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REVIEW ARTICLE

Assessing and Treating Chronic Pain in Patients with End-Stage Renal Disease

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Abstract

Pain is one of the most common symptoms among patients with end-stage renal disease (ESRD), and is often under recognized and not adequately managed in hemodialysis (HD) patients. Barriers to adequate pain management include poor awareness of the problem, insufficient medical education, fears of possible drug-related side effects, and common misconceptions about the inevitability of pain in elderly and HD patients. Caregivers working in HD should be aware of the possible consequences of inadequate pain assessment and management. Common pain syndromes in HD patients include musculoskeletal diseases and metabolic neuropathies, associated with typical intradialytic pain. Evaluating the etiology, nature, and intensity of pain is crucial for choosing the correct analgesic. A mechanism-based approach to pain management may result in a better outcome. Pharmacokinetic considerations on clearance alterations and possible toxicity in patients with ESRD should drive the right analgesic prescription. Comorbidities and polymedications may increase the risk of drug–drug interactions, therefore drug metabolism should be taken into account when selecting analgesic drugs. Automedication is common among HD patients but should be avoided to reduce the risk of hazardous drug administration. Further research is warranted to define the efficacy and safety of analgesic drugs and techniques in the context of patients with ESRD as generalizing information from studies conducted in the general population could be inappropriate and potentially dangerous. A multidisciplinary approach is recommended for the management of complex pain syndromes in frail patients, such as those suffering from ESRD.

Key Points

Barriers to adequate pain management in ESRD involve patients and caregivers, i.e. inadequate education, fears or unawareness of side effects, and common misconceptions.

Managing chronic pain requires a clear understanding of the pathophysiological mechanisms leading to the painful syndrome.

Accurate knowledge of the pharmacokinetics of analgesic drugs is required to avoid potentially harmful side effects.

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1 Introduction

Chronic kidney disease (CKD) is defined as the persistence of structural and/or functional abnormalities of the kidney for 3 or more months. The prevalence of CKD has increased in the last decades, becoming a worldwide health burden with a high economic cost. According to the estimated glomerular filtration rate (eGFR), five stages of ESRD are recognized, with end-stage renal disease (ESRD) being the last (stage 5, eGFR < 15), with a prevalence of 0.1% [1].

Pain is one of the most common symptoms among patients with ESRD; up to 50–60% of hemodialysis (HD) patients experience pain, which is often severe and not adequately managed [2]. Pain is often associated with other factors that significantly affect quality of life (QoL), such as depression and altered sleep patterns. Patients undergoing HD may also experience nausea, dry mouth, poor appetite, anxiety, drowsiness, itch, breathlessness, and fatigue [3]. Moreover, pain may impair dialysis adequacy, rendering patients unable to endure full sessions and increasing the likeliness of withdrawal from dialysis [4].

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2 Chronic Pain in End-Stage Renal Disease (ESRD)

Pain in HD patients is a very common problem that is frequently misunderstood and underestimated. In 2009, Calls et al. stated that 77% of the studied HD patients suffered from chronic pain and 92% of these experienced pain during dialysis sessions [5]. Davison found a 50% prevalence of chronic pain among HD patients, particularly in those who underwent long-term dialysis treatment [2]. In a scoping review published in 2014, Davison et al. analyzed 55 publications from 1992 to 2009, for a total of over 7500 patients with CKD. Most of the data came from HD patients, showing that 58% of the evaluated patients experienced pain and 49% reported pain as moderate to severe. The main reason for chronic pain was musculoskeletal diseases, but neuropathic pain and mixed syndromes were also common [6]. A recent systematic review, including 52 studies for a total of approximately 7000 patients, reported a prevalence of acute and chronic pain in HD patients of up to 82% and 92%, respectively. Few studies analyzed the characteristics of pain, but the prevalence of severe pain was reported to be up to 76% [7].

From these findings the high prevalence of pain in HD patients is evident, but analysis of the reviews also showed the considerable gaps and limitations in the pharmacological approach to pain in these patients. In fact, very few studies evaluating the use of analgesics in HD patients are available.

In a recent systematic review, Brkovic et al. analyzed the risk factors associated with pain in HD patients; 67 studies for a total of 7818 patients were included. The results were inconsistent between studies. General risk factors were identified, such as age, sex, body mass index, race/ethnicity, marital status, duration of HD treatment, and comorbidities [8]. Biochemical parameters, such as hyperuricemia and calcium x phosphate product levels, significantly correlated with chronic musculoskeletal pain in CKD patients [9].

The role of chronic pain in the perception of health-related QoL (HRQoL) in HD patients also seems to be underestimated. The number and severity of physical and mental symptoms reported by HD patients appear to be similar to those reported by palliative care patients, and these symptoms are responsible for the worsening of QoL in dialysis patients [10]. Among the major psychic symptoms present in patients with CKD, depression has been strongly correlated with worsening of QoL, with a consequent reduction in the gratifications deriving from a satisfactory work, social, and family life. Depression occurs in approximately 18% of HD patients, which is higher than that in the general population, however the depressive symptoms do not seem to correlate with the poor adherence to dialysis therapy and/or the mortality of HD patients [11]. Depression is also a common comorbidity of chronic pain in the general population, therefore HD patients suffering from chronic pain are more prone to this mood disturbance. The relationship between emotional sphere and pain is rather complex and appears as a self-feeding vicious circle. Chronic pain and depression often coexist, with a rate of comorbidity ranging between 30 and 70%; therefore, it is difficult to understand which of the two aspects is the head of the problem. It is true in fact that chronic pain can lead to a reduction in mood, due either directly to the negative sensation that the patient experiences or to the reduction of daily and social activities that were previously performed, but it is also true that depression by itself can worsen the perception of painful symptoms and lower the individual pain threshold. Indeed, pain and depression share the same monoaminergic pathway of noradrenaline and serotonin, which ensures a role for antidepressants in chronic pain management [12].

The concept of 'total pain' emphasizes the complex nature of chronic pain, which results from the combination of four different variables: physical (due to nociception, comorbidities, and treatments), psychological (anxiety and depression), social (loss of work, financial worries, loss of social status), and spiritual (anger, loss of faith, search for the meaning of life). An adequate approach to HD patients with chronic pain cannot preclude the biopsychosocial model of pain. Pharmacological treatments are important, but they should be part of a more comprehensive pain management plan, requiring a multidisciplinary approach (pain therapists, nephrologists, psychologists, and physiotherapists). Considering pain relief as the unique goal of pain treatment is wrong. The targets of adequate pain management should be normal daily activities and improvement in QoL, as well as patient satisfaction.

2.1 Etiology of Pain in ESRD

Understanding the etiology of pain in HD patients is crucial for improving pain management and choosing the right treatment. A broad variety of conditions and different pathophysiological mechanisms are involved in pain manifestations in ESRD. The main causes of chronic pain are related to comorbidities, primary renal disease, and CKD complications [10].

The most relevant comorbidities leading to chronic pain in HD patients are:

- osteoarthritis,
- osteoporosis,
- cancer,

- peripheral neuropathies, such as painful diabetic peripheral neuropathy (PDPN),
- peripheral vasculopathies,
- ischemic heart disease.

Pain may result from primary kidney disease:

- autosomic dominant polycystic kidney disease (ADPKD),
- urinary tract infections,
- vasculitis,
- diabetic nephropathy.

Among the complications of ESRD causing chronic pain are soft tissue calcification, calciphylaxis, osteomalacia, fractures, hyperuricemia and gout, and amyloidosis.

Chronic pain should be distinguished from intradialytic pain, which is associated with the HD procedure and characterized by well-defined symptoms. Causes of intradialytic pain are:

- ischemic limb, following the packaging of the vascular access, for a reduction or inversion of the flow from the distal segment of the artery towards the fistula, due to the reduced hemodynamic resistance created by the fistula itself,
- pain in the puncture of vascular access,
- infections caused by the central venous catheter,
- exacerbation of arthritic pain due to immobility during the dialysis session,
- itching,
- cramps,
- headache.

In clinical practice, the etiology of chronic pain in HD patients can be divided in renal-specific pain, musculoskeletal pain, neuropathic pain, and ischemic pain, as reported in Table 1.

