The Role of Opioids in Pain Management in Elderly Patients with Chronic Kidney Disease: A Review Article

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Abstract

Chronic kidney disease (CKD) is a global public health problem. Pain is one of the most generally experienced symptoms by CKD patients. Pain management is a key clinical activity; nonetheless, insufficient pain management by health professionals keeps it up. Opioids as pain relievers are a class of naturally-derived and synthetic medications. They act through interactions with receptors in peripheral nerves. Numerous pharmacokinetic alterations happen with aging that influence drug disposition, metabolism, and quality of life. Acetaminophen alone, or combined with low-potency opioid dose is regarded as the safest pain-relieving choice for CKD. Morphine and codeine are probably eluded in renal impairment patients and used with excessive carefulness. Tramadol, oxycodone, and hydromorphone can be used by patient monitoring, while methadone, transdermal fentanyl, and buprenorphine seem to be safe to use in older non-dialysis patients with renal impairment. Consistent with the available literature, the main aim of this review was to explore the occurrence of chronic pain and its opioid treatment in CKD patients. According to this review, more and well-made randomized controlled trials are necessary to find appropriate opioid doses and explore the occurrence of side effects.

Keywords: Pain Management, Opioids, Chronic Kidney Disease, Dialysis

1. Context

Chronic kidney disease (CKD) is described as the perseverance of structural and/or functional anomalies of the kidney for three or more months (1). The overall prevalence of CKD is approximately 13.1% in adults, so that 50% of the patients with CKD are older than 70 years (2). More than 26 million people are affected in the United States (US), and its prevalence will increase to 35% in individuals over the age of 70 years in the next 10 years (3). The majority of CKD patients suffer from mild-to-moderate CKD stages I-III (12.7%); however, severe CKD stages IV and V are rare (0.35% and 0.11%, respectively) (2). There has been a constant rise in the number of older patients with CKD leading to end-stage renal disease (ESRD) in need of dialysis (4). ESRD is described by the National Kidney Foundation as the furthermost stage of renal failure stage V (with estimated glomerular filtration rate (eGFR) < 15 mL/min) (5).

In the US, patients older than 65 years comprise 40% of ESRD patients (6). The causes of CKD consist of diabetes, hypertension, renovascular diseases, primary glomerulonephritis, and inherited kidney diseases. Proteinuria, renal hypertension, anemia, and nerve damages are also developed with the progression of CKD (7). Fatigue is observed in 71% of patients, pruritus in 55%, nervousness in 38%, dyspnea in 35%, nausea in 33%, and depression in 27%, all leading to the decreased quality of life (QoL) of patients (8, 9). Pain is among the most commonly described symptoms, predicted to have impacts on more than 58% of CKD patients, of which 49% is moderate to severe in intensity (10, 11). Common types of pain in dialysis patients include musculoskeletal pain (63%) due to osteoarthritis, neuropathic pain, and pain associated with the dialysis procedure, such as arteriovenous (AV) (12). Other causes of pain comprise peripheral vascular disease, renal osteodys-

trophy, inflammatory arthritis, and polycystic kidney disease (13). It is predicted that up to 48% of dialysis patients have dialysis-related headaches (DH) (14). The traditional management of CKD includes the control and treatment of hypertension to decrease the progress of CKD, salt restriction, use of statins, diabetes control, home care, oral sodium bicarbonate, anti-aging, antioxidant, and anti-inflammatory agents, and dialysis (15). Kidney transplantation provides older patients with good longstanding transplant endurance and quality of life; nonetheless, it entails a greater risk of malignancy, infection, and car-diovascular disorder (16).

