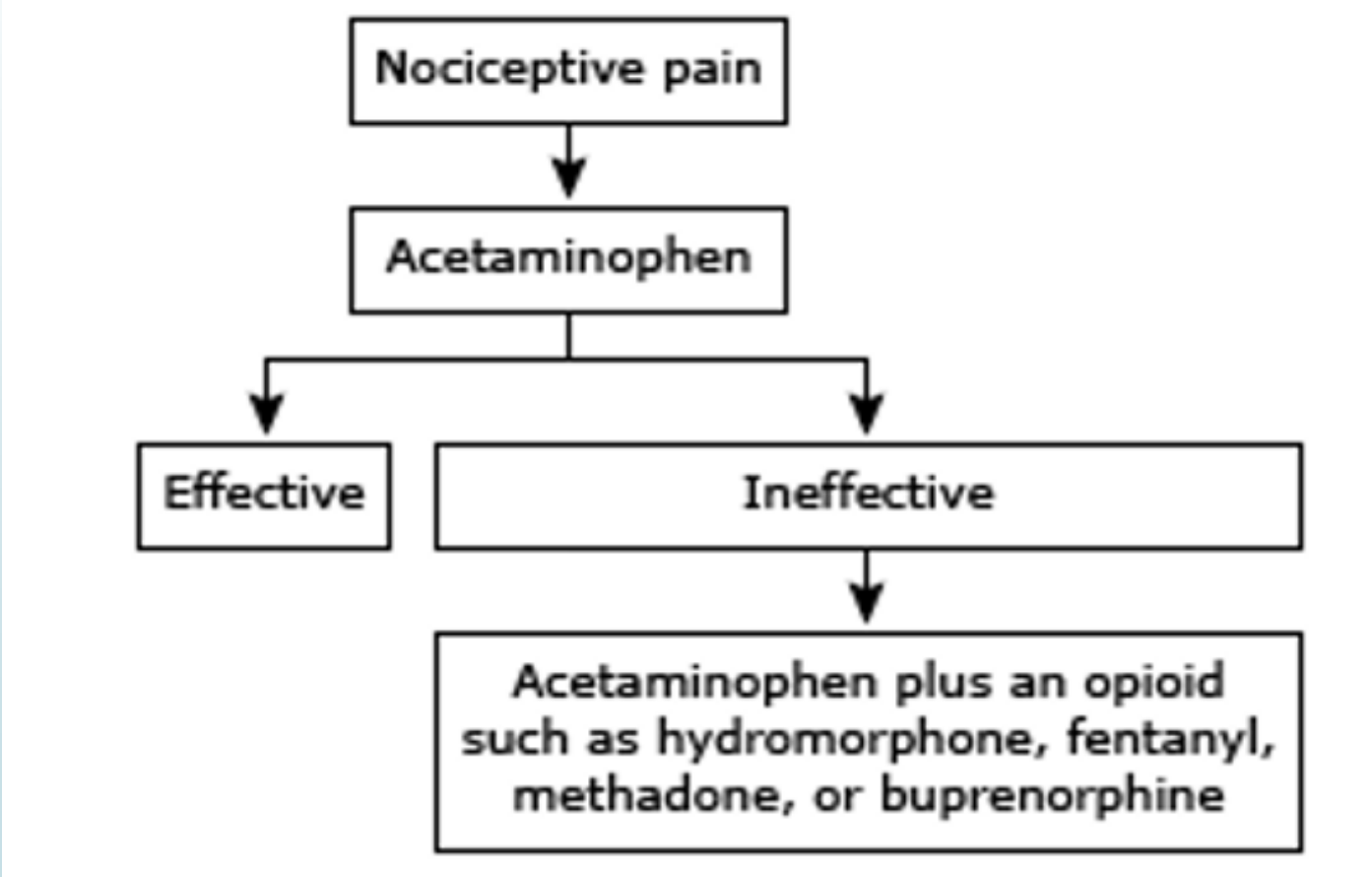
2.The severity of pain :

- Patients who present with severe pain may require the initiation of stronger agents at the outset.