Table 1 Most common causes of pain in end-stage renal disease Modified according to Douglas [3]

Chronic pain	
Renal-specific pain	Polycystic kidneys Amyloid Calciphylaxis
Musculoskeletal pain	Arthritis and joint pain Osteoporosis Restless leg syndrome Muscle spasms and cramps Renal osteodystrophy Osteomyelitis
Neuropathic pain	Painful diabetic peripheral neuropathy Carpal tunnel syndrome
Ischemic pain	Peripheral vascular disease Vasculitis
Intradialytic pain	
Dialysis-specific pain	Steal syndrome Abdominal pain Fistula problems Headache

2.2 Clinical Presentation of Chronic Pain in ESRD

The International Association for the Study of Pain (IASP) has defined pain as "an unpleasant sensory and emotional experience, associated with an actual or potential harm to the body". In patients with ESRD, pain may be multifactorial.

Chronic pain is classified as nociceptive, neuropathic, and mixed pain. By definition, *nociceptive* is pain that arises from actual or threatened damage to non-neural tissue and is due to the activation of nociceptors, while *neuropathic* is a clinical description that requires a demonstrable lesion or a disease that affects the somatosensory nervous system. In many chronic conditions, such as low back pain, osteoarthritis, and cancer pain, patients may present a mixed syndrome, where both elements are recognized [13, 14]. The persistence of the nociceptive stimulus leads to a number of functional and structural modifications of the central nervous system, known as central sensitization. The 'neuroplasticity' observed in the transition from acute to chronic pain may result in sensitization (i.e. increased receptor fields) or desensitization (i.e. neuronal shrinking). Many chronic pain conditions are characterized by central sensitization, widespread pain, and altered descending pain modulation [15]. The IASP has recently introduced a new definition of *nociplastic* pain, referring to all conditions that arise from altered nociception, without clear evidence of actual or threatened tissue damage or lesion, or disease of the somatosensory nervous system.

Patients with ESRD may suffer from nociceptive (vascular access pain, ischemic pain), neuropathic (painful diabetic and uremic neuropathies, carpal tunnel syndrome), or mixed syndromes (low back pain, osteoarthritis). Recognizing the mechanism of chronic pain is essential in the choice of analgesic treatment [16]. Pain intensity is only one of the criteria for choosing an analgesic therapy. Evaluating pain quality in subjects with ESRD is essential for the correct approach to the different pain syndromes that may affect this group of patients. Pain management requires a mechanism-based approach to pain.

2.2.1 Renal-Specific Pain

Pain occurs in 60% of patients with ADPKD and is characterized by abdominal, back, and flank distribution. Episodes of acute pain are related to infected cysts, rupture of cysts, and renal colic. In ADPKD, chronic pain may be due to cyst enlargement that stretches the kidney and compresses

on the surrounding structures, causing a dull pain. Differential diagnosis with other gastrointestinal pathologies or musculoskeletal diseases can be challenging in patients with ADPKD [17].

Dialysis-related amyloidosis (DRA) is a complication of long-term dialysis. Deposition of β2-amyloid fibrils in periarticular and articular spaces cause typical manifestations, i.e. carpal tunnel syndrome, shoulder pain, and destructive arthropathy [18]. Despite the same pathophysiological mechanism of disease (amyloidosis), these conditions differ in terms of type of chronic pain and the required treatment. Carpal tunnel syndrome is a typical neuropathic pain condition, characterized by numbness and tingling in the hand and arm due to the entrapment of the median nerve, caused by the narrowing of the carpal canal on the palmar side of the wrist. Conversely, shoulder pain, caused by scapulahumeral periarthritis, is a result of degenerative disease and is mainly nociceptive. Adhesive capsulitis, also known as frozen shoulder, is characterized by stiffness and severe pain. The recent use of high-flux membranes and ultrapure, acetate-free dialysates significantly reduced inflammation of the β2-amyloid accumulation, leading to a decrease in the incidence of DRA.

Calciphylaxis is the result of altered calcium and phosphate metabolism, which causes arteriolar calcifications and vascular ischemia. Ischemic skin lesions and necrosis cause severe, excruciating pain, which may be particularly difficult to manage [19]. Spinal cord stimulation has been shown to be effective in improving pain severity and quality of sleep in patients with critical limb ischemic disease [20], however no data are available in patients with ESRD.

2.2.2 Musculoskeletal Pain

Musculoskeletal disease is the leading cause of pain in the general population and in patients with ESRD. As with the general population, aging, obesity, female sex, and the presence of comorbidities are risk factors for musculoskeletal pain. Muscle cramps affect 33–85% of HD patients and may contribute to early discontinuation of dialysis sessions. Cramps may be caused by hypotension, volume contraction, tissue hypoxia, and carnitine deficiency [21].

Restless leg syndrome (RLS) is a sleep-related, sensorimotor, neurological disorder characterized by sore sensations in the legs and accompanied by an urge to move the legs. The prevalence rate among HD patients is approximately 20–30%, compared with 5–10% in the general population [22]. One of the reasons for the observed difference in patients with ESRD is the use of drugs that increase the risk, such as antidepressants, neuroleptics, antihistamines, and medications with antiemesis functions with significant dopamine blockade [23].

2.2.3 Neuropathic Pain

Diabetes, the leading cause of ESRD in the US, can lead to painful neuropathies and ischemic ulcers, affecting over 50% of patients with long-term metabolic disorders. Moreover, peripheral uremic neuropathy is present in > 90% of severe CKD patients. These polyneuropathies share similar clinical features; they are usually symmetrical and progressive, and start in the lower limb nerves. They lead to sensory symptoms and motor involvement in the late stages only. Neurophysiological studies showed a critical role of altered Na^+ conductances and Na^+/K^+ pump dysfunction in PDPN and axonal dysfunction in uremic neuropathy [24]. Peripheral neuropathies, together with diabetes, peripheral artery disease, and coronary artery disease, increase the risk of foot ulceration and lower extremity amputation in HD patients [25].

2.2.4 Ischemic Pain

Ischemic pain is common in HD patients and is related to peripheral vascular disease and vasculitis. It is particularly difficult to manage with traditional analgesics. Ischemic pain may also be unrelated to arterial occlusion, but is caused by spontaneous necrosis of skeletal muscle in diabetic patients in ESRD. Diabetic muscle infarction usually involves proximal limb musculature, with typical clinical features of muscle swelling and severe pain [26].

2.2.5 Intradialytic Pain

Several differences appear between intradialytic and chronic pain. Intradialytic pain may be related to the vascular access, and includes cannulation discomfort, steal syndrome, and central vein stenosis. Pain is more common and severe if the arteriovenous fistula (AVF) is more recent (less than 1 year) and is brachiobasilic [27]. Headache is a common symptom during dialysis sessions, affecting approximately 50% of HD patients. Dialysis-related headache develops during at least half of each HD session and resolves within 72 h. The causative factors are still unclear; ion alterations (calcium and magnesium) have been involved [28].

2.2.6 Pain in Patients Undergoing Hemodialysis and Peritoneal Dialysis

The most common complication of peritoneal dialysis (PD) is peritonitis, responsible for severe acute pain and significant morbidity, including death. Antimicrobial agents, PD catheter removal, and change to HD are recommended [29].

Few studies have investigated the differences in chronic pain syndromes between patients undergoing HD and PD. No differences were observed in the frequency of upper

extremity musculoskeletal complications in dialysis patients undergoing HD or PD; however, in both groups osteoporosis and supraspinatus tendinitis were most common [30]. Similarly, carpal tunnel syndrome occurs with similar incidence in PD and HD patients as the pathogenesis is not affected by the dialytic modality, but is a metabolic complication of ESRD [31]. No studies are available that have investigated the incidence of PDPN among HD and PD patients.

According to Stojimirovic et al., the incidence of primary headache among patients with predialysis headache is significantly higher in HD patients. Similarly, headache during HD is more common, which is associated with more remarkable hemodynamic variations [32]. In the same way (in regard to gastrointestinal symptoms), HD is more often associated with abdominal pain, together with diarrhea and constipation, compared with PD [33].

In general, PD is associated with better patient satisfaction and less impact on general QoL compared with HD, however modality selection of the type of dialysis for treating ESRD is influenced by multiple specific factors [34].

2.3 Pain Assessment in ESRD

Chronic pain assessment includes several aspects, such as pain severity, pain quality (nociceptive, neuropathic, nociplastic), eliciting and attenuating factors, impact of pain on daily activities, pain interference with mood and sleep, and effects of pain on QoL.