Opioids are also used for pain management in CKD patients (17). The short-term efficiency of opioid use (≤ 12 weeks) has been recognized among older adults (18). Despite evidence about the advantages of opioids and accessibility of these drugs, some studies have suggested that pain is inefficiently cured in patients on hemodialysis (HD), and side effects may be an obstacle to operative pain management (19). The frequency of analgesic use in ESRD patients is very different; nonetheless, it is estimated at 24%, which less than 15% are prescribed opioids, and even acetaminophen use is low at 6% (20). One of the main obstacles to efficient pain control is opioid addiction (21). Opioids can also increase the risk of falls in elderly patients, which is a principal reason for injuries, hospitalization, and deaths among the elderly (22). Opioid therapy worsens the symptoms, including orthostatic hypotension, impaired cognition, nausea, and poor appetite., fatigue, and constipation (21). General practitioners are now unwilling to recommend chronic opioids to patients with CKD due to severe side effects, including depressive effects on the respiratory and central nervous systems and psychological addiction (23, 24). In 2016, more than 42,000 deaths were attributed to opioid overdose, and 40% of them were attributed to prescribed opioids (25). The World Health Organization (WHO) step 1 - 3 pain relievers are essential to pain management (26). Mild pain must be treated by step 1 analgesics, con-taining acetaminophen (paracetamol (1g qds)) or nonsteroidal anti-inflammatory drugs (NSAIDs) (27). Step 2 applies to moderate pain and includes weak opiates such as tramadol (50 - 100 mg qds) and low-dose opioids such as hydromorphone (1 - 2 mg) or oxycodone (2.5 - 5 mg) (28). Step 3 is used for severe pain, with greater doses of oxycodone or hydromorphone and drugs with long-lasting effects, including fentanyl (25 micrograms as initial dose subcutaneously and "25" patch upwards, transdermal every 72 hours) (29). Consistent with the available literature, the main aim of this review was to examine the

opioid management of chronic pain in CKD patients and related adverse effects.

2. Opioid Use in Chronic Pain Management

Between September 2001 and July 2002, one study of 205 HD patients in Canada assessed the prevalence, strictness, reasons, and management of pain in this population and establish that 50% of the patients described the pain as a symptom. Patients with pain were on hemodialysis therapy longer than patients without pain were (52.2 months vs. 37.7 months) (30). Of these patients, 32% were prescribed with no analgesics, 29.1% ad-ministered non-opioids, 26.2% were provided with weak opioids, and only 9.7% received strong opioids. The efficiency of therapy was described as acceptable by only 6% of the patients, whereas 74.8% reported their treatment as insufficient (30). In 2006, a cohort study was conducted on 45 patients on chronic HD who had pain. Short-form MPQ (SF-MPQ) was used for pain assessment at baseline, and the patients were then managed according to a WHO analgesic ladder for more than four weeks (31). The mean age was 65 ± 12.5 years, and 49% of the patients had diabetic nephropathy as a reason for ESRD. Early pain was rated severe by 76% of the patients. In total, 43 patients described sufficient analgesia at four weeks, and there was a numerically substantial decline in the mean pain score compared to baseline (31). From 1995 to 2004 in 12 countries of diverse regions, a systematic review investigated 10 studies reporting opioid use in > 26,000 patients with ESRD, including 90% dialysis patients (19). The described prevalence of opioid use was in the range of 5% to 36%. The most common recommended opioids in Canada were codeine and oxycodone although, in the US, the propoxyphene-acetaminophen combination was the most common recommended opioid (19). A study by Barrantes et al. (32) in 2013 investigated the results of kidney transplants according to the patients' history of chronic opioid use before transplantation. Among 1,064 adult kidney transplant patients, 42.5% described the existence of numerous body pains. This study documented that a history of previous chronic opioid use was individually related to a higher risk of death (adjusted hazard ratio (aHR) = 1.65; 95% CI, 1.04 - 2.60). Therefore, a history of chronic opioid use before transplantation seems to be accompanied by enhanced mortality risk (32). A Swiss survey of 123 patients aged 36 - 90 years on dialysis for 3.5 years found that 68 patients had chronic pain, and the pain intensity in two-thirds of the patients was higher than five on a Visual Analog scale