3.The severity of kidney dysfunction :

- Many analgesic agents should have dose reductions or should not be used among individuals with advanced CKD.
- This is because the pharmacokinetics and pharmacodynamics of many analgesics and most opioids are altered among such patients, and the risk of toxicity from accumulation of renally excreted drugs and their metabolites is high.
- Pharmacokinetic data on analgesic medications in the context of advanced CKD may differ from that in the general population .

Management of chronic nociceptive pain in patients with advanced chronic kidney disease



Acetaminophen :

- Acetaminophen is an antipyretic analgesic with weak anti-inflammatory activity.
- Acetaminophen, prescribed in standard doses, is the first-line analgesic for patients with advanced CKD who have nociceptive pain.
- Acetaminophen is extensively metabolized in the liver, and only 2 to 5 percent of the therapeutic dose is excreted unchanged in the urine.
- Acetaminophen elimination is not significantly reduced among patients with decreased eGFR .
- Cumulative doses of acetaminophen likely do not affect CKD progression.
- Liver injury can be seen with acetaminophen doses of,4000 mg; therefore, the recommended maximum daily dose is 3000 mg.

Opioid:

Opioid Metabolism and Advanced CKD:

- Patients with kidney failure are at increased risk for adverse effects of opioids due to reduced elimination and increased accumulation of the parent analgesic and/or active metabolites.

- Analgesics may also be removed by dialysis, leading to uncertain analgesic effects during treatment.

- For patients who do not respond to acetaminophen alone, we treat with acetaminophen plus a strong opioid.

- Preferred opioids include hydromorphone, fentanyl, methadone, or buprenorphine.

- We do not use codeine, tramadol, morphine, meperidine/pethidine, hydrocodone, or propoxyphene among patients with advanced CKD .

- Opioids should be used with caution among patients with advanced CKD since such patients are at higher risk for toxic side effects compared with patients with normal kidney function.
- normal-release (short-acting), not modified-release (long-acting), preparations are preferred when available .
- Oral or transdermal agents, rather than parenteral routes, should be used.
- Patients should be evaluated closely for evidence of benefit and/or toxicity.

Hydromorphone :

- Hydromorphone appears to be better tolerated than morphine when immediate-release preparations are used for pain relief .
- Hydromorphone should be used with caution among all CKD patients, with close observation for side effects.
- Hydromorphone has a high potential for respiratory depression and addiction.
- Hydromorphone is metabolized primarily in the liver to conjugates, hydromorphone-3-glucuronide (H3G), which are excreted in the urine and accumulate in patients with reduced eGFR .
- Case reports have suggested that the accumulation of H3G conjugate may lead to myoclonus and delirium among patients with severely reduced eGFR .

- In one study of anuric hemodialysis patients, H3G accumulated between dialysis treatments but appeared to be removed effectively during hemodialysis .

- Among such patients, the clinician should be especially vigilant for toxic side effects. For such patients who develop side effects, other opioids (such as fentanyl, methadone, or buprenorphine) may be preferred.

- Fentanyl is particularly effective among patients who have withdrawn from dialysis in the last days of life since it is transdermally administered.

Methadone :

- Methadone may be particularly useful for the management of severe chronic pain in patients with advanced CKD.
- It is excreted mainly in the feces, although approximately 20 percent is excreted unchanged in the urine .
- In anuric patients, it is excreted exclusively in feces, with no accumulation in plasma.
- The parent drug and metabolites do not seem to be removed substantially by hemodialysis, so supplemental methadone is not required post-dialysis treatment .

- These factors would suggest that methadone may be a safe, effective analgesic for use in patients with advanced CKD by those familiar with its use as careful monitoring is essential, including monitoring for prolongation of the QT interval .

