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2017 update on pain management in patients with chronic kidney disease

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CKJ REVIEW

2017 update on pain management in patients with chronic kidney disease

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Abstract

The prevalence of pain has been reported to be >60–70% among patients with advanced and end-stage kidney disease. Although the underlying etiologies of pain may vary, pain per se has been linked to lower quality of life and depression. The latter is of great concern given its known association with reduced survival among patients with end-stage kidney disease. We herein discuss and update the management of pain in patients with chronic kidney disease with and without requirement for renal replacement therapy with the focus on optimizing pain control while minimizing therapy-induced complications.

Key words: CKD, dialysis, kidney transplantation, NSAIDS, opioids, pain

Introduction

Based on the 2012 National Health Interview Survey, 126.1 million adults in the USA (~50% of the adult population) reported some form of pain within the previous 3 months of the survey, 25.3 million suffered from chronic pain daily and 23.4 million rated their pain as severe [1]. Accordingly, the National Institute on Drug Abuse found that >200 million opioid prescriptions were dispensed by US retail pharmacies over the same year [2].

Similar to the general population, pain prevalence in patients with chronic kidney disease (CKD) has been reported to be in the range of 40–60% for patients receiving renal replacement therapy (RRT), 60–70% for pre-end-stage kidney disease (ESKD) and up to 100% for hospitalized CKD patients. Musculoskeletal pain predominates at 60–70% in both the general and CKD populations [3, 4]. While data on the actual number of opioid prescriptions written specifically for CKD patients are lacking, it

would be of grave concern if CKD patients had received an equivalent number of prescriptions as reported for the general population, because opioids are not well tolerated and potentially life-threatening in this subpopulation, even at lower doses.

We herein provide an update of our previously published review on the underlying pathophysiology and management of pain with special considerations for patients with CKD with or without a requirement for RRT [4].

Pain assessment

A comprehensive pain assessment is critical to provide an appropriate treatment plan. Identifying the underlying etiology of pain for prompt correction is both critical and ideal but does not always lead to complete pain resolution. The management of persistent pain requires a firm understanding of the underlying pathogenesis for targeted therapy rather than nonselective use of omnipotent opioids as well as an accurate assessment of duration and intensity.

While nonrecurring acute pain may be managed with short-term use of low doses of weak opioids without major concerns for abuse and addiction, chronic pain management requires a cautious stepwise approach to ensure optimal pain control while minimizing long-term adverse effects and opioid-abuse potential.

Pathophysiology of pain

Acute pain

Acute pain has been defined as a 'complex, unpleasant experience with emotional and cognitive, as well as sensory, features that occur in response to tissue trauma' [5]. Clinical features of acute pain include pain onset that is usually concordant with the degree of tissue damage and often associated with autonomic nervous system and other protective reflex responses (e.g. muscle spasm or splinting). Additionally, acute pain reflects activation of nociceptors and/or sensitized central neurons and remits with resolution of the inciting injury [6]. Nociceptors are ubiquitous sensory neurons that receive input from outer body tissue injury, giving rise to somatic pain or input from internal organs, leading to visceral pain. Nociceptors can be stimulated by mechanical, thermal, chemical or inflammatory stimuli. Substances released from tissue injury, including vasoactive peptides (e.g. calcitonin gene-related protein, substance P and neurokinin A) and mediators (e.g. prostaglandin E2, serotonin, bradykinin and epinephrine), can sensitize peripheral nociceptors [7, 8].

Nociceptors transmit their input centrally via two different types of axons, the rapidly conducting thinly myelinated Aδ fiber and the more slowly conducting unmyelinated C fiber axons. Pain sensed in the first phase, e.g. the initial extremely sharp pain, is associated with the fast-conducting Aδ fibers, while pain sensed in the second phase, typically a more prolonged and lower intensity pain, is mediated by the slowly conducting C fiber axons. The pain signal may be modulated at various points in both segmental and descending pathways by neurochemical mediators, including endogenous opioids and monoamines involving serotonin and epinephrine. Central nervous system (CNS)-active drugs such as opioids, antidepressants and anticonvulsants alleviate pain by interacting with specific pain-modulating opioid receptors (i.e. μ, κ and δ opioid receptors) and neurochemicals [8–11].

Chronic pain

Chronic pain may arise from prolonged tissue injury with persistent activation of nociceptors, a lesion or disease affecting the somatosensory system (known as neuropathic pain) or other undefined mechanisms. In tissue injury where there is persistent infiltration of inflammatory cells, the associated inflammatory reactions become the noxious stimuli that stimulate nociceptors to cause chronic nociceptive pain [9–13].