(VAS) (33). Besides, 35 patients recognized musculoskeletal pain as the most troubling pain (33). In these patients, musculoskeletal pain was a prominent reason for sleep disturbances including problems in awakening, nightmares, interrupted sleep, sleep apnea syndrome, and restless leg syndrome, and it was cured with opioids in only a small number of patients (33). Opioids were suggested for only 21% of these patients; and non-opioid analgesics (principally NSAIDs) were in use by 80% of the patients (34). A study used the data on baseline visits from 308 patients with CKD. The chronic pain severity was evaluated by the Wong-Baker FACES Pain Rating scale (35). In this study, 60.7% of the patients stated chronic pain, and 5.8% with no chronic pain were on NSAIDs (36). Mild and severe chronic pains were related to analgesics with a drug-related problem (DRP), with odds ratios (OR) of 3.04 and 5.46, respectively (35). Olivo et al. (37) examined opioid management approaches in 191 HD patients; 27% of them were longstanding opioid users (more than 90 days). The most usually recommended opioids were paracetamol-comprising opioid drugs (98%), principally, hydrocodone-paracetamol (90%), and oxycodone-paracetamol (42%) (37). The safest opioids, fentanyl, and methadone were recommended in 6% and 4% of the cases, respectively (37). A recent systematic review of 52 studies with an overall of 6,917 patients described a prevalence of acute (82%) and chronic (92%) pain in HD patients (38). A small number of studies investigated the features of pain, but the prevalence of severe pain was described to be up to 76% (38). One cohort study during 2006 - 2010 evaluated opioid treatment and the relationship of opioid recommendation and dose with patient outcomes (39). In the study period, 64% of the dialysis patients received at least one opioid recommendation, 41% of the patients had a short-term prescription, and 23% received a chronic opioid recommendation ($\geq$ 90-day supply) (39). In the 2010 cohort, patients with temporary (1 - 89 days) and chronic opioid treatments showed more hospitalization, dialysis discontinuation, and mortality than did patients without an opioid prescription (39). In a study, among 1,256 opioid users who died of an opioid-associated reason and 4,619 controls who also used opioids, the first experience was simultaneous gabapentin use in 120 days before the index date; a sensitivity analysis studied the effect of simultaneous (NSAID) use in previous 120 days (40). The simultaneous use of opioids and gabapentin was correlated with a considerably enhanced odds of opioid-associated death (approximately 60%) compared to opioid prescription alone (40). There was no substantial link between the simultaneous use of opioids and NSAIDs and opioid-

related death (40). Gabapentin is a drug frequently used in combination with opioids, and both of them have revealed to inhibit breathing, which can be lethal (40). The simultaneous opioid use raises the amount of gabapentin absorbed, and it was accompanied by a 49% higher risk of becoming extinct from an opioid overdose (40). One cohort study assessed connotation during opioid use and time to hospitalization or first visit because of falls, fracture, and altered mental status among 140,899 adults on hemodialysis (41). Opioids were related to adverse results in patients on HD; 64% received opioids; besides, fall (7646 events), fracture (4151 events), and episode of altered mental status (15,658 events) happened (41). The prevalence rates of opioid prescriptions (containing methadone, tramadol, and buprenorphine), NSAIDs, and across stages of kidney function in primary care patients were assessed by the Geisinger Health System between 2011 and 2016 and Johns Hopkins Medicine between 2013 and 2016 (42). The NSAID use was less in patients with minor eGFR in both cohorts (42). The proportion of patients who used opioids of methadone and buprenorphine was 0.9% at Geisinger and 0.3% at Johns Hopkins Medicine (42). These results emphasize higher awareness. regarding opioid and gabapentinoid use in CKD patients and the need for further studies to conclude the safety of such drugs in clinical trials (42). Some studies carefully chosen for information on opioids use in chronic pain management are summarized in Table 1.

3. Opioids

The 2018 United States Renal Data System reported that 43.8% of CKD patients were prescribed at least one opioid in 2016 (46). Morphine is used for treating cancer pain. The pain-relieving effect of morphine peaks 90 min after oral administration and 30 min after the intravenous (IV) administration (47). The plasma half-life is two to three hours after an IV bolus (48). Morphine and its metabolites are responsible for a more powerful analgesic effect and accumulate in patients with renal impairment, bringing to bear intense analgesia and sedation and possibly severe neurotoxicity (49). In a case-controlled study, after a single dose of 30 mg of morphine, morphine-6-glucuronide (M6G) was accumulated in patients with renal impairment (50). At 24 h, in the CSF, the concentration of the accumulated metabolite was at least 15 times greater than in those patients with normal renal function (51). These results show that morphine should be avoided in older CKD patients. Codeine is a methyl derivative of morphine and