No instruments have been specifically designed for pain assessment in HD patients, however several approaches can be used, including one-dimensional and multidimensional scales. One-dimensional scales are instruments for pain-intensity assessment, while multidimensional scales reflect the biopsycosocial model of chronic pain [35].

The most commonly used one-dimensional scales for pain evaluation are the 11-point numeric rating scale (NRS), where 0 indicates no pain and 10 is the worst imaginable pain, and the 10 cm (100 mm) continuous visual analog scale (VAS), anchored by the two verbal descriptors for each extreme ('no pain' and 'pain as bad as it could be'). The 5-point verbal rating scale (VRS) may be easier to understand for some patients, particularly the elderly—adjectives are used to describe different levels of pain (no pain, mild, moderate, severe, extreme) [36].

The McGill Pain Questionnaire (MPQ) and the Brief Pain Inventory (BPI) are the most common multidimensional scales. The MPQ is the most extensive instrument to evaluate pain affection, using three major classes of word descriptors—sensory, affective, and evaluative. It consists of three major measures (the pain-rating index, the number of words chosen in five sets to describe the pain affect, and the actual pain intensity based on a 1–5 intensity scale), and evaluates quantitative and qualitative aspects of pain, such as location, grade, temporal characteristics, and intensity [37]. The BPI, initially developed for cancer patients, uses an 11-point NRS for pain intensity, requests the patient to draw the site(s) of pain on a body diagram, and uses an 11-point NRS for the interference of pain in seven domains, including general activity, mood, walking ability, work, relations with other people, sleep, and enjoyment of life [38].

Calls et al. evaluated 27 patients undergoing HD using the VAS, pain management index (PMI), and the MPQ. All these scales were useful for pain assessment, although not specifically designed for the evaluative needs of HD patients. According to this study, HD patients experienced everyday mild to moderate pain, particularly during the day and for a prolonged period. Pain significantly affected walking activity, daily tasks, and mood [5].

Specific scales have been validated for assessing neuropathic pain, such as the Leeds Assessment of Neuropathic Symptoms and Signs (LANSS) pain scale, Douleur Neuropathique en 4 questions (DN4), PainDETECT, and Neuropathic Pain Score (NPS).

The LANSS was the first scale to be introduced for neuropathic pain and consists of a pain questionnaire with five sensory items and two clinical examination findings (allodynia and altered pinprick threshold). It has a sensitivity and specificity ranging from 82 to 91% and 80 to 94%, respectively [39]. The DN4 is the easiest-to-use neuropathic pain scale, consisting of two self-administered questions and two examination questions, for a total of 10 answers. Scores higher than 3 are indicative of neuropathic pain. A sensitivity of 83% and specificity of 90% have been reported [40]. Pain DETECT has recently been introduced to identify neuropathic pain in chronic low back pain, and to screen patients for positive, uncertain, and negative neuropathic pain, with a sensitivity of 85% and specificity of 80% [41]. NPS uses 11 descriptors for assessing patients with neuropathic pain and is the only tool currently validated for central neuropathic pain [42].

Most studies evaluated HD patients by only considering pain intensity and its causes. The characteristics of pain were reported in only a few studies. However, HD patients are likely to have neuropathic pain syndromes, particularly PDPN, or chronic pain with a neuropathic pain component arising from musculoskeletal diseases. Therefore, using a specific neuropathic pain scale in HD patients may be very useful for orienting therapy and using a mechanism-based approach to pain management [14]. DN4 has been used for evaluating neuropathic pain in a small cohort of HD patients. Overall, 22.8% of chronic pain patients had a DN4 $\geq$ 4. The presence of a neuropathic pain component was weakly correlated with worst pain intensity (R^2 0.23). Diabetic nephropathy was the leading cause of ESRD, with 75.6% of patients suffering from chronic pain [43].

Chronic pain affects different areas, with great impact on QoL, particularly mood, psychological aspects, and mental status in general; anxiety and depression are common comorbidities in HD patients.

The Hospital Anxiety and Depression Scale (HADS) is a widely used scale that assesses the risk of anxiety and depression in a hospital or community setting. Preljevic et al. evaluated 109 HD patients for anxiety and depression and showed that HADS is a reliable screening tool in these patients, similar to the Beck Depression Inventory (BDI) and the Cognitive Depression Index (CDI) [44]. Weisbord et al. studied the association of depressive symptoms and pain in 286 HD patients by using the self-administered Patient Health Questionnaire-9 (PHQ-9) [45]. According to this study, 25.5% of HD patients reported moderate-to-severe depressive symptoms on at least one assessment and 9% on three-quarters of their assessments [11].

QoL measurement is important to assess the global impact of a condition on the patient's life and the effect of treatments. Patients with chronic pain undergoing HD are more likely to have depressive symptoms and lower QoL than those without pain [46]. The 36-item Short-Form 36 Health Survey Questionnaire (SF-36) is commonly used for evaluating QoL, even in HD patients—the lower the score, the more disability. The eight domains the SF-36 measures are vitality, physical functioning, bodily pain, general health perception, physical role functioning, emotional role functioning, social role functioning, and mental health. Furthermore, two summary measures of the SF-36 are physical and mental health status.

The European Quality of Life Instrument (EQ-5D) is a standardized instrument developed by the EuroQol Group as a measure of HRQoL. It measures five domains (mobility, self-care, usual activity, pain, and mood) against a 5-point descriptor scale of symptom/impact intensity. The EQ-5D has been used for identifying factors affecting QoL in HD patients, showing that social conditions, such as marriage, employment, and educational level, may affect QoL. Conversely, a negative association has been shown between QoL in HD patients and age, total number of chronic comorbidities, and total number of chronic medications [47, 48].

3 Current Unmet Needs in Chronic Pain Management in ESRD

Chronic pain is common in patients with CKD and ESRD, however it continues to be underrecognized and often undermanaged. Uncontrolled pain leads to reduced patient mobility, impaired QoL, increased healthcare resource utilization, and longer hospital stay. Inadequate pain management may lead HD patients to consider withdrawing from dialysis or prematurely stopping dialysis sessions [21].

Reasons for inadequate management include inappropriate assessment, fears about analgesic-related side effects, and misconceptions. Adequate pain assessment requires accurate medical history, physical examination, and use of validated tools for identification of pain intensity and quality. Pain should be regularly assessed in each HD session. Lack of standardization of pain assessment significantly affects the quality of pain management. As for any other disease, even chronic pain requires an appropriate diagnosis of its underling pathophysiological mechanism to be adequately treated [49].

Pain is generally undertreated in patients with ESRD because of fears about potential toxicity of analgesic drugs. Inappropriate dosing may cause overtreatment or inadequate analgesia. Unfortunately, data on pharmacokinetics and clinical efficacy and safety of analgesics in this population are still lacking. Extrapolation of the pharmacological pain management methods used in non-CKD populations can be hazardous as patients with ESRD have a reduced renal capacity and altered pharmacokinetics [50]. Metabolism alterations may induce potential risks. Dose adjustments are needed for most analgesics.

One of the most common misconceptions is that pain is an unavoidable outcome of aging and of dialysis. The other common misconception in clinical practice is use of the World Health Organization (WHO) three-step analgesic ladder, created for managing cancer pain, for treatment of chronic pain of any origin. The main limitation of this step ladder is the intensity-based approach, which does not take into account the type of chronic pain (nociceptive vs. neuropathic).

Other important unmet needs are revealed by the current patterns of analgesic use in HD patients, which does not reflect the pharmacokinetic information and safety profile of drugs. Indeed, codeine is one of the most commonly used opioids, despite the strong recommendation to avoid it in patients with ESRD. Similarly, non-steroidal anti-inflammatory drugs (NSAIDs), which should be avoided in patients with CKD, continue to be used as prescribed drugs or in automedication [51]. Unfortunately, referral to pain specialists is still episodic among nephrologists and this could increase the risk of inadequate pain management. The consequences of chronic pain are highly invalidating for HD patients. Pain impairs physical activity, reduces QoL, and increases the prevalence of depression.

4 Current Treatment Options in ESRD

4.1 Non-Pharmacological

The non-pharmacological approach is the first step in pain management. In particular, in patients where the use of

drugs is not free of risks, non-pharmacological techniques should be encouraged.