Neuropathic pain has been defined as pain that arises as a direct consequence of a lesion or disease that affects the somatosensory system [12]. Neuropathic pain is thought to involve peripheral and/or central sensitization. Peripheral sensitization occurs when regenerated C fibers of damaged axons develop pathological spontaneous activity and amplified excitability and sensitivity to various mechanical, chemical or thermal stimuli. Central sensitivity refers to the increase in general excitability of spinal cord dorsal horn neurons as a result of peripheral nerve injury. The hyperexcitability of spinal cord neurons has been attributed to increased neuronal background activity, enhanced activity in response to noxious stimuli and expanded neuronal receptive fields. Other mechanisms of neuropathic pain include loss of inhibitory interneuronal activity, development of abnormal electrical communication across adjacent demyelinated axons (also known as ephaptic cross talk), release of neuroexcitatory substances by nonneural glial cells or the spontaneous firing of higher-order neurons in the presence of injured or disrupted peripheral sensory pathways, a process known as deafferentation. The latter is thought to give rise to phantom limb pain, diabetic neuropathy and postherpetic neuralgia. Ephaptic cross talk between sensory and sympathetic fibers is thought to be responsible for sympathetic pain associated with the complex regional pain syndrome, also known as reflex sympathetic dystrophy, a condition whereby a noxious stimulus can trigger autonomic activity at the same dermatomal level of the spinal cord [9–11, 14, 15].

Pain conditions with neuropathic features but without any known injury or dysfunction of the nervous system may be classified as nonneuropathic pain. Whereas patients with peripheral neuropathic pain often report intense hot, cold, sensitive, itchy and surface pain, patients with nonneuropathic pain more commonly report intense dull and deep pain [16]. Common neuropathic and nonneuropathic pain syndromes are listed in Table 1.

Preferred nonopioid pharmacologic agents in the initial treatment of common neuropathic and nonneuropathic pain syndromes are shown in Table 2 [17–22].

Rating pain intensity

Pain intensity can be measured based on one of three major types of scales reflecting verbal, visual or numerical input from patients. Pain assessment tools that are commonly used include the McGill Pain Questionnaire (verbal), Wong–Baker faces (visual) or just a simple 0–10 numerical pain scale (numerical). The McGill Pain Questionnaire lists 20 groups of words that are used to describe and rate the intensity of pain. The 20 groups of words chosen are divided into four major groups to describe sensory qualities (e.g. flickering, pinching, itchy, dull), affects (e.g. tiring, frightful, vicious, blinding), overall evaluation (e.g. annoying, intense, unbearable) and other miscellaneous characteristics (e.g. radiating, tight, cool, nauseating). The higher the score obtained out of 78 maximum points, the greater the pain [23]. The Wong–Baker faces pain rating scale involves pictures of a smiling face indicating the presence of pain (0 out of 5

Table 1. Symptoms of common nonneuropathic and neuropathic pain syndromes

Pain syndromes	Pain characteristics
Nonneuropathic pain syndromes	
Chronic tension headache	Dull achy pain or tight sensation in forehead, sides, top or encircling head
Chronic migraine	Chronic throbbing headaches that may be associated with nausea and/or vomiting
Chronic neck or back pain	Chronic dull or sharp pain that may be associated with muscle stiffness
Fibromyalgia	Diffuse muscular pain associated with stiffness, fatigue and sleep disturbances. Focal pain may be triggered with pressure over areas
Myofascial pain syndrome	Constant deep pain associated with and caused by 'trigger points'; trigger points are localized and often painful contracture 'knots' in any skeletal muscle.
Neuropathic pain syndromes	
Post-stroke pain	Throbbing, shooting or burning pain; loss of temperature differentiation
Trigeminal neuralgia	Occasional twinges of mild to severe shooting pain that may be triggered by manipulation of areas supplied by the affected trigeminal nerve
Sciatica	Mild to sharp, burning, electric shock–like pain radiating from the lumbar spine to buttock and down the back of the leg, with or without muscle weakness or numbness in affected areas
Complex regional pain	Intense burning or aching pain in association with edema, skin discoloration, change in temperature, abnormal sweating and hypersensitivity in affected areas
Diabetic neuropathy	Numbness and/or burning pain in the distal extremities
Phantom limb pain	Feelings of cold, warmth, itchiness, tingling or tearing

Adapted from Pham *et al.* [4].

Table 2. Pharmacologic management of common nonneuropathic and neuropathic pain syndromes