- Not every patient experiences Q-T interval prolongation with methadone, but risk factors include female sex, hypokalemia, high-dose methadone, drug interactions, and underlying cardiac conditions.

- In addition, it may be more effective for neuropathic pain than other opioids .

Fentanyl:

- Fentanyl is rapidly metabolized in the liver, with only 5 to 10 percent excreted unchanged in the urine . Its metabolites are considered to be inactive.

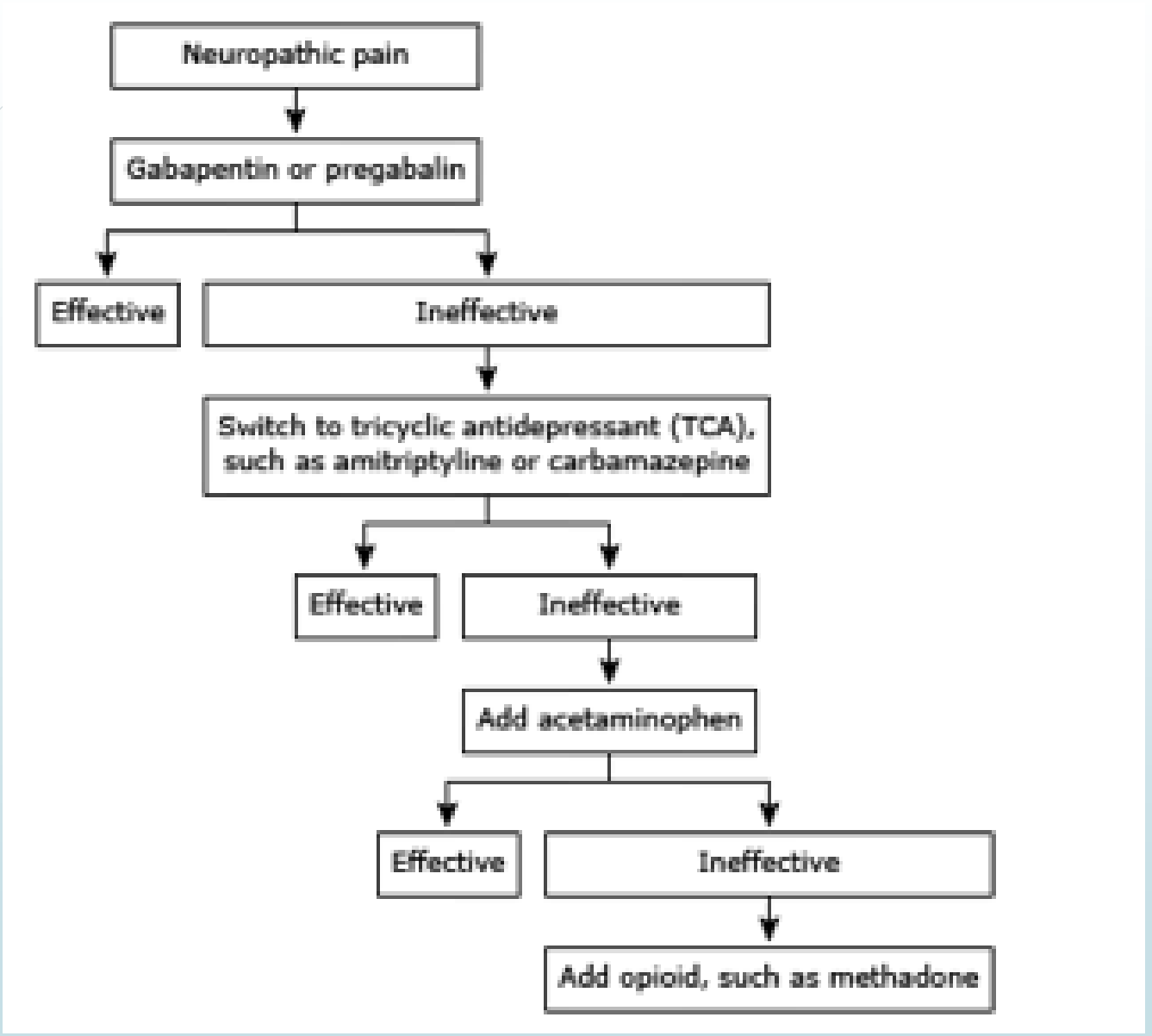
- There does not appear to be any clinically significant accumulation of fentanyl when administered to patients with advanced CKD .