In acute pain, cryotherapy may help to reduce local inflammation induced by a nociceptive stimulus. Similarly, heat may be useful for alleviating pain from muscle spasms. In chronic pain management, non-pharmacological interventions include biofeedback, cognitive behavioral therapy, massages, and exercise programs. In HD patients, mirror therapy is indicated for phantom limb pain in amputated patients [52].

The potential benefits of complementary and alternative medicine (CAM) have not been adequately investigated in patients with ESRD; however, massage, relaxation, meditation, and other non-pharmacological techniques could be potentially helpful in these patients [53].

A recent Cochrane analysis evaluated 24 studies on the various types of acupuncture in patients with CKD. There was a paucity of evidence on the efficacy of acupuncture for fatigue, depression, sleep disturbance, and uremic pruritus in HD patients. Moreover, data on possible acupuncture-related harm are lacking, therefore no conclusions may be drawn on its safety [54].

Transcutaneous electrical nerve stimulation (TENS) has been proposed for the management of acute and chronic pain, and was shown to be better than placebo during therapy in the management of low back pain; however, the poor quality of clinical trials led to inconclusive evidence of its benefits [55]. Similarly, TENS has been used in many types of procedural pain, including venipuncture, without sufficient data to make a definitive conclusion about its effectiveness [56]. Venipuncture is one of the reasons of intradialytic pain, but no data are available on the use of TENS in HD patients.

Listening to music has been used to reduce pain, anxiety, and other complications during dialysis sessions [57–59].

Further studies are warranted on the effectiveness of non-pharmacological treatments in frail patients, such as those suffering from ESRD, where the use of analgesic drugs is limited by the potential adverse events.

In the multimodal approach to chronic pain, invasive techniques may play a role in treating pain refractory to conventional pharmacological treatment or to reduce the dose of analgesics in patients with organ failure. In particular, spinal cord stimulation could be useful in HD patients suffering from peripheral vascular disease, stump pain after amputation, and PDPN, but current evidence suggests only a weak recommendation [60]. Moreover, specific studies in this population are currently not available.

4.2 Pharmacological

A pharmacological approach to chronic pain in ESRD requires generic and specific principles. Drug selection requires deep knowledge of the mechanism of action and pharmacokinetic properties in order to avoid side effects and toxicity. Next to the well-known problems related to anti-inflammatory drugs, even the use of opioids may be challenging because CKD affects renal drug elimination and other processes involved in drug disposition; therefore, drug dosing adjustments may be indispensable.

4.2.1 Drug Dosing in ESRD

Metabolism is the conversion of a drug to less lipid soluble and more easily excreted compounds, called metabolites. The elimination of most drugs and their metabolites partially or completely depends on renal function. Awareness of the pharmacokinetic properties of different drugs is essential to understand the alteration of drug metabolism that could occur in ESRD and to prevent adverse events and toxicity.

General principles of drug dosing in CKD include:

- Drug accumulation may be a concern if the fraction of drug eliminated unchanged in the urine of patients with normal renal function is $\geq 30\%$.
- Endogenous organic acids accumulate in plasma in CKD.
- Hypoalbuminemia reduces protein binding of drugs.
- Drugs need to pass across a membrane to be removed during all forms of dialysis [61].

The unbound (free) drug is responsible for both therapeutic effect and toxicity; therefore, protein binding has a key role as a storage pool for the drug, which remains confined into the vasculature. Patients with ESRD may have binding alterations, particularly for drugs that bind primarily to albumin, such as acidic drugs, which are more affected by uremia. Malnutrition and proteinuria reduce the protein pool and increase the free fraction of drugs.

Clearance is the rate of elimination of a drug by all routes (hepatic, renal, respiratory, biliary, and extracorporeal). Renal clearance is directly correlated with renal function. The drug removal rate is usually expressed as the elimination half-life ($t_{½}$), which may result in prolonged renal impairment. Renal excretion by the kidney is virtually unavailable in HD patients, therefore it is dependent on extracorporeal techniques of dialysis. In general, drugs eliminated by glomerular filtration are partially dialyzable, while those eliminated by tubular secretion may not to be dialyzable. Drug properties that affect the dialytic clearance are summarized in Table 2. Drug clearance may also be affected by hemodialyzer properties (pore size, blood flow rate, surface area, and membrane binding) and dialysate properties (dialysate flow rate, solute concentration, pH, and temperature) [62].

Drug adjustments may be required in ESRD. Two major methods of dosing regimen adjustment are applied in clinical practice: (1) to extend the time between doses while maintaining the same dose size (reducing the number of daily

Table 2 Drug properties that affect dialyzability

Molecular weight	There is an inverse relationship between MW and dialysis clearance
Protein binding	Drugs with high protein binding have a lower proportion of drug available for removal by dialysis. Heparin administered during dialysis may increase FFAs, which compete with many drugs for the albumin binding site, causing an increase in the free proportion of drugs
Volume of distribution	Drugs with a lower V_d are more readily dialyzed than those with similar MW and protein binding but with a high V_d. Even if the extraction of a drug by dialysis is 100%, if the V_d is high and the fraction of intravascular drug is low, dialytic removal will be insignificant
Charge	Molecular charge, together with MW and shape, may affect the flux of a drug through the dialysis membrane pores. Charged drugs are not as dialyzable as those uncharged
Water or lipid solubility	Water solubility is a key factor for dialyzability as dialysate is aqueous and drugs poorly soluble in water cannot be dialyzable
Membrane binding	Dialysis membranes may be negatively charged, causing interactions with solutes and drugs
Alternative excretory pathway	Other pathways for drug excretion may include the excretion of drug into bile, sweat, saliva, milk (via lactation), other body fluids, or expired air for volatile drugs

MW molecular weight, V_d volume of distribution, *FFAs* free fatty acids

doses); or (2) to reduce the size of the individual prescribed dose at the same dosing interval. Sometimes a combination method can be needed, when both these methods (interval extension and dose reduction) are used. The interval extension method is not indicated for drugs with a short half-life, due to the risk of a prolonged period of time with a subtherapeutic drug concentration, but is recommended for drugs with a relatively long half-life. The dose reduction method is more appropriate when it is desirable to minimize fluctuations in serum drug concentrations [63].

Among analgesics, NSAIDs should be avoided, while paracetamol can be safely used without any adjustment. Most opioids and gabapentinoids require dosing adjustment in terms of dose reduction and interval extension [64].

4.2.2 Non-Opioid Analgesics

Paracetamol (or acetaminophen) is the most commonly used non-opioid analgesic in ESRD [65]. According to guidelines, paracetamol, at an optimal oral daily dose of 4 g, is the first-choice analgesic for osteoarthritis. Proposed adjustment in HD patients suggests dosing every 8 h [66]. The National Kidney Foundation recommends paracetamol as the non-opioid analgesic for mild to moderate pain in patients with CKD.

Clinical studies have shown effective removal of paracetamol and metabolites by HD [67]. HD has also been used in paracetamol-induced fulminant hepatic failure associated with acute kidney injury (AKI). However, dose adjustment of *N*-acetylcysteine is needed during HD as bioavailability decreases to 41%, while no significant extraction has been observed with continuous hemofiltration [68]

NSAIDs are commonly prescribed in primary care for their analgesic properties; however, they are known to have gastrointestinal, cardiovascular, and renal toxicity. The Choosing Wisely campaign recommends avoiding NSAIDs in individuals with hypertension, heart failure, or CKD of all causes, including diabetes. The use of NSAIDs, including specific inhibitors of cyclooxygenase (COX)-2, for the pharmacological treatment of osteoarthritis and other musculoskeletal diseases may elevate blood pressure, cause fluid retention, and worsen kidney function. Acetaminophen and weak opioids seem to be safer than, and as effective as, NSAIDs [69].

NSAIDs may also induce AKI by reducing renal blood flow, causing tubular obstruction through crystal deposition and through direct cytotoxicity and cell-mediated immune injury [70]. The risk of developing AKI is increased in people exposed to NSAIDs, and is doubled in older people, people with CKD, and those who received other nephrotoxic drugs. In these susceptible patients, clinicians should minimize NSAID exposure [71].

Clinical investigations on NSAIDs in patients with ESRD are typically single-dose studies or trials conducted for short periods of time. These studies have not been designed to evaluate efficacy and safety, but are designed for obtaining pharmacokinetic data. Limited information is available on their use in HD patients.