Pain syndromes	Suggested nonopioid pharmacologic agents
Nonneuropathic pain syndromes	
Chronic tension headache	NSAIDs (e.g. aspirin, acetaminophen, ibuprofen and naproxen)
	TCAs (e.g. amitriptyline, doxepin and nortriptyline)
	Muscle relaxants (e.g. cyclobenzaprine, orphenadrine citrate, baclofen and tizanidine)
Chronic migraine	Antidepressants: TCAs, SSRIs (e.g. fluoxetine, sertraline and citalopram), SNRIs (e.g. duloxetine and venlafaxine)
	Antihypertensives: beta-blockers (e.g. propranolol, metoprolol, timolol, nadolol, atenolol and bisoprolol); calcium channel blockers (e.g. amlodipine, diltiazem and verapamil)
	Anticonvulsants (e.g. topiramate and gabapentin)
Chronic neck or back pain	NSAIDs
Fibromyalgia	TCAs (e.g. amitriptyline and cyclobenzaprine), SNRIs (e.g. duloxetine and milnacipran), SSRIs (e.g. fluoxetine, sertraline and paroxetine)
	Anticonvulsants (e.g. gabapentin and pregabalin), muscle relaxants, tramadol
Myofascial pain syndrome	NSAIDs, COX-2 inhibitors
	Limited evidence: tizanidine, benzodiazepines, thiocolchicoside (competitive $GABA_A$ antagonist and glycine agonist that also functions as an anti-inflammatory and analgesic agent as well as muscle relaxant)
	Limited efficacy: topical diclofenac and lidocaine patches
Neuropathic pain syndromes	
Post-stroke pain	Early phase: NSAIDs, muscle relaxants
	Anticonvulsants (pregabalin and gabapentin), TCAs, SNRIs (e.g. duloxetine and venlafaxine)
Trigeminal neuralgia	Anticonvulsants (carbamazepine andgabapentin), TCAs (e.g. amitriptyline and nortriptyline), consider baclofen
Sciatica	NSAIDs, short course of corticosteroids
	Muscle relaxants
	Antidepressants for low back pain
Complex regional pain	Anticonvulsants (e.g. gabapentin, pregabalin and carbamazepine), TCAs (e.g. amitriptyline and nortriptyline)
	Other suggested therapies: short course of corticosteroids, bisphosphonates have been suggested to reduce pain in nonstroke patients
Diabetic neuropathy	Pregabalin, gabapentin and sodium valproate
	Antidepressants (e.g. amitriptyline, venlafaxine and duloxetine)
	Consider topical capsaicin or transdermal lidocaine for localized pain
Phantom limb pain	NSAIDs and acetaminophen
	Anticonvulsants (e.g. carbamazepine, gabapentin and pregabalin)
	Antidepressants (e.g. amitriptyline, nortriptyline and mirtazapine)
	Others: memantine, beta-blocker and calcium channel blocker

TCAs, tricyclic antidepressants; GABA, gamma-aminobutyric acid, SSRI, selective serotonin reuptake inhibitor; SNRI, serotonin-norepinephrine reuptake inhibitor; NSAIDS, non-steroidal anti-inflammatory drugs.
Modified from Pham *et al.* [4].

score) to severe facial grimacing and tearing for the worst pain (5 out of 5 score). The Wong–Baker pain rating scale is particularly useful for pediatric patients and those with poor verbal communication [24]. Finally, a numerical rating scale ranging from 0 to 10 is perhaps the most widely used system. A numerical rating scale is generally based on a subjective 10-point scoring system, where 0 denotes the absence of pain and 10 is the worst pain imaginable (reviewed in Pham *et al.* [4]).

There are multiple other symptom assessment tools with varying goals and depths that have been validated specifically for CKD patients. While some assessment tools are relatively short and practical for use in routine clinical care (e.g. Modified Edmonton Symptom Assessment System, Palliative Care Outcome Scale–Renal, Dialysis Symptom Index, Brief Pain Inventory), others are more extensive [e.g. Kidney Dialysis Quality of Life–Short Form/36-item Short Form Health Survey (SF-36) or CHOICE Health Experience Questionnaire (CHEQ) + SF-36] (reviewed in Davison *et al.* [3]).

General considerations for pharmacologic management of pain in non-CKD patients

In 1986 the World Health Organization established an evidence-based '3-step ladder' pharmacologic management guide for pain associated with malignancy that has since been adapted and widely used for other populations, including those with CKD and ESKD with persistent nonmalignant and malignant pain (Table 3). The 3-steps refers to the three levels of pain, where mild pain is estimated as having an intensity rating of 1–3 out of a maximum 10-point pain score, moderate as having a score of 4–6 and severe as having a score of 7–10 [25, 26].

Unless otherwise indicated (Table 3), the 'first-step' pharmacologic intervention for mild pain typically involves the use of nonopioid analgesics, including acetaminophen and nonsteroidal anti-inflammatory drugs (NSAIDs).

For moderate pain, the 'second step' allows the addition of low-potency opioids such as codeine, oxycodone, dihydrocodeine

or hydrocodone. In addition, the use of tramadol may also be considered.

For severe pain, the 'third step' allows the addition of more potent opioids, including morphine, hydromorphone, methadone and fentanyl.

At any step in the ladder of pain management, adjuvant therapies should be considered as indicated for the specific underlying etiology of pain. These agents include antidepressants for various chronic neuropathic and nonneuropathic pain conditions, short-term corticosteroids and possibly fish oil for inflammatory conditions, anticonvulsants and antidepressants for neuropathic pain, muscle relaxants for musculoskeletal pain or spasms and bisphosphonates for malignancy-associated bone pain [27–29]. Severe edema arising from various conditions may exaggerate preexisting pain conditions and must be treated based on the underlying etiologies. Treatment of edema is beyond the scope of the current review. In the authors' opinion, the use of intermittent pneumatic compression stockings and elevation of affected limbs should also be considered.