Table 1. Detailed Description of Studies of Opioid Use in Chronic Pain Management

Study (References)	Therapy	Patient Population	Findings
Opioids Use in Chronic Pain Management			
A small study at a tertiary referral medical center in Los Angeles, California (11)	-	130 patients with CKD	Sources of pain: musculoskeletal (62%); gastrointestinal (13%); genitourinary (10%); hematological/oncological (10%); central and peripheral nervous system (9%); cardiovascular (7%)
A prospective cohort study at the University of Alberta (30)	26.2% were on weak opioids (codeine, propoxyphene, and oxycodone); 9.7% were on strong opioids (hydromorphone, methadone, fentanyl, and morphine)	205 Canadian hemodialysis patients	Musculoskeletal pain was most common (50.5%); peripheral neuropathy; peripheral vascular disease pain; effectiveness of therapy was 6% in the patients
A cohort study (31)	Treatment based on a WHO analgesic ladder/algorithm; Over 4 weeks	45 patients on chronic hemodialysis	40% nociceptive pain; 31% neuropathic; 29% both; 96% of patients reported adequate analgesia at 4 weeks
A retrospective study (32)	Chronic opioid use before transplantation	1064 adult kidney transplant patients	Increased risk of death
A cross-sectional, observational, multicenter study (33)	21% used opioids; 80% used non-opioid analgesics (mainly NSAIDs)	123 patients with CKD stage 5 on dialysis	Asthenia and fatigue
A cohort study between 2011 and 2013 in the Safe Kidney Care in Baltimore, Maryland (35)	Analgesic prescriptions up to 30 days before visits	308 patients with CKD	Mild chronic pain: analgesics with a DRP, with OR of 3.04; severe chronic pain: analgesics with a DRP, with OR of 5.46
A cohort study from a single center (37)	52 patients were long-term opioid recipients; 78 patients had opioid for fewer than 90 days; 8 patients had only a non-opioid prescription	191 HD patients	Findings of this study may not be generalizable to all HD patients due to the small sample size from one setting
A cohort study of the US Renal Data System (39)	Over 60% of dialysis patients received at least one opioid; 20% had chronic opioid prescription ($\geq$ 90-day supply)	671,281 patients on maintenance dialysis	Most prescribed opioids: hydrocodone (11.7%); oxycodone (5.4%); tramadol (2.5%); propoxyphene (1.4%)
A cohort study in Ontario, Canada, between August 1, 1997, and December 31, 2013 (40)	Simultaneous gabapentin use in 120 days; gabapentin dose as low (< 900 mg daily), moderate (900 to 1,799 mg daily), and high (-1,800 mg daily); concomitant (NSAID) use in the preceding 120 days	1,256 opioid users died of an opioid-related cause; 4,619 controls also used opioids	Co-prescription of opioids and gabapentin was correlated with a considerably increased odds of opioid-related death; no significant association between co-prescription of opioids and NSAIDs and opioid-related death
A cohort study using the US Renal Data System (41)	64% of patients received opioids	140,899 adults receiving hemodialysis	Opioid use was associated with a risk of: Altered mental status; fall; fracture
A cohort study in Geisinger Health System, in Pennsylvania, and Johns Hopkins Medicine, in Maryland (42)	31.8% received at least one opioid prescription in Geisinger; -22.7% received at least one opioid prescription in Johns Hopkins Medicine	In 2016; 181,107 patients in Geisinger; 109,219 patients in Johns Hopkins Medicine	Gabapentin and pregabalin prescriptions were less common in the overall cohort at 9.9% of Geisinger and 6.3% of Johns Hopkins Medicine; NSAID use was similar across the two cohorts and was lower in patients with lower eGFR in both cohorts; -prescription opioids: methadone and buprenorphine were 0.9% at Geisinger and 0.3% at Johns Hopkins Medicine
A prospective observational study between May 1996 and September 2001 (DOPPS) (43)	Dialysis patients: 15% were on an opioid; 1.7% on an opioid with acetaminophen; 1.2% on an opioid with COX-2; -0.6% on an opioid with NSAIDs	3749 dialysis patients	The proportion of patients prescribed any analgesic decreased from 30.2% to 24.3%; narcotic prescriptions decreased from 18.0% to 14.9%; propoxyphene and acetaminophen were most commonly prescribed (47.2%)
A prospective cohort study (44)	Chronic opioid derivative	308 patients on thrice-weekly HD	12.7% with a median age of 74.7 years fell at least once during 8 weeks; 3.9% experienced a fall-related fracture during 12 months; 28% who fell were on an opioid derivative; 9.7% were not on opioids
A prospective cohort study (45)	Opioid; benzodiazepines; + opioid; adrenal cortical; steroids; antidepressants	12,782 HD patients	Opioid pain medications; combination opioid medications