Acetic acid derivatives were shown to induce significant renal blood flow reduction in patients with renal disease after only a few days of treatment. Sulindac showed the lowest reduction in creatinine clearance (CrCl) [72] and a high dialyzability that reduced the plasma concentration during dialysis; therefore, supplementary doses may be required to obtain the analgesic effect [73]. Etodolac, bromfenac, and indomethacin do not require any dose adjustments in patients with ESRD [6]. Propionic acid derivatives, such as ibuprofen, naproxen, ketoprofen, and benoxaprofen, showed different pharmacokinetic profiles in patients with ESRD. No dose adjustments are required for ximoprofen and naproxen,

which showed no difference in half-life but decreased bioavailability in CKD [74]. A 50% decrease in dose is required for benoxaprofen, whose half-life was shown to be increased in CKD [75]. Ketoprofen showed significant accumulation after repeated dosing in HD patients [76]. The enolic acid derivative tenoxicam does not require any adjustment as no difference in its metabolism has been observed [77].

Among NSAIDs, celecoxib was the first COX-2 inhibitor approved to treat patients with rheumatism and osteoarthritis.

Pharmacokinetic data showed that bioavailability of celecoxib is 43% lower in patients with chronic renal insufficiency, with a 47% increase in clearance, presumed due to decreased protein binding or reduced tubular reabsorption, leading to changes in hepatic clearance, reduced gastrointestinal absorption, and increased biliary excretion [78]. Rofecoxib showed no change in pharmacokinetics in patients with severe renal insufficiency compared with healthy controls, suggesting no requirement for dose adjustments [79]; however, it has been withdrawn from the market due to increased cardiovascular adverse events following chronic use.

Considering the potential nephrotoxicity, it is strongly recommended to avoid NSAIDs in people with CKD; however, according to the literature and to the market, they continue to be commonly prescribed in this population. In a cohort study on 972 subjects with CKD, 16.9% used NSAIDs every day or several times a week, and this percentage rose to 35% among those on HD. Musculoskeletal pain (osteoarthritis, CKD mineral and bone disorders, or arthralgia) and headache were the most common causes of NSAID administration. Patients used NSAIDs in automedication in 46.7% of cases without being aware of the potential side effects of the painkillers; the remaining were prescribed by physicians or pharmacists. Over 40% of the exposed patients experienced renal function deterioration, 37.6% experienced peptic ulcer disease, and 18.2% experienced altered blood pressure control [80].

Despite the strong recommendation against use, when appropriate, the use of short-term NSAIDs should be preferred. Clinicians should avoid using other medications that may hemodynamically compromise renal blood flow, such as renin inhibitors, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, and radiocontrast media agents [52].

4.2.3 Opioids

Opioids are widely used in chronic pain management, and are the mainstay of pharmacological treatment for severe chronic pain; however, there is no high-quality clinical evidence for their use in chronic non-cancer pain, and systematic reviews have shown a moderate benefit [81]. Moreover, the recent opioid misuse epidemic involving the US [82], Australia, and Canada raised some concerns about their use. Current Centers for Disease Control and Prevention (CDC) guidelines recommend cautious opioid prescription: non-opioid therapy is indicated as the preferred treatment for chronic pain and opioid use is suggested only when benefits for pain and function are expected to outweigh the risks [83]. Conversely, in many countries in Europe, unnecessarily strict rules have created inappropriate restrictions on opioid supply, even though opioids may represent an important part of a multimodal approach to chronic pain. Therefore, in Europe, misplaced barriers to access, negative perception about controlled drugs, and lack of education about pain medicine are often responsible for inadequate pain treatment [84, 85].

Compared with the general population, patients with ESRD are likely to be undertreated with opioids because of physicians' concerns about reduced clearance and increased risk of adverse events [86].

A systematic review analyzed 10 studies describing opioid use in > 26,000 patients with ESRD, from 1995 to 2004 and from 12 countries of different continents; over 90% were dialysis patients. The reported prevalence of opioid use was variable among centers and ranged from 5 to 36%. The most common prescribed opioid in the US was the propoxyphene-acetaminophen combination, while in Canada the most common prescribed opioids were codeine and oxycodone. Only 1 of the 10 studies examined the reasons for opioid prescription, with musculoskeletal pain being the most common diagnosis (65%). Opioid prescription positively correlated with time on dialysis, women, cancer, cardiovascular disease, and psychiatric disorders [87].

In 2015, Olivo et al. investigated opioid management strategies in 191 HD patients from a single center. Twenty-seven percent were long-term opioid users (more than 90 days), and only 48% of these patients had a documented medical indication for their use. The most commonly prescribed opioids were the acetaminophen-containing opioid medications (98%), particularly those associated with hydrocodone (90%) and oxycodone (42%). Fentanyl and methadone, which are among the safest opioids in patients with renal disease because they do not have active metabolites, were prescribed in 6% and 4% of cases, respectively. The main indications were peripheral neuropathy (11.5%), musculoskeletal disease (9.6%), and trauma (7.7%) [88]

Kimmel et al. have recently assessed the association between opioid prescription and patient outcome in a cohort of 271,285 unique patients with at least 365 days of dialysis treatment, using 2006–2010 US Renal Data System information. During the study period, over 60% of dialysis patients received at least one opioid prescription, while over 20% had chronic (≥ 90-day supply) opioid prescription, ranging from 9.5 to 40.6% in different

US states. Women, young (20–44 years) and middle-aged (45–64 years) patients, White population, nursing home residents, cancer patients, and subjects with prior pain-related hospitalizations were more likely to receive opioid prescriptions. The most prescribed opioids in 2010 were hydrocodone (11.7%) and oxycodone (5.4%), followed by tramadol (2.5%) and propoxyphene (1.4%) [89]. According to these data, the reported opioid use in patients with ESRD is lower than in the general population and is much lower than expected, considering that these patients report significantly higher pain and worse physical functioning compared with the general population. Moreover, all opioid drugs have been associated with increased mortality, dialysis discontinuation, and hospitalization. However, as a causal relationship cannot be identified, it is reasonable to conclude the opioid use is just a further marker of impaired general physical status [89]. Similarly, Ishida et al. observed that all opioids in adults receiving HD are associated with an increased risk of falls, fractures, and altered mental status, and this risk was also present at lower doses and for drugs that are recommended in guidelines [90].

However, despite these observed adverse events, opioid prescription has increased over time and is likely to become similar to that in the general population. One reason for this could be that in patients with ESRD, due to the renal toxicity of NSAIDs, opioids may be perceived as a valid alternative for chronic pain management, even in this vulnerable population [91]. Recorded morbidity has not been directly correlated with opioid use and the reasons for opioid prescription in ESRD patients were not always clear. Therefore, data on the appropriateness of opioid prescribing are lacking. In addition to the risk of underprescription, inappropriate use could be a concern. In general, these studies highlighted the need for quality investigations examining opioid use in ESRD.

Recommendations for using opioids in chronic pain patients with ESRD are limited (Table 3). The most commonly prescribed opioids in patients with ESRD reflected exactly the most popular opioids in the general population, where hydrocodone and oxycodone accounted for 51% and 16% of total prescriptions, respectively [92]. Therefore, nephrologists and other prescribers seem to be indifferent to the pharmacological profile of different opioids, which differ in pharmacokinetics in renal impairment. Indeed, pharmacological characteristics would suggest the use of other molecules, such as buprenorphine, fentanyl and methadone, which are least likely to cause harm when used appropriately [93].

In clinical practice, opioids are conventionally classified as weak (tramadol and codeine) or strong (morphine, fentanyl, oxycodone, hydrocodone, hydromorphone, buprenorphine, tapentadol, and methadone). Weak opioids are indicated for mild to moderate chronic pain, while strong opioids are indicated for severe chronic pain management.