Nonpharmacologic intervention

In addition to medical therapies, adjunctive nonpharmacologic interventions must be considered whenever applicable. Topical thermal therapy and exercise programs in conjunction with the use of physical modalities, including transcutaneous electrical stimulation (TENS), may be explored in various pain conditions.

Topical thermal therapy applied to the affected area is a simple measure that may be beneficial for acute pain in many instances. While both heat and cryotherapy (warm versus cold compress) are widely used, cryotherapy is thought to offer a better restorative and therapeutic effect compared with topical heat therapy [30]. Cryotherapy 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. Nonetheless, topical

Table 3. Stepwise approach for nociceptive pain management in patients with CKD

Severity[a]	Pharmacologic options for non-CKD	Special considerations for CKD
Mild	Nonopioids ± adjuvants: NSAIDs, acetylsalicylic acid and acetaminophen	Acetaminophen is preferred (dose minimization is warranted) NSAIDs and COX-2 inhibitors likely adversely affect renal hemodynamics equally Use of short-acting NSAIDs is suggested; consider topical analgesics when appropriate (see Table 4) Consider sulindac or salsalate[b] Avoid concomitant use of other hemodynamically compromising drugs (e.g. renin inhibitors, ACEIs, ARBs and radiocontrast agents) Optimize cardiac output and volume status; avoid NSAIDs in volume depletion
Moderate	Nonopioids ± adjuvants ± weak opioids (codeine, dihydrocodeine, hydrocodone, tramadol)	Tramadol may be considered Codeine and dihydrocodeine are not recommended in patients with advanced CKD Opioids: toxic parent and metabolite compounds may accumulate (see Table 5)
Severe	Nonopioids ± adjuvants ± moderate to strong opioids (fentanyl, morphine, hydromorphone, methadone, levorphanol and oxycodone)	Methadone or fentanyl may be acceptable; dose and frequency reduction are advisable. Warning on the use of fentanyl: potential life-threatening respiratory depression in non-tolerant patients and improper dosing. Codeine and dihydrocodeine are not recommended in patients with advanced CKD

Modified from Pham *et al.* [4].
ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker.
[a]Mild: pain score ranges from 1 to 3 out of 10; moderate: pain score ranges from 4 to 6 out of 10; severe: pain score ranges from 7 to 10 out of 10.
[b]May have lower intrarenal prostaglandin inhibitory effect than other NSAIDs, actual clinical benefit over other NSAIDs is not known.

heat has been suggested to be beneficial in reducing local muscle spasm and pain in the acute phase of injury [30–32].

The use of TENS in experimental models has been shown to modulate pain perception via alterations in the peripheral nervous system as well as spinal cord and descending inhibitory pathways {32, 33}. While TENS has been proposed to be beneficial for both acute and chronic pain, it is thought to be most effective for postoperative pain, osteoarthritis and chronic musculoskeletal pain [32–35]. A recent Cochrane review involving 19 trials provided tentative evidence that TENS reduces pain intensity over and above that seen with placebo for acute pain (e.g. cervical laser treatment, venopuncture, screening flexible sigmoidoscopy and nonprocedural pain such as postpartum uterine contractions and rib fractures in adults) [36].

The effectiveness of ultrasound therapy for musculoskeletal pain remains unproven. The use of ultrasound in the treatment of musculoskeletal disorders or as a tool to augment the beneficial effect of exercise therapy lacks firm evidence [37].

Other nonpharmacologic therapies of varying benefits include biofeedback, cognitive behavioral therapy and mirror therapy (for phantom limb pain) [21]. Mirror therapy involves the use of a mirror to create a reflective illusion of the affected limb in order to trick the brain into thinking movement has occurred without pain [38].

The National Center for Complementary and Alternative Medicine has also recognized six general categories of therapies that may benefit pain control. These include mind–body interventions, diet and lifestyle modification, herbal remedies, manual healing, bioelectromagnetics and pharmacologic–biologic treatments. Complementary and alternative medical options may be considered in cases where benefit–risk ratios are unequivocally favorable [4, 39, 40]. Table 4 lists nonpharmacological management options for common musculoskeletal pain conditions. Finally, evaluation for surgically corrective options and modification of psychosocial issues must be explored whenever applicable.

Special considerations for pain management in patients with CKD and ESKD receiving RRT

The management of pain in patients with CKD and ESKD similarly follow the WHO 3-step ladder approach, albeit with special considerations due to altered drug pharmacokinetics and various physiological aspects associated with reduced kidney function.

Increased drug levels and associated adverse effects may occur due to reduced renal clearance and accumulation of a toxic parent compound and/or its metabolite or increased free drug levels due to reduced protein binding associated with hypoproteinemia/hypoalbuminemia and/or acidemia [41]. Drug removal by various modes of dialysis must also be considered.