Abbreviations: aHR, adjusted hazard ratio; CI, confidence interval; CKD, chronic kidney disease; DOPPS, dialysis outcomes and practice patterns study; DRP, drug-related problem; ESRD, end-stage renal disease; HD, hemodialysis; HRQOL, health-related quality of life; HR, hazard ratio; HTEMS, high-tone external muscle stimulation; IRR, incidence rate ratio; LHID2000, longitudinal health insurance database 2000; NHRI, National Health Research Institutes; NSAID, nonsteroidal anti-inflammatory drugs; OR, odds ratio; QoL, quality of life; RCT, randomized clinical trial; WHO, World Health Organization.

brings to bear powerful cough-suppressant and modest pain-relieving effects (52). Codeine has a very little plasma protein binding (7%) and needs a dose change in patients with renal failure (52). Codeine is usually recommended in combination with acetaminophen (52). Renal clearance of codeine in patients with moderate to severe renal impairment is considerably reduced, and their accumulation causes sedation, respiratory depression, and hypotension (53). Thus, a cautious dose adjustment is necessary when a renal failure exists. Hydromorphone is a chosen short-acting opioid in ESRD patients. It is five times as effective as morphine when assumed through the oral route, and 8.5 times as powerful as morphine when administered intravenously (54). It has low protein binding (19%) (55). A long-lasting half-life of 39.4 ± 16 hours happens in severe renal impairment as compared to 14.8 ± 11.3 hours in normal renal function (56). Hydromorphone is not considerably accumulated in renal impairment because of the rapid change to its primary metabolite, which is without pain-relieving activity and typical opioid-related adverse events; therefore, this drug is more favorable in safety than is morphine (57). More than 80% of patients with cancer and kidney failure, who experienced side effects mainly with morphine, improved after a change to hydromorphone (58). In a study of 54 patients with kidney diseases (stage 3 - 5), hydromorphone had little neuroexcitatory signs until its metabolite, hydromorphone-3-glucuronide (H3G), accumulated more than the neurotoxic threshold. In another study, side effects happened with a rising dose or duration, including agitation (48%), cognitive dysfunction (39%), myoclonus (20%), and tremor (20%) (59). Oxycodone is a semi-synthetic opioid with parallel clinical efficiency with morphine. It has fewer adverse events, such as nausea, vomiting, and confusion (60). Oxycodone has a higher protein binding ability (46%) than hydromorphone, suggesting that it may be dialyzed (60). Pain relief from oxycodone starts in one hour and persists for 12 hours after administration (60). A case report of controlled-release oxycodone exhibited that after two hours of dialysis, the plasma levels of the drug and derivatives decreased by 32% - 52% (61). Kirvela et al. (62) administered one dose of oxycodone to 10 patients with severe renal impairment. There was a substantial postponement in the clearance of oxycodone, and the removal of metabolites was elongated. Fitzgerald indicated that normal doses of oxycodone used by patients with severe renal impairment can cause CNS toxicity and sedation (63). Broadbent recommends when CrCl is 10 - 50 mL/min, 75% of the normal dose of oxycodone should be used and when CrCl is