Tramadol is a racemic mixture that requires liver metabolism to be converted in the active compounds. It is a prodrug, metabolized by the cytochrome P450 (CYP) enzyme CYP2D6 to its more potent opioid analgesic metabolite O-demethylation product M1. Tramadol has a dual mechanism of action, working as a mu opioid (MOP) receptor agonist and an inhibitor of noradrenaline and serotonin reuptake. Tramadol and its metabolite M1 are MOP agonists. The potency of tramadol on the MOP receptor is 1000-fold lower that of morphine, and therefore it is usually prescribed for mild to moderate chronic pain, even in association with paracetamol [94, 95]. After oral administration, 90% of tramadol is excreted by the kidney. In patients with moderate renal impairment (CrCl 10–30 mL/min), the elimination half-life increased 1.5- to 2-fold, and adjustment of the dosing regimen in this patient population is recommended [96]. In advanced CKD, excretion of tramadol and its metabolite M1 is reduced; therefore, it is suggested the maximum dose not exceed 100 mg orally every 12 h and 50 mg twice daily for patients undergoing HD [97]. The total amount of tramadol and M1 removed during a 4-h HD period is lower than 7%. Two cases of tramadol-induced respiratory depression have been described in patients with ESRD undergoing HD, caused by accidental overdose. An intravenous dose of 400 mg could be well tolerated in patients with normal liver and kidney functions, but resulted in overdose in a patient undergoing HD [98, 99].

Codeine is a prodrug with a 200-fold weaker affinity for MOP receptors than morphine. Its analgesic activity is completely dependent on O-demethylation to morphine, which is its active form, via CYP2D6, and accounts for approximately 15% of its metabolism. Up to 70% of codeine is converted to the other metabolite, codeine-6-glucuronide, and the remaining 15% is N-demethylated, via CYP3A4, to norcodeine. Both these metabolites have a similar affinity to codeine for the MOP receptor. It is well known that patients with inactive copies of the CYP2D6 gene (poor metabolizers [PMs]) suffer from poor analgesia from codeine, while patients with gene duplication, expressing more than two copies (extensive metabolizers [EMs]), may experience an increased analgesic response, or even a potentially dangerous opioidergic effect, including respiratory depression [100]. These pharmacokinetic variables may significantly affect codeine disposition in HD patients. Molanaei et al. evaluated 228 HD patients according to the CYP2D6 polymorphisms. Nine EMs and two PMs were administered a single oral dose of codeine 50 mg. The concentrations of morphine metabolites, morphine-3-glucuronide (M3G) and morphine-6-glucuronide (M6G), were affected by CYP2D6 genotype and were significantly lower in PMs compared with EMs (M3G was 210 nM in EMs vs. 3.5 nM in PMs).

Table 3 Pharmacological treatment for chronic pain management in ESRD

Drugs	Route of administration	Starting dosage	Indications	Clinical considerations
Non-opioids				
Acetaminophen	Oral	1 g tid	Mild to moderate chronic pain (first-choice treatment)	Safer profile
Opioids				
Buprenorphine patch	Transdermal	5 µg/h	Severe chronic pain	Safer profile
Fentanyl patch	Transdermal	12 µg/h	Severe chronic pain	Safer profile. No clinically significant accumulation in CKD
Hydromorphone	Oral	4 mg bid	Severe chronic pain (second-line treatment)	Safe, but use with caution. Dose adjustment required
Oxycodone	Oral	5 mg bid	Severe chronic pain (second-line treatment)	Safe, but use with caution. Dose adjustment required
Tramadol	Oral	50 mg bid	Severe chronic pain (second-line treatment)	Safe, but use with caution. Dose adjustment required
Tapentadol	Oral	25 mg bid	Severe chronic pain (second-line treatment)	No dose adjustment needed for CrCl ≥ 30 ml/min. Data are not available in ESRD
Morphine				Not recommended due to accumulation. To be avoided
Codeine				Not recommended due to accumulation. To be avoided
Adjuvants				
Gabapentin	Oral	Up to 100 mg tid	Neuropathic pain	Safe, but use with caution. Easily dialyzable. Supplemental dose after each HD session
Pregabalin	Oral	25 mg od (up to 75 mg od)	Neuropathic pain	Safe, but use with caution. Easily dialyzable. Supplemental dose after each HD session
Amitryptiline	Oral	12.5 mg od	Neuropathic pain	Safe, but use with caution. Dose adjustment required
Topic treatments				
Lidocaine 5%	Topical	Up to three patches for 12 h/day	Localized neuropathic pain	Negligible systemic absorption
Capsaicin 8%	Topical	One patch every 2–3 months	Localized neuropathic pain	Negligible systemic absorption

od once-daily, *bid* twice daily, *tid* three times daily, *CKD* chronic kidney disease, *HD* hemodialysis, *ESRD* end-stage renal disease, *CrCl* creatinine clearance

Elimination of the glucuronides M3G and M6G was dependent on HD, which significantly reduces the concentration of these metabolites [101].

Codeine has a very low plasma protein binding (7%) and requires dose adjustment (approximately 50% of the normal dose) in patients with impaired renal function. No data are available on dose supplement for dialysis, but, in general, codeine is not recommended in patients undergoing HD because of known accumulation of potentially toxic metabolites [102]. However, in cohort studies, codeine, together with paracetamol, appears to be one of the most commonly prescribed drugs in HD patients [2]. Codeine is available, and commonly prescribed, in association with paracetamol; in patients with moderate renal failure, the use of paracetamol may be useful for its opioid-sparing effect to reduce the dose of codeine [103]. A case of codeine-induced respiratory arrest has been described in a child with chronic renal failure undergoing tonsillectomy–adenoidectomy, after domiciliary administration of paracetamol/codeine 120/12 mg every 4 h, corresponding to 0.7 mg codeine per kilogram [104]. Nowadays, codeine is contraindicated to treat pain or cough in children younger than 12 years of age and in adolescents with severe respiratory diseases.

Morphine is widely used for chronic cancer pain, both in its short-acting and long-acting formulations. Oral morphine undergoes an extensive first-pass liver metabolism, which reduced the delivered dose to one-third. It is metabolized primarily by the liver to two major metabolites, M3G without any analgesic property and M6G with analgesic activity higher than morphine itself. Both these metabolites are

excreted in the urine, therefore renal failure strongly affects morphine concentrations in the blood. Morphine should be avoided in patients with CKD and in patients undergoing HD because of the accumulation of active metabolites. However, a recent systematic review on the use of opioids in cancer pain with renal impairment concluded that there is very little evidence of a relationship between morphine, creatinine levels, and morphine-related adverse events [105].

Fentanyl is one of the most commonly prescribed opioids in patients with chronic pain. It is a highly potent synthetic opioid with a short half-life. Due to its low molecular weight, lipophilicity, and high potency, fentanyl is ideal for transdermal and transmucosal delivery. It is available in 3-day transdermal patches for chronic pain management, and as rapid-onset opioid formulations for breakthrough cancer pain. After the first application of a transdermal patch, the steady-state concentration is reached in 24 h, and fentanyl is constantly delivered for the 72 h period. The elimination half-life after patch removal is 13–22 h because of the skin depot. Fentanyl is metabolized primarily by CYP3A4 to inactive metabolites, and approximately 75% of the dose is excreted in urine. According to prescribing information, transdermal fentanyl is not recommended in patients with severe renal impairment; however, few case reports have described the safe use of this drug in patients undergoing HD. Joshi et al. described a case series of HD patients with diabetic muscle infarction, treated with success by using low doses of transdermal fentanyl (25 µg/h) and physiotherapy [106]. Han et al. recently described two patients undergoing HD receiving transdermal fentanyl for chronic pain at higher doses (up to 500 µg/h) and for long-term treatment (up to 3 years) without experiencing significant adverse events [107]. The large volume of distribution and the high protein binding (80%) do not favor removal by dialysis.

Alfentanil, sufentanil and remifentanil are fentanyl-derived synthetic molecules that are not available in parenteral formulations for domiciliary chronic pain management. Their use is mainly related to acute pain control during anesthesia or intensive care management.