NSAIDs and cyclooxygenase 2 inhibitors

Drug-induced fluid and electrolyte disturbances or drug-associated vasoactive effects can also lead to altered hemodynamics, cardiovascular adverse outcomes and worsening of underlying kidney function. Drugs belonging in this category include NSAIDs and cyclooxygenase 2 (COX-2) inhibitors. As a class, NSAIDs are known to have direct nephrotoxic effects including afferent vasoconstriction leading to reduced glomerular filtration; allergic reactions leading to tubulointerstitial nephritis; nephrotic syndromes, which commonly include minimal change disease and membranous glomerulonephropathy; fluid and sodium retention; worsening of preexisting hypertension; papillary necrosis and various electrolyte disturbances, including hyponatremia, hyperkalemia and type 4 renal tubular acidosis [42].

In a retrospective cohort study of adult hypertensive patients, Aljadhey *et al.* [43] reported that compared with patients using acetaminophen, NSAIDs users (ibuprofen, naproxen and celecoxib) had a 2 mmHg increase in mean systolic blood pressure (SBP). Of the three NSAIDs analyzed, ibuprofen appeared to

Table 4. Nonpharmacological options for the management of common musculoskeletal pain conditions

Conditions	Therapeutic options	Source
Acute or subacute low back pain	Superficial heat effect, moderate; QOE, moderate	ACP
	Massage: effect, small to moderate; QOE, low	
	Acupuncture or spinal manipulation: effect, small; QOE, low	
Chronic low back pain	Multidisciplinary rehabilitation, acupuncture: effect, moderate; QOE, moderate	ACP
	Exercise, mindfulness-based stress reduction: effect, small; QOE, moderate	
	Tai chi, yoga, motor control exercises, progressive relaxation, electromyography biofeedback, cognitive behavioral therapy: effect, moderate; QOE, low quality	
	Operant therapy, spinal manipulation, low-level laser therapy: effect, small; QOE, low	
Knee osteoarthritis	Exercise (land-based or water-based), strength training, self-management and education, weight management: recommendation, appropriate; QOE, good	ORSI
	Balneotherapy (use of bath containing mineral water)/spa therapy: recommendation, appropriate for individuals with multiple-joint OA and relevant comorbidities; uncertain for individuals without relevant comorbidities, uncertain for individuals with knee-only OA; QOE, fair	
	Biomechanical interventions (e.g. use of knee braces, knee sleeves, foot orthoses and lateral wedge insoles): recommendation, appropriate; QOE, fair	
	Cane (walking stick): recommendation, appropriate for knee-only OA, uncertain for multiple-joint OA; QOE, fair	
	Acupuncture: recommendation, uncertain; QOE, good	
	Crutches: recommendation, uncertain; no available trials	
	TENS, ultrasound: recommendation, uncertain for knee-only OA, not appropriate for multiple-joint OA; QOE, good	
	Electrotherapy/neuromuscular electrical stimulation: recommendation, not appropriate; QOE, fair	

QOE, quality of evidence; ACP, American College of Physicians; ORSI, Osteoarthritis Research Society International; OA, osteoarthritis; TENS, transcutaneous electrical nerve stimulation.

induce the highest hypertensive effect, 3 mmHg increase in SBP compared to naproxen and 5 mmHg increased compared to celecoxib. Additionally, a greater SBP increase was noted with beta-blockers, followed by either calcium channel blockers and angiotensin-converting enzyme inhibitors, and negligible SBP change in patients prescribed diuretics or multiple antihypertensive medications [43]. In the authors' opinion, the use of NSAIDs should be minimized among patients with Stage 3 CKD and avoided in those with Stage 4 or Stage 5 CKD with residual kidney function or recipients of kidney transplant regardless of CKD stage. It is conceivable that compromised intraglomerular hemodynamics may be potentiated with concurrent use of NSAIDs and calcineurin inhibitors in the transplant setting.

Whenever NSAIDs use must be considered due to the lack of effective alternatives, short-acting are preferred over long-acting agents to avoid prolonged NSAID-induced intraglomerular hemodynamic compromise. NSAIDs suggested to induce relatively low renal hemodynamic compromise include sulindac and salsalate. The renal-sparing effect of sulindac and salsalate has been attributed to the relative preservation of renal prostaglandin synthesis and weak prostaglandin inhibition at therapeutic doses, respectively [44]. During NSAIDs use, optimization of volume status and cardiac function are highly advised, frequency of administration should be reduced and concurrent use with inhibitors of the renin–angiotensin system should be cautioned to prevent synergistic reduction in glomerular filtration.