< 10 mL/min, 50% of the normal dose of oxycodone could be used, with normal dosing intervals (64). Plasma concentrations of oxycodone and its metabolites reduced within 240 min of dialysis, causing a little enhance in post-dialytic pain intensity (65). Hydrocodone is a recommended opioid in HD patients, predominantly in combination with acetaminophen (66). About 26% of hydrocodone is excreted unchanged or as metabolites in the urine; thus, kidney failure is anticipated to have only an insignificant effect on drug clearance. In a single open-label study, plasma hydrocodone concentrations and mean bio-availability were influenced after a single use of hydrocodone 45 mg in patients with different stages of renal failure; thus, a 50% dose adjustment may be suggested for moderate to severe renal failure (CrCl < 30 mL/min) (67). Tramadol is an unusual pain-relieving compound structurally associated with codeine and morphine. It is suggested that 90% of tramadol is excreted by the kidney after oral administration (68). Dialysis slightly clears (7%) the drug. The occurrence of side effects ranges from 1% to 6% (68). Careful use in dialysis patients entails a decrease in dose and increase in dosing interim, for instance beginning at 50 mg every 12 hours and a maximum dose of 200 mg every day (69). Respiratory depression has been reported in patients with ESRD experiencing HD because of the overdose of tramadol (70). Propoxyphene is structurally associated with methadone and has a pain-relieving effect similar to codeine (71). In renal failure, serum concentrations of propoxyphene will be enhanced, and its accumulation can cause severe and possibly life-threatening side effects such as hypotension, arrhythmias, numerous CNS injuries, and sedation (71). Furthermore, this agent cannot be dialyzed in considerable quantities. Consequently, a suitable dosing adjustment should be considered, and its use should be evaded for pain controlling in elderly patients (72). Methadone is a synthetic opioid, being 5 - 10 folds more effective than morphine and a chosen agent in ESRD patients (73). Methadone exerts a beneficial anti-N-methyl-D-aspartate (NMDA) influence. Consequently, this agent is used for decreasing moderate-to-severe pain and relieving neuropathic pain (73). Methadone has an elongated half-life of 8 to 80 hours in different individuals after recurrent administration; furthermore, the half-life rises with age (74). Methadone is not accumulated in patients with renal impairment, nor is eliminated by HD (75). Meperidine is a synthetic opioid with a half-life of about 3.5 hours; it is metabolized to normeperidine in the liver (76), which is more toxic and durable. Meperidine has been described to cause CNS and respiratory depression, seizures, and psy-

chosis (77). In a study of 48 patients who had meperidine-associated adverse effects, 29% had a renal deficiency. According to the probable neurotoxicity of metabolites of meperidine, the use of a parental agent in patients with ESRD is avoided (77). Buprenorphine is a semisynthetic, extremely lipophilic opioid, and may be a beneficial strong opioid in ESRD (78). Buprenorphine is at least 30 times stronger than morphine (79). One study investigated the disposition of transdermal (TD) buprenorphine and norbuprenorphine in patients with CKD stage IV. There was no rise in the levels of buprenorphine and norbuprenorphine at doses up to 70 lg/h (78). Its properties, including extraordinary protein binding (96%) and great volume of distribution, do not favor elimination in dialysis (80). TD buprenorphine has a greater safety threshold than other opioids; the maximum amount for respiratory depression has been reported when this drug is used in devoid of other CNS depressants (81). Dosing recommendation starts at 5 mg/h transdermally every 7 days (82). Fentanyl is a synthetic drug with highly lipid soluble properties, which is about 80 times more powerful than morphine; it is very common for transdermal administration (83). It can be administered intravenously for acute titration. It is well-tolerated by ESRD patients (84). Its extraordinary protein binding (80%) and little water solubility cause to not be cleared well by dialysis (85). The stable state plasma fentanyl concentrations reach after almost 12 hours and are sustained for nearly 72 hours (86). There is a decline in the clearance of fentanyl in patients with severe renal impairment who are assumed a single bolus dose of the drug. This may cause respiratory depression (87). Han et al. (88) reported two patients experiencing HD receiving transdermal fentanyl at greater doses (up to 500 μg/h) for longstanding treatment (up to 3 years) without suffering substantial side effects. TD buprenorphine was as operative, safe, and acceptable as fentanyl (89). Alfentanil is a fentanyl derivative synthetic molecule. Alfentanil is a very short-acting opioid with a pain-relieving effect, which persists between 5 and 10 min (90). Only a small volume of injection is essential, when a patient needs high pain-relieving doses, constant subcutaneous infusion could be a benefit over fentanyl (91). Tapentadol is an unusual strong opioid. It has a 50-fold lower affinity than morphine (92). In patients with CrCl < 30 mL/min, the plasma levels of tapentadol-O-glucuronide raise up to 6.1 folds. Thus, because of limited evidence about its use in severe kidney deficiency, tapentadol is yet not suggested in patients with ESRD (93).