Buprenorphine:

- Buprenorphine is an effective, long-acting opioid analgesic with an apparent ceiling effect on respiration.
- It can be administered sublingually or via a transdermal patch.
- Buprenorphine is a particularly useful analgesic for patients with severely reduced eGFR.
- Buprenorphine is completely metabolized by the liver, with little unchanged drug found in the urine .
- Caution is required when using buprenorphine because the reversal of buprenorphine-induced respiratory depression may be delayed and inconsistent, requiring large doses of naloxone.

Management of chronic neuropathic pain in patients with advanced chronic kidney disease

- Below is our pharmacologic approach to neuropathic pain, which uses adjuvant therapies such as gabapentin or pregabalin as first-line agents.


Neuropathic pain
Gabapentin or pregabalin
Effective
Ineffective
Switch to tricyclic antidepressant (TCA), such as amitriptyline or carbamazepine
Effective
Ineffective
Add acetaminophen
Effective
Ineffective
Add opioid, such as methadone

Gabapentin and pregabalin:

- We treat patients with chronic neuropathic pain with antiepileptic drugs (AEDs), including gabapentin and pregabalin.
- Gabapentin is cleared by the kidney, and elimination is markedly reduced in patients with low GFR .
- Gabapentin is almost exclusively cleared by the kidneys and substantial dose reduction is required as the GFR declines to avoid toxicity(increased risk for side effects such as neurotoxicity) .
- Adverse effects include somnolence, dizziness, peripheral edema, and gait disturbances.

- Approximately 50% of serum drug is removed during a 4-h session. Supplemental dosing postdialysis may be required.

- Gabapentin is also cleared by continuous ambulatory PD although this is a slow method to treat toxicity .

- Dosing Recommendations :
- ✓ eGFR 60–89 ml/min: 400- 600 mg t.i.d
- ✓ eGFR 30–59 ml/min: 200-300 mg t.i.d
- ✓ eGFR15-29 ml/min: 200- 300 mg once per day
- ✓ eGFR < 15 ml/min: 100-150 mg daily or 300 mg every other day

- Dose post HD:
- ✓ older patients or those with only mild neuropathic pain, it is reasonable to start at an even lower dose than permissible by eGFR (eg, 100 mg post dialysis in hemodialysis patients and 100 mg every second night in nondialysis CKD patients with eGFR <15 mL/min/1.73 m^2 who are not on dialysis).

Pregabalin:

- There have been case reports of neurotoxicity when using pregabalin in CKD patients .
- 95% is excreted unchanged by the kidneys. Approximately 50% of serum drug is removed during a 4-h session. Supplemental dosing post HD may be required.
- It may be reasonable, especially for older patients, or those with moderate rather than severe neuropathic pain, to start with doses as low as 25 mg post HD or 25 mg every second night in patients with stage 5 CKD managed Conservatively.

- ✓ eGFR>60 ml/min: 100 mg t.i.d
- ✓ eGFR 30–59 ml/min: 50 mg b.i.d
- ✓ eGFR 15–29 ml/min: 75 mg once per d
- ✓ eGFR <15 ml/min: 25-50 mg once per d

- ➢ Among patients with severely reduced GFR, gabapentin and pregabalin may have a beneficial effect on other common symptoms among patients with advanced CKD, including pruritus, restless legs syndrome, and poor sleep.