Additionally, whenever applicable and safe, topical administration of analgesics may be preferred over oral or nontopical parenteral routes to reduce systemic drug concentrations, thereby minimizing drug interactions and systemic toxicities [45]. Topical analgesics including diclofenac, ibuprofen, ketoprofen and combination salicylates plus diethyl ether have been shown in small studies to be effective in relieving both soft tissue injuries and various inflammatory musculoskeletal conditions. While topical NSAIDs have been reported to confer more favorable tolerability profiles, including gastrointestinal and cardiovascular events, compared with oral agents, data on renal toxicities are lacking [46]. Of interest, however, the use of topical ibuprofen has been linked to the recurrence of NSAID-induced nephrotic syndrome and kidney injury in one case report [47]. Current data also support the use of topical lidocaine and capsaicin for neuropathic pain. Table 5 summarizes topical analgesics that are of potential benefit in the treatment of localized pain [22, 46]. Despite having relatively lower blood levels with the use of topical analgesics, caution must still be exercised with prolonged or high-dose use, due to skin absorption and systemic accumulation, to avoid serious systemic toxicities. Data comparing renal and fluid/electrolyte adverse effect profiles between topical and systemic NSAIDs are lacking. In the authors' opinion, the use of topical NSAIDs in patients with advanced CKD (i.e. CKD Stage 4 or greater with residual kidney function) and recipients of kidney transplants cannot be routinely recommended, particularly when prolonged or high-dose use is necessary.

Selective COX-2 inhibitors induce similar adverse effects as NSAIDs and should be similarly avoided [48].

Opioids

Accumulation of renally excreted opioids and their toxic metabolites in patients with reduced kidney function may lead to potentially life-threatening neurological complications, including severe oversedation, myoclonus and seizures, clinically significant suppression of respiratory drive and even death. Suppression of respiratory drive may lead to potentially disastrous outcomes among patients with marked kidney failure–associated metabolic acidosis who rely on respiratory compensation to maintain safe acid–base homeostasis. Other potential complications associated with the use of opioids in patients with renal impairment that should not be overlooked include worsening of kidney function with opioid-induced hypotension and thus renal hypoperfusion, urinary retention and hyperkalemia with opioid-induced severe constipation.

Table 5. Topical analgesics in the management of acute and chronic pain

Topical analgesics (formulations)	Common pain conditions tested	Comments
[a]Diclofenac (1% gel)	Minor sports soft tissue injuries, acute ankle sprains, knee osteoarthritis and chronic lateral epicondylitis	Topical NSAIDs (particularly diclofenac and ibuprofen) are more widely studied than any other agents. Available evidence suggests that topical NSAIDs can be recommended for short-term pain relief in patients with acute soft tissue injuries or chronic joint-related conditions such as osteoarthritis
[a]Ibuprofen (5% cream or gel)	Chronic knee pain, chronic leg ulcers, soft tissue injuries and acute ankle sprains	
[a]Ketoprofen (2.5% gel, total daily dose of 250 mg)	Soft tissue injuries	
Salicylates (750 mg aspirin plus diethyl ether mixture or 75 mg/mL of aspirin alone)	Acute and postherpetic neuralgia	Effective formulation involves a mixture of both aspirin and diethyl ether
Lidocaine (5% lidocaine medicated patch or plaster)	Postherpetic neuralgia and diabetic neuropathy	Available data suggest better pain control of postherpetic neuralgia compared with oral pregabalin
Capsaicin (0.025–0.075% cream, 8% patch)	Neuropathic pain, postherpetic neuralgia and acute migraine	Weak evidence
Amitriptyline (1–5% cream)	Neuropathic pain	Poor data
Glyceryl trinitrate (0.72 mg/day)	Lateral epicondylitis, chronic noninsertional Achilles tendinopathy and post-hemorrhoidectomy	Improved wound healing reported
Others: opioids, menthol (chronic knee pain), pimecrolimus (vulvar lichen sclerosus, oral lichen planus), phenytoin (superficial burns and chronic leg ulcers)		Scant data

References Finnerup *et al.* [22] and Argoff [46].
[a]Although the use of topical NSAIDs may result in lower blood levels and induce fewer systemic effects, data comparing the effects of an equivalent dose of oral versus topical NSAIDs on renal function are lacking. Prolonged and high-dose use in advanced CKD is not recommended.

Tramadol

Tramadol, an increasingly popular analgesic due to its lower abuse potential, is a prodrug that is metabolized by cytochrome P450 (CYP) enzymes CYP2D6 and CYP3A4 to its more potent opioid analgesic metabolite O-demethylation product M1 [49, 50]. Tramadol has a dual action of pain relief, acting both as a central opiate agonist and CNS reuptake inhibitor of norepinephrine and serotonin. Tramadol and M1 act as selective mu-receptor agonists to alter the release of nociceptive neurotransmitters. The mu activity of tramadol is 10-fold lower than that of codeine but the M1 metabolite has 300 times higher affinity for the mu-receptor compared with tramadol. Additionally, tramadol and M1 inhibit serotonin and norepinephrine reuptake, respectively, both leading to enhancement of the inhibitory descending pathways associated with pain transmission in the CNS [49–51].