Oxycodone is a semisynthetic opioid widely used for the treatment of a variety of pain conditions. According to epidemiological data, oxycodone is the second most commonly prescribed opioid, accounting for 16% of total prescriptions in the general population and 5.4% in patients with ESRD [89, 92]. Compared with morphine, oxycodone has a higher oral bioavailability, faster onset, and a twice relative oral potency. Oxycodone is a pure opioid agonist, extensively metabolized by the liver in noroxycodone by CYP3A4, and in oxymorphone by CYP2D6. Noroxycodone has a weaker opioid effect compared with oxycodone, while oxymorphone has an estimated analgesic potency that is 14 times that of oxycodone; however, it is present in only a small amount after oral administration of oxycodone, therefore its plasma concentration is too low to attribute the analgesic effect of oxycodone to its metabolite. Oxycodone and its metabolites are excreted primarily through the kidney. Less than 10% is excreted unchanged in the urine. Renal failure significantly impairs oxycodone elimination due to an increased volume of distribution and reduced clearance, leading to plasma peak concentrations 50% higher than normal subjects [108]. Samolsky Dekel et al. investigated the dialyzability of oxycodone in chronic non-cancer pain patients with ESRD treated with controlled-release oxycodone twice daily. Two different dialysis techniques have been evaluated—standard HD and online hemodiafiltration. In both groups, plasma concentrations of oxycodone and noroxycodone decreased during the 240 min of dialysis, leading to a slightly but not significant increase in post-dialytic pain intensity, without the need for opioid rescue doses [109]. The dialyzability of a drug depends on many factors. Oxycodone has a low molecular weight, limited volume of distribution, and high hydrophilicity, therefore it is more likely to be removed during HD; however, according to the literature, oxycodone is potentially dialyzable, but in a limited proportion [110, 111].

Hydrocodone is the most prescribed opioid in HD patients, particularly in fixed combinations with acetaminophen [77]. A single open-label study evaluated the effects of renal impairment on the pharmacokinetics of extended-release (ER) hydrocodone. Forty-eight patients with various stages of renal impairment were studied after a single administration of hydrocodone ER 45 mg. Plasma hydrocodone concentrations and mean bioavailability were affected in the renally impaired population, therefore a 50% dose adjustment may be recommended for moderate to severe renal impairment (ClCr < 30 mL/min) [112].

Hydromorphone is available as an ER formulation for chronic pain management. It is primarily metabolized by the liver and excreted as water-soluble metabolites in urine. Although similar in structure to morphine, hydromorphone does not have an analgesic active 6-glucuronide metabolite, therefore it is a good alternative to morphine in patients with renal impairment [113]. However, accumulation of the two and a half times more potent active metabolite hydromorphone-3-glucuronide can cause neuroexcitatory symptoms, such as myoclonus, delirium, and seizures. Dose adjustment is required. Hydromorphone exposure is doubled with CrCl of 40–60 mL/min, and tripled with CrCl < 30 mL/min [52].

Buprenorphine is a full opioid agonist for analgesia in clinical practice, but displays a ceiling effect for respiratory depression. It has a higher mu opioid receptor (MOR) affinity compared with morphine, and low intrinsic activity [114]. Buprenorphine has been largely used in its transdermal formulations (patches lasting 4 or 7 days) for chronic pain management [115], and is extensively metabolized by the liver into inactive buprenorphine-3-glucucoronide and norbuprenorphine, which has weak analgesic effects. Renal

clearance of both buprenorphine and norbuprenorphine is approximately 30%, therefore buprenorphine is considered one of the safest opioids to use in patients with ESRD and undergoing dialysis [116, 117]. It is likely buprenorphine is not cleared by dialysis, given the large volume of distribution and high protein binding (96%). A German study on 10 patients undergoing intermittent HD analyzed plasma concentrations of buprenorphine and its metabolites before and 10–20 min after standard treatment. The results showed that buprenorphine was not removed by HD, and, in 70% of patients, norbuprenorphine was undetectable. Therefore, the authors concluded that no dose adjustment is suggested for patients receiving buprenorphine up to 70 µg/h, but use with caution is recommended [118].

Tapentadol is an 'atypical' strong opioid. It is the first of a new class of drugs called MOR/NRI due to a dual mechanism of action—MOP receptor agonist (50-fold lower affinity than morphine) and noradrenaline reuptake inhibitor. It has been studied in many chronic pain conditions, particularly in musculoskeletal diseases (osteoarthritis and low back pain) and neuropathic pain (PDPN) [13]. According to the FDA recommendations, tapentadol is the first-choice opioid analgesic to be used in PDPN. It is widely metabolized (97%) via glucuronidation to inactive compounds, and its metabolites are primarily (99%) excreted via kidneys [119]. Bioavailability and maximum concentration are not modified in mild renal disease, and dose adjustments are not required for mild to moderate liver or kidney impairment. A 6.1-fold elevation in the plasma levels of tapentadol-O-glucuronide was observed in patients with CrCl < 30 mL/min. Therefore, due to the limited information regarding its use in severe kidney insufficiency, tapentadol is still not recommended in patients with ESRD [21, 120].

Methadone is mainly used in cancer patients for chronic pain management, as well as opioid detoxification and maintenance therapy. It is metabolized by the liver and its inactive metabolites are excreted by urine and stools. Fecal excretion increases in patients with renal impairment, therefore accumulation of the parent drug and its metabolites is minimal [121]. For these features, methadone is considered one of the opioids that can be used in HD patients; however, dose reduction is required in ESRD because its half-life is very long and unpredictable, therefore the onset of adverse events and toxicity may be delayed.

4.2.4 Anticonvulsants

Anticonvulsants, particularly gabapentinoids, are strongly recommended as first-line treatment for the management of neuropathic pain conditions [122]. By definition, neuropathic pain arises from an injury or a disease of the nervous system. It is characterized by abnormal sensations: paresthesias, dysesthesia, hyperalgesia, and allodynia [123]. Patients describe the pain as stabbing, burning, tingling, or prickling.

Gabapentin and its successor pregabalin are ligands of the α2-delta subunit of the high-voltage activated calcium channel. They block the opening of the voltage-gated calcium channel and prevent the influx of calcium in the presynaptic neuron. The net effect is the reduction in neurotransmitter release (i.e. glutamate) and attenuation of post-synaptic excitability. Gabapentin and pregabalin are indicated in conditions where pain arises from ectopic neuron discharge. Gabapentin and pregabalin have been specifically evaluated in patients with ESRD. PDPN is one of the most common syndromes causing pain in HD patients. Therefore, gabapentinoids, the first-choice drugs in these conditions, could produce very useful results. However, dose adjustment is required in terms of dose reduction and interval extension.

Gabapentin has a favorable pharmacokinetic profile. It is excreted unchanged by the kidneys in urine. Plasma concentrations and toxicity correlate with impaired renal function. Its half-life, 6–8 h in healthy subjects, decreases to 4 h after HD and increases to 132 h without HD in ESRD patients [124]. The low protein binding makes gabapentin easy to be dialyzed (approximately 35%). The recommended dose in HD patients is up to 300 mg daily, with a supplemental 200–300 mg dose after each HD session [125].

Similarly, pregabalin is easily dialyzable because it has a low molecular weight (159.23 Da), a low volume of distribution (0.5 L/kg), and is not bound to plasma protein [126]. The maximum recommended dose of pregabalin in ESRD patients is reduced to 25–75 mg/day, with supplemental doses after dialysis. However, a recent prospective, open-label, single-arm study on pregabalin for neuropathic pain in patients undergoing HD evaluated 45 patients carefully titrated to 150 mg during a 12-week study period. The authors reported a 22.2% withdrawal rate due to side effects (mainly drowsiness and dizziness), without serious drug-related adverse events. Pregabalin was shown to be effective in reducing pain scores and improving QoL [127].

Myoclonus has been described as a possible complication of gabapentinoid toxicity in patients with AKI or ESRD [128, 129]. Serum concentrations > 15 µg/mL have been associated with symptomatic neurotoxicity, which may require discontinuation of gabapentin treatment [125].

Gabapentinoids have been used for the treatment of uremic pruritus, a common symptom in patients requiring dialysis. Accumulation of pruritogenic substances, elevated concentrations of calcium and phosphorus, xerosis, secondary hyperparathyroidism, aging, and drug-related reactions are common contributors for generation of pruritus in HD patients. Neuropathies are very common in HD patients with pruritus. Primary lesions or dysfunction of the peripheral or central somatosensory neurons are postulated mechanisms

of neuropathic itch [130]. No differences were observed between gabapentin and pregabalin in terms of efficacy against itch and tolerability [131]. According to a recent meta-analysis, the recommended dose of gabapentin for the treatment of uremic pruritus is 100 mg orally after HD [132].

Gabapentin has been used for the management of muscle cramps during HD, at a dose of 300 mg before each dialysis session. Gabapentin significantly reduced the frequency and intensity of cramps, without any major adverse events [133].