Daily offered mean doses of opioids include morphine (50 mg), codeine (93.3 mg), hydromorphone (33.6 mg), oxy-codone (11.9 mg), propoxyphene (238 mg), methadone (21.7 mg), meperidine (100 mg), and fentanyl (37.5 μg/h) (30, 92). Metabolism and clinical consideration of opioids use in patients with renal failure are summarized in Table 2.

The kidney plays a major role in pharmacokinetics and pharmacodynamics of drugs; consequently, it recommends carefulness with opioids in the treatment of patients with CKD. (94). A decline in renal function in old patients influences the removal of drugs such as opioids, needing dose regulation and careful checking for side effects. Generally, lower doses must be used when starting narcotic therapy in the elderly (95). Acetaminophen was the most usually used pain-relieving (34% of the entire CKD cohort), although the higher doses of acetaminophen used chronically have been accompanied by analgesic nephropathy (96). To avoid toxicity, it is proposed to not exceed 3 g/day of acetaminophen (97). For moderate pain, tramadol is preferred, given its low risk of direct nephrotoxicity (98). The use of fentanyl, alfentanil, and hydromorphone is relatively safe in dialysis patients, but doses should be adjusted to minimize the risk of respiratory depression (97). However, adjuvant medications are useful for improving pain scores, decreasing opioid doses, and treating neuropathic components of pain in dialysis patients (99). The accumulation of opioid metabolites can lead to respiratory and central nervous system depression, hypotension, and seizures in patients with advanced CKD. For severe pain in CKD patients, methadone and fentanyl can be used (100). If a patient's condition worsens, particularly near the end of life, alternatives are necessary, such as subcutaneous fentanyl. With the minimal variations in kinetics in kidney impairment, hydromorphone, fentanyl, methadone, and buprenorphine may be possibly beneficial opioids (101).

Pain is the most common symptom experienced by renal patients (102). Pain controlling in renal patients is challenging, as the space between pain relief and toxicity is minor (103, 104). The most usually recommended opioids in patients with ESRD are hydrocodone and oxycodone, used in 51% and 16% of total treatments, respectively (105, 106). Basic skills for pain management include the acknowledgment of the type of pain syndromes (nociceptive, neuropathic, and mixed pain) and suitable history-taking skills (107). Neuropathic pain is often poorly reactive to opioids, needing doses that are related to intolerable toxicity (108). A meta-analysis described that 72% of patients prescribed opioids such as morphine, hydromorphone, and oxycodone also had risk factors for drug-drug interactions (109). As a consequence of these risks,

Table 2. Metabolism and Clinical Consideration of Opioid Use in Patients Suffering From Kidney Failure