Tramadol is generally preferred for moderate pain in CKD patients because it is not directly nephrotoxic. Nonetheless, tramadol and its metabolite accumulate with advanced CKD (estimated glomerular filtration rate <30 mL/min/1.73 m^2) [52, 53].

Increased blood levels of the compound may induce respiratory depression and reduce the seizure threshold. Tramadol has been increasingly recognized to precipitate the serotonin syndrome either as a single agent in genetically susceptible individuals or in those taking selective serotonergic drugs, including selective serotonin reuptake inhibitors (SSRIs), serotonin–norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants, monoamine oxidase inhibitors and triptans (e.g. fluoxetine, sertraline, paroxetine), drugs that impair the metabolism of serotonin, including monoamine oxidase inhibitors, and drugs that impair the metabolism of tramadol (CYP2D6 and CYP3A4 inhibitors) [49]. The maximum dose of tramadol prescribed to advanced CKD patients is suggested to not exceed 100 mg orally twice daily and 50 mg twice daily for dialysis patients [54].

With the exception of methadone, the majority of opioids recommended for moderate and severe pain undergo hepatic biotransformation followed by renal excretion as the primary route of elimination. Accumulation of commonly used agents including morphine, oxycodone and propoxyphene among

Table 6. Special considerations for opioid use in patients with CKD

Medications (US schedule)[a]	MME conversion factor[b]	Comments
Tramadol (IV)	0.1	Renal clearance: 30%; exposure to active metabolite is up to 20–40% with mild to moderate renal impairment; maximum dose: 100 mg every 12 h in CKD (CrCl <30 mL/min), 50 mg twice a day in dialysis; HDD: 7%; PDD: unknown
Buprenorphine (III)	10	Extensively hepatically metabolized; metabolites (norbuprenorphine) have weak analgesic effect; renal clearance of both buprenorphine and norbuprenorphine: 30%; appears safe for advanced CKD and dialysis; no dose reduction suggested at this time, but use with caution; HDD: yes, PDD: yes
Meperidine	0.1	Contraindicated in CKD and dialysis; high neurotoxicity
Fentanyl (II)	0.13–0.18	Potency depends on route of administration; highest MME for film or oral spray, lowest for tablets No clinically significant accumulation in CKD; HDD: no; PDD: no
Codeine (II)	0.15	Not recommended in CKD; hepatically metabolized to codeine-6-glucuronide, norcodeine and morphine metabolites; renal clearance: 90%, 10% of which is parent compound. Accumulation of metabolites can lead to serious adverse effects (e.g. respiratory arrest, narcolepsy and severe hypotension); respiratory depression and death have been reported in children who are ultrarapid metabolizers of codeine due to a CYP2D6 polymorphism; HDD: no; PDD: no
Dihydrocodeine (II)	0.25	Same as codeine above
Tapentadol (II)	0.4	Not recommended for CrCl <30 mL/min; no dose adjustment needed for CrCl ≥30 mL/min. Renal clearance: 99%; HDD: likely yes; PDD: unknown
Morphine (II)	1	Avoid in CKD (CrCl <30 mL/min) and dialysis due to accumulation of active metabolites (morphine-6-glucuronide, morphine-3-glucuronide). Metabolites accumulate interdialytically: extra dosing may be needed during or after dialysis. Morphine is best avoided in dialysis patients. HDD: yes; PDD: no
Hydrocodone (II)	1	Renal clearance: 25%, 12% of which is parent compound; 50% dose adjustment recommended for moderate to severe renal impairment (CrCl <30 mL/min); HDD: unknown; PDD: unknown
Oxycodone (II)	1.5	May be used among patients with CKD if monitored closely but is considered a second-line agent; both parent compound and metabolites are substantially renally excreted; oxymorphone, an oxycodone metabolite, and the parent compound accumulate in renal failure; dose adjustment is recommended; data in CKD are poor; HDD: yes, PDD: unknown
Oxymorphone (II)	3	For patients with prior opioid use and CrCl <50 mL/min, 50% dose reduction followed by cautious upotitration as needed; HDD: no; PDD: no
Methadone (II)	3	Extensive biotransformation followed by renal and fecal excretion; no dose adjustment for CKD; HDD: yes; PDD: yes
Hydromorphone (II)	4	Accumulation of active metabolite hydromorphone-3-glucuronide can cause neuroexcitatory symptoms (e.g. myoclonus, delirium and seizures). Hydromorphone exposure after a 4 mg oral dose is doubled with CrCl of 40–60 mL/min and tripled with CrCl <30 mL/min. Accordingly, dose reduction is required. HDD: yes; PDD: unknown

MME, morphine milligram equivalent (e.g. 3 mg of oral morphine is equipotent to 1 mg of methadone); HDD, hemodialysis dialyzability; PDD, peritoneal dialysis dialyzability; CrCl, creatinine clearance.
[a]US opioid schedule: II, high abuse potential, may lead to severe psychological or physical dependence; III, moderate to low potential for psychological or physical dependence; IV, low potential for abuse and risk for dependence.
[b]Opioids are listed based on potency compared with oral morphine.

advanced CKD patients can lead to profound CNS and respiratory depression and hypotension [26, 55]. Myoclonus and seizures are well-recognized serious neurological complications associated with the use of high doses of morphine, hydromorphone and fentanyl [26, 55, 56]. In general, dose reduction is required for most opioids among CKD patients. The use of methadone and fentanyl may be acceptable in CKD patients.