Tricyclic antidepressants (TCA) :

- For patients with neuropathic pain that is unrelieved by the maximum safe dose of gabapentin or pregabalin, we switch to a TCA.
- **TCA** are effective in the management of neuropathic pain but are less well tolerated than the gabapentinoids in patients with CKD because of anticholinergic, histaminergic, and adrenergic side effects resulting in symptoms such as dry mouth, orthostatic hypotension, somnolence and TCA-induced tachyarrhythmias .
- For these reasons, TCAs are considered second-line therapy for neuropathic pain in advanced CKD.
- Although dose reduction of tricyclic antidepressants is not necessarily required, patients with CKD will often respond to lower doses.

- Amitriptyline has been the most widely studied TCA in chronic pain , although a number of others, including doxepin, imipramine, nortriptyline, and desipramine, also have been used with success.

- We generally start amitriptyline at 10 mg daily. It can take up to six weeks, including two weeks at the highest dose tolerated, for an adequate trial of treatment with TCA, although the onset of analgesia may be after one week.

- TCAs (mainly those with greater anticholinergic effects) are relatively contraindicated in patients with severe cardiac disease, particularly conduction disturbances.

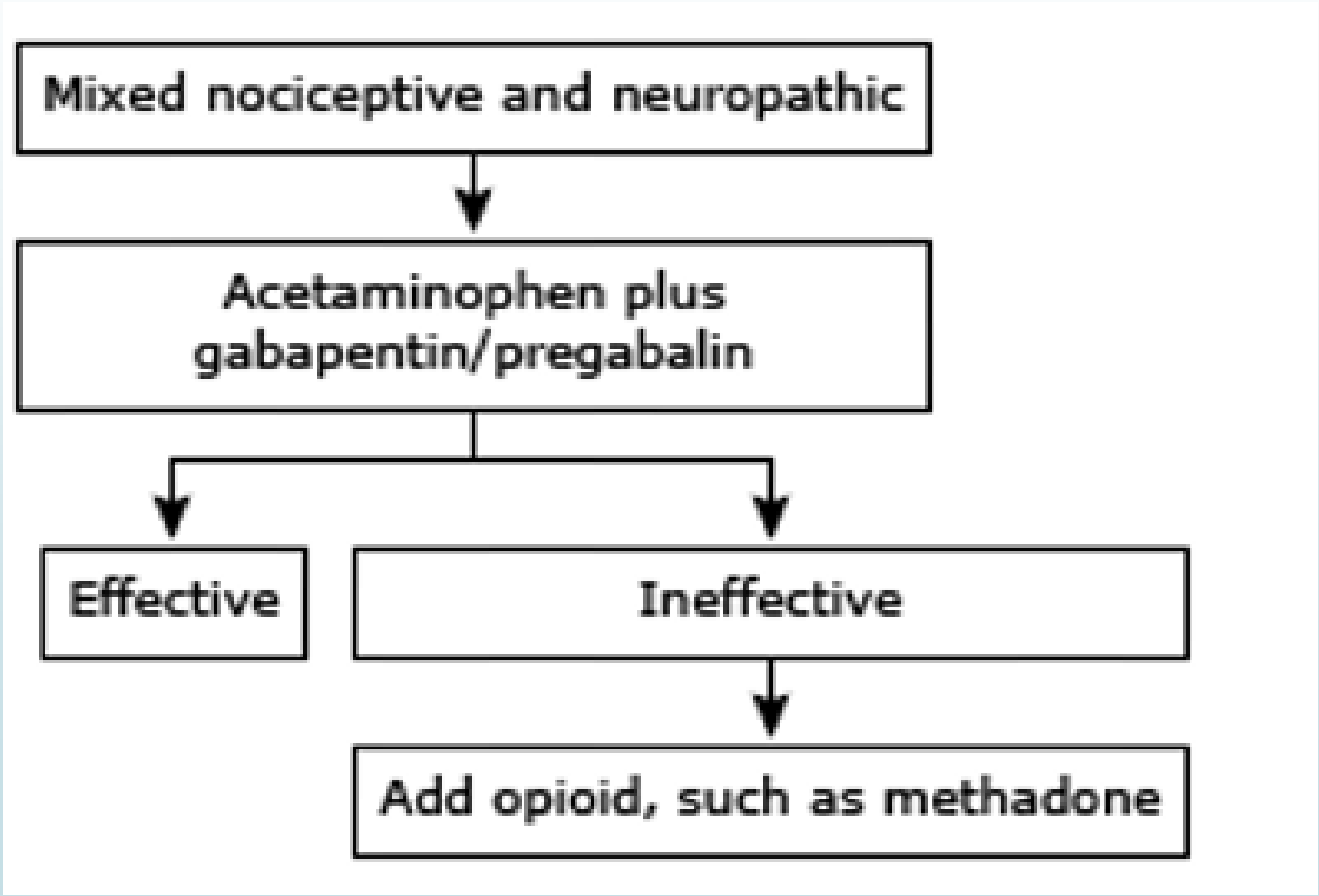
- Not dialyzed with HD or PD. No dose reduction is required.