Opioid	Metabolism	Recommended Dosing	T 1/2 Normal, h	T 1/2 Dialysis (ESRD), h	Clinical Considerations	Dosage Consideration Based on Renal Dysfunction and Dialysis
Morphine (47-49)	Morphine and its metabolites (M6G) have moderate water solubility and can be dialyzed	_ᵃ	2 - 3	Unchanged	Nausea; vomiting; myoclonus; seizures; sedation; respiratory depression	Avoided in patients with severe renal failure of eGFR < 30 mL/min (51)
Codeine (52, 53)	Metabolized via CYP2D6 to: C6G, 81%; morphine, 10%; normorphine, 2%; M6G; M3G	15 - 60 mg every 4 h	2.5 - 4	13 - 18.9	Sedation; respiratory depression; hypotension	Is not recommended in patients undergoing HD because of the accumulation of toxic metabolites (52)
Hydromorphone (54, 56, 57)	Metabolized to: hydromorphone-3-glucuronide; dihydroisomorphine-6-glucoside	1 - 2 mg every 3 - 4 h	2 - 5	3.2 on dialysis; 5.9 non-dialysis days	Tremor; myoclonus; agitation; cognitive dysfunction	A growing AUC with declining renal function at a ratio of 1:2:4 for patients with normal (CrCl > 80 ml/minute); moderate (CrCl 40 - 60 mL/minute); severe (< 30 mL/minute) renal dysfunction (55)
Oxycodone (60, 62-64)	Metabolized to active noroxycodone; oxymorphone; glucuronides	2.5 - 5 mg every 4 - 6 h	2 - 4	3 - 5	Nausea; confusion; hallucinations; CNS toxicity; respiratory depression	Avoided in patients with eGFR less than 60 mL/min; increased the half-life, and metabolites in patients with renal dysfunction (CrCl < 60 ml/minute) (61)
Tramadol (69, 70)	Active metabolites formed; by CYP2D6: M1; O-desmethyl tramadol	25 - 50 mg every 6 h; Age > 75 y: 300 mg/day	6	11	Headaches; dizziness; sweating; dry mouth; respiratory depression	Overdose through an IV dose of 400 mg in a patient undergoing HD (70)
Methadone (73, 75)	Converted to: 2-ethylidene-1; 5-dimethyl-3; 3-diphenylpyrrolidene; 2-ethyl-5-methyl-; 3,3-diphenylpyraline	_ᵃ	15 - 60	13 - 47	Risk of hypoxemia; No important adverse effects	In ESRD patients, close monitoring is proposed with the beginning doses 50% - 75% of normal post-dialysis (75)
Buprenorphine (78, 79, 81)	Metabolized to: norbuprenorphine; -N-deal kylbuprenorphine	5 μg/h patch every 7 days	30	Unchanged	Sedation; nausea; vomiting; dizziness; headaches	TD buprenorphine has higher safety (81)
Fentanyl (85-87)	Primarily oxidized to; norfentanyl	12 μg/h patch every 72 h	2 -7	Possibly increased	Respiratory depression	TD fentanyl has higher safety (88, 89)

Abbreviations: AUC, area under the curve; CrCl, creatinine clearance; C6G, codeine-6-glucuronide; CKD, chronic kidney disease; CYP2D6, cytochrome P450 2D6 enzyme; GFR, glomerular filtration rate; HD, hemodialysis; IV, intravenous; M3G, morphine-3-glucuronide; M6G, morphine-6-glucuronide; TD, transdermal.
ᵃConsult with specialists for the proper dose.

it is significant to accentuate that opioids should be prescribed only to older, non-dialysis chronic kidney disease patients when they are absolutely indicated (110). Furthermore, considering the increasing number of elderly people (over 65 years of age) often afflicted with numerous comorbidities and chronic pain syndromes demanding efficient pain-relieving treatments, the safe and impressive administration of opioids in damaged renal function is the most important issue (111). Also, the physician must monitor the patient's glomerular filtration rate and creatinine to determine the appropriate dosing (112).

4. Conclusions

Pain in patients with CKD should be known as a significant health problem, and the nephrology community should support pain treatment in HD patients as a clinical and research importance to improve the patients' quality of life and pain-related debility. It is probable, according to information on opioid pharmacokinetics, to propose carefulness with particular opioids in the pain management of patients with CKD. Modifications in the dosing or choice of drugs are essential in CKD because of complications due to the decreased removal of drugs or their metabolites. One of the restrictions of this study is that we were attentive only to opioid management and ignored non-opioid studies in patients with CKD. Unfortunately, clinical studies are lacking concerning maintenance opioids' effectiveness and safety, particularly as they are associated with chronic pain management. More randomized controlled trials are critically required evaluating the effectiveness of opioids and other drugs for the proper treatment of chronic pain among patients with CKD.

Footnotes

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