Fentanyl

Fentanyl is a potent synthetic opioid that follows a similar pattern of drug elimination as other opioids. Its metabolites, however, are inactive and nontoxic [57, 58]. The use of the fentanyl transdermal system, however, is reserved for opioid-tolerant patients with persistent moderate to severe chronic pain that requires continuous and prolonged opioid administration and who have failed other pharmacologic interventions, due to its high potential for serious and life-threatening complications with hypoventilation.

Methadone

Methadone is an orally administered agonist of the mu-opioid receptor with slow onset of action and prolonged half-life up to 36 h that serves well as medical therapy for both opioid detoxification and maintenance therapy. Generally methadone is initiated at 5–20 mg/day with a gradual increase in 5–10 mg increments until an optimal effect is achieved (typical daily target dose 80–120 mg) and maintained over an extended period of time, which may be years to a lifetime, in order to confer protective benefits while optimizing the chances of psychosocial rehabilitation success. Methadone is metabolized by the liver with its main metabolite excreted via both gastrointestinal and renal routes. There is evidence to suggest that compensatory fecal excretion of methadone metabolites occurs in patients with reduced kidney clearance [56]. Accumulation of methadone and its metabolite is, therefore, minimal in patients with CKD. Despite its favorable pharmacokinetic profile for use in the CKD population, it must be cautioned that similar to all opioids, methadone-related deaths can occur due to toxicity, drug–drug interaction or unintentional overdose [59].

Table 6 lists commonly used opioids in order of abuse and dependence potential and analgesic potency compared with oral morphine, along with special considerations for the pre-ESKD and dialysis population.

Special considerations for postoperative pain management after kidney transplant

In the immediate postoperative setting following kidney transplant, analgesia is usually delivered via patient-controlled analgesia (PCA) during the initial 24–48 h. Use of the PCA administrative technique has been shown to improve pain control, reduce opioid-related complications such as sedation and improve patient satisfaction [60]. Hydromorphone may be the agent of choice in this setting, as it has some pharmacokinetic advantages over morphine. The substitution of a keto group for a hydroxyl group at position six of the benzol ring allows for more rapid distribution to the CNS, allowing for faster analgesic dose titration, and greatly reduces glucuronide metabolite formation that requires renal clearance. In the setting of fluctuating renal function, this may help reduce metabolite accumulation and the associated adverse events [61].

Recovery after kidney transplant may be delayed with postoperative ileus, a complication exacerbated by the use of opioids. In addition to the routine management of constipation, including the use of a good bowel regimen, early ambulation and a high-fiber diet, the use of a peripherally acting mu-opioid receptor antagonist may be considered. Due to their quaternary or charged structure, these compounds do not cross the blood–brain barrier to counteract the analgesic properties of opioids in use, but they can reduce the peripheral adverse effect of constipation. Previously approved agents by the US Food and Drug Administration (methylnaltrexone and alvimopan) require parenteral administration, but a recently approved agent, naloxegol, may be administered orally. While it has not been specifically studied in kidney transplant recipients, the use of this agent should be considered in patients who experience opioid-induced constipation. Naloxegol is metabolized via CYP3A4 and is a P-glycoprotein substrate. As such, it has a similar drug–drug interaction profile as the calcineurin inhibitors [62, 63].

Opioid abuse and misuse

Finally, basic guidelines in prescribing opioids must be followed to avoid abuse and misuse. The most important considerations include preferential use of nonopioid over opioid therapy in the treatment of chronic pain, evaluation of risks and benefits prior to opioid prescription, determination and patient discussion of treatment goals, use of the lowest effective dose, avoidance of concurrent opioids and benzodiazepines whenever possible and regular patient follow-up (3-month intervals or more frequently) for the assessment of risks and benefits of continuing opioid use. For patients with opioid use disorder, clinicians should offer or arrange evidence-based therapies, including medication-assisted treatment, behavioral changes and psychosocial support [64].

Conclusions

Similar to the general population, pain is a common problem among patients with pre-ESKD and those requiring RRT. Suboptimal pain control is associated with poor quality of life, depression and possibly long-term survival. Nonetheless, adequate medical pain control remains a challenge due to both drug-induced complications and abuse and dependence potentials. The management of pain is further complicated in the CKD and dialysis population, where drug clearance is altered with kidney impairment and altered electrolyte and fluid derangements. Clinicians must master 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.

Conflict of interest statement

None declared.

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