Carbamazepine :

- It is used for treatment of seizure disorders and as a mood stabilizer.
- Carbamazepine may be as effective as gabapentin for treating neuropathic pain with fewer adverse effects.
- Unlike gabapentin and pregabalin, it requires no dose adjustment in patients with advanced CKD.
- We generally start carbamazepine at 100 mg once or twice daily and slowly increase the dose by 100 mg per day to a maximum of 1200 mg per day.

- For patients with neuropathic pain who are unresponsive to gabapentin, pregabalin, TCAs, or carbamazepine, we add traditional analgesics in a stepwise manner, starting with acetaminophen.
- For patients who do not respond to adding acetaminophen, an opioid may be added to acetaminophen.
- Methadone may be effective for severe neuropathic pain .
- We do not use codeine, tramadol, morphine, meperidine/pethidine, or propoxyphene among patients with advanced CKD.
- Oxycodone may be used among patients with advanced CKD but is considered a second-line agent compared with other opioids discussed above.

Management of chronic mixed pain in patients with advanced chronic kidney disease



DRUGS THAT SHOULD BE AVOIDED:

- We generally do not use

NSAIDs, codeine, tramadol, morphine, meperidine , propoxyphene, or pethidine among patients with advanced CKD for the treatment of chronic pain.

Non steroidal anti inflammatory drugs :

- NSAIDs may cause an acute reduction in GFR, sodium and water retention, hypertension, and hyperkalemia and potentially contribute to the progression of CKD .
- NSAIDs also compromise the gastrointestinal mucosa, inhibit platelet function, and are associated with increased risk of cardiovascular morbidity and mortality.
- Older age and Concomitant use of antiplatelet drugs such as aspirin, anticoagulants, and SSRIs further increases bleeding risk.
- We avoid NSAIDs, if possible, among patients with estimated GFR (eGFR) <60 mL/min/1.73 m^2, especially in older adults >75 years.

- Although the gastrointestinal safety profile of COX-2 inhibitors is superior to nonselective NSAIDs, nephrotoxic and cardiovascular adverse effects remain significant.

- In patients with residual kidney function, NSAIDs may also cause: a reduction in GFR that can be severe and irreversible if the patient has decreased effective circulating volume; sodium and water retention, which may aggravate hypertension and hyperkalemia

- The elderly may be at increased risk for NSAIDs-associated psychiatric events such as agitation, depression, anxiety, paranoia, delirium, and hallucinations

- The American Geriatric Society recommends that the chronic use of all oral NSAIDs, including high-dose aspirin, be avoided, especially in the elderly >75 years.

- Avoiding the use of NSAIDs is associated with increased opioid use in an effort to control pain.

- Therefore, the risk profile of NSAIDs versus low-dose opioids needs to be ascertained for any given patient.

- Topical NSAIDs can provide effective pain relief without the systemic adverse events associated with oral NSAIDs when used for both acute and chronic pain.

- Where pain is present in joints or no ulcerated skin, this may be a useful alternative to oral administration.

Morphine :

- We do not use morphine for patients with advanced CKD, although it is considered by many to be the drug of choice for the treatment of severe pain in patients with normal kidney function.

- Only a small percentage is excreted unchanged in the urine (5 to 10 percent of the dose). The active metabolites, however, accumulate rapidly in patients with GFR <30 mL/min/1.73 m^2 , potentially causing life-threatening or fatal respiratory depression, and chronic use is associated with significant toxicity.

- Alternative strong opioids such as hydromorphone, alfentanil and fentanyl, methadone, and buprenorphine are generally more appropriate, especially for patients with eGFR <30 mL/min/1.73 m^2

- Morphine may not be completely removed during dialysis.
- There are many reports in the literature of profound toxicity in patients with advanced CKD

Codeine :

- A weak opioid that is metabolized by the enzyme CYP2D6 in the liver to its active metabolite morphine, which provides the analgesic effect.
- The percentage conversion of codeine to morphine in individual patients is highly variable due to the genetic polymorphism of the *CYP2D6* gene. Such variable conversion to morphine can result in life-threatening or fatal respiratory depression due to high plasma levels of morphine, even with trivial doses in some and poor analgesic response in others with standard or higher doses .
- Morphine is renally excreted and accumulates in patients with kidney failure .
- There have been several case reports of prolonged narcosis in patients with CKD following ingestion of codeine, mostly among patients with eGFR <30 mL/min/1.73 m^2.

Codeine :

- For this reason, codeine should be avoided among patients with advanced kidney disease, if possible, even though some CKD patients are able to tolerate regular doses of codeine for a prolonged period without experiencing toxicity.

Tramadol:

- Tramadol is metabolized in the liver by the enzyme CYP2D6 with unpredictable bioavailability due to the genetic polymorphism of the *CYP2D6* gene.
- Ninety percent of tramadol and its metabolites are excreted in the urine.
- Even low doses of tramadol among patients with advanced CKD may cause significant side effects, including central nervous system depression.

Dextropropoxyphene :

- Dextropropoxyphene is an opioid for mild to moderate pain, usually prescribed in combination with acetaminophen.
- A weak opioid that has been withdrawn from the market in the United Kingdom, Europe, New Zealand, and Canada due to its weak analgesic effect, addictiveness, and its association with deaths and possible arrhythmias.However, it appears to be available in Asia, and South America.
- Dextropropoxyphene is contraindicated in patients with eGFR <30 mL/min/1.73 m^2.
- Decreased elimination of dextropropoxyphene and its major pharmacologically active metabolite, norpropoxyphene, has been reported in such patients , and its use has been associated with CNS toxicity, respiratory depression, and cardiotoxicity .

Oxycodone :

- We avoid use of oxycodone among patients with advanced CKD, whenever possible, due to the risk of respiratory depression.
- Oxycodone may be used among patients with CKD as a second-line agent after hydromorphone, fentanyl, methadone, or buprenorphine has been attempted.
- Oxycodone is eliminated mainly by metabolism in the liver to noroxycodone and oxymorphone, both of which were shown to accumulate in patients with advanced CKD.

Meperidine/pethidine:

- Meperidine or pethidine is contraindicated in all patients with CKD.
- Meperidine/pethidine is metabolized in the liver mainly to active metabolites with proconvulsive activity, which accumulate in patients with kidney impairment .

The Effect of Dialyzability of Analgesics on Pain Management

- Stability of analgesia during dialysis will vary among different analgesics.
- Opioids that are well dialyzed will likely require supplemental dosing during or after HD and patients could be at higher risk for opioid withdrawal symptoms after dialysis.
- Opioids that are not well dialyzed will have more stable analgesia.

Thank you for attenuation