Nociceptor sensitization in neuropathic pain could also be related to a decreased threshold for sodium channel activation, particularly in the region of spike initiation. Conversely to gabapentinoids, carbamazepine acts by stabilizing sodium channels in an inactivate status, and is considered the first-line treatment for trigeminal neuralgia as prophylactic medication [134]. Carbamazepine is moderately dialyzable because it has a relatively low molecular weight but a high protein binding (75%), which makes elimination by diffusion removal difficult [135]. Moreover, carbamazepine is a potent CYP450 inducer, therefore it may cause drug–drug interactions in polymedicated patients. Extracorporeal removal techniques are effective therapeutic options in patients with carbamazepine poisoning when refractory seizures, life-threatening dysrhythmias, respiratory depression, and/or coma are present [136]. Intermittent dialysis techniques are preferred on continuous renal replacement therapy (CRRT). Dosing recommendations for antiepileptic drugs in patients undergoing CRRT require further investigation [137].

4.2.5 Antidepressants

Antidepressants act as an analgesic in neuropathic pain conditions by increasing the physiological activity of the inhibitory descending pathway. They inhibit the reuptake of two main neurotransmitters (noradrenaline and serotonin) and increase their availability in the synaptic cleft [138].

Randomized controlled trials showed that tricyclic antidepressants (TCAs) are the most effective drugs in the majority of neuropathic pain conditions. They have the lowest number needed to treat compared with selective serotonin reuptake inhibitors (SSRIs), which are not indicated as an analgesic. Newer antidepressants, such as duloxetine and venlafaxine, have a balanced activity on both neurotransmitters, without the antihistaminergic, anti-α1-adrenergic, and anticholinergic (muscarinic) effects of TCAs [139].

Anticholinergic side effects of TCAs may cause urinary retention and orthostatic hypotension, which may limit ultrafiltration. TCA toxicity may cause confusion, excessive sedation, dry mouth, and QT prolongation. Amitriptyline is indicated for neuropathic pain at a starting oral daily dose of 12.5–25 mg, up to a maintenance dose of 150 mg. The clinical meaning of the increased concentration of conjugated TCA metabolites is still unknown. No dose adjustment is required for patients with ESRD.

Duloxetine, which is strongly recommended for PDPN, should be avoided in patients with CrCL < 30 mL/min because of the significant increase (twofold) in bioavailability [140].

Venlafaxine clearance is significantly affected by renal disease. The half-life of venlafaxine and its CYP2D6 active metabolite O-desmethylvenlafaxine is prolonged in subjects receiving HD, therefore dose adjustment (50% of the standard dose) is required for patients with ESRD [141]. No supplement is required for dialysis sessions. Drug interactions and genetic polymorphism may elevate the risk of toxicity.

Antidepressants may be useful in HD patients for the management of painful neuropathies, but they also play a role for their antidepressant activity as depression is a very common comorbidity of chronic pain and chronic HD. SSRIs are the preferred drugs to be used as a result of their antidepressant activity and safe tolerability profile. However, patients and caregivers are often reluctant to receive and prescribe antidepressants, therefore these patients are often undertreated [142]. Milnacipran and levomilnacipran are excreted unchanged in urine in 55% and 58% of patients, respectively; therefore their half-lives are prolonged in patients with ESRD [143].

A recent systematic review concluded that most studies on antidepressants for depression in ESRD patients involved a small number of subjects and were observational, leading to possible bias. Dose reduction is currently recommended for selegiline, amitriptylinoxide, venlafaxine, desvenlafaxine, milnacipran, bupropion, reboxetine and tianeptine [144].

In general, antidepressants should be started at lower doses and carefully titrated to the effective dose in order to reduce the risk of side effects [145].

4.2.6 Topical Treatments

Topical treatments are a convenient and safe way of administering a drug, particularly indicated in frail patients, when systemic absorption is not desired and drug delivery directly on the site of pain perception is likely to be effective.

Two topical analgesic patches are currently licensed for neuropathic pain management—lidocaine 5% medicated plaster and capsaicin 8% patch. Both patches have been proven to be effective in localized neuropathic pain and may reduce the risk of adverse events related to systemic analgesia, such as constipation and CNS side effects (dizziness, somnolence, and cognitive impairment). Topical treatment can be used as monotherapy or add-on therapy to reduce the dose of oral therapy, particularly in patients where the safety and tolerability of systemic analgesia is a concern [146, 147].

Lidocaine 5% medicated plaster is the recommended first-line treatment for post-herpetic neuralgia [148, 149], where it has been shown to be as effective, but better tolerated, when compared head-to-head with the oral standard of care (pregabalin) [150]. In PDPN, lidocaine 5% medicated plaster has been shown to have comparable efficacy and greater tolerability than systemic agents [151]. However, the small number, and size and quality, of clinical trials limited the grade of recommendation of lidocaine 5% plaster in this condition.

Lidocaine acts by blocking sensitized Nav1.7 and Nav1.8 sodium channels in the dermal nociceptors of A delta and C fibers, thereby reducing the number of ectopic discharges. The bioavailability of lidocaine from the plaster formulation is approximately 3%, and is similar after single and repeated doses. The maximum concentration remains far below clinically relevant levels, therefore the toxicity of lidocaine seems to not be a significant risk [152]. Less than 10% of lidocaine is excreted unchanged. No data are available on the use of lidocaine 5% medicated plasters in patients undergoing HD; however, due to the residual systemic absorption and prevalence of neuropathic pain in patients with ESRD, lidocaine 5% medicated plaster could be considered a reasonable alternative [153].

Topical capsaicin 8% (Qutenza®) is a dermal patch designed for the rapid delivery of capsaicin into the skin. Capsaicin binds TRPV-1 receptors expressed by cutaneous sensory nerve endings. The high concentration of capsaicin results in reversible desensitization of these fibers and reduction in nerve fiber density in the epidermis. After a single administration, topical capsaicin 8% has been shown to be effective for approximately 3 months in patients suffering from post-herpetic neuralgia, painful peripheral neuropathies, and HIV neuralgia [154].

When topical capsaicin 8% is applied for 60 min, systemic absorption is minimal and clinically insignificant, and the elimination half-life is very rapid (1.64 h) [155]. However, although topical administration is unlikely to produce systemic effects, severe uncontrolled hypertension (systolic blood pressure > 200 mmHg) and a history of cardiac events during the preceding 3 months are considered contraindications.

Aitken et al. evaluated 20 patients with ESRD suffering from neuropathic pain from critical ischemia, including 20% of diabetic subjects. Patients were treated with a single topic application and followed up at 12 weeks. Capsaicin 8% patch was effective and well tolerated. The median morphine equivalent dose was halved at 12 weeks [156].

Possible limitations of topical treatments are areas of broken or ulcerated skin, where both patches are contraindicated, or size of the area where the patient refers neuropathic pain. Topical patches are indicated for localized neuropathic pain—the area must be small enough to be covered by three lidocaine 5% plasters or one capsaicin 8% patch.

Topical treatment can also be used for the management of intradialytic pain related to the arteriovenous access. A topical anesthetic mixture of 2.5% lidocaine and 2.5% prilocaine has been used for pain management of AVF cannulation; however, the anesthetic cream requires 45–60 min of application to be effective [157]. Conversely, the ethyl chloride vapocoolant spray, which acts by decreasing skin temperature and inducing desensitization of peripheral receptors, may be applied a few seconds prior to acupuncture [158].

4.2.7 Cannabinoids

Cannabinoids have been used for many painful conditions, including neuropathic pain and spasticity from multiple sclerosis [159]. However, there is still moderate-quality evidence to support cannabinoid analgesia, which is still under discussion, being potentially associated with memory deficits and cognitive impairment [160].

Cannabinoids have also been used for treating nausea, vomiting, anorexia, and cachexia, typical symptoms experienced by HD patients. Patients receiving dialysis could theoretically benefit from treatment with cannabinoids; however, data on this population are still lacking and careful assessment of beneficial and adverse effects should be evaluated in future studies [161].

4.2.8 Bisphosphonates

Bone mineral disorders are implicated in some painful syndromes in HD patients, such as calcific uremic arteriolopathy, leading to painful nodule and subcutaneous skin/fat necrosis. Vascular calcifications have a bad prognosis and increase the mortality of HD patients as they may be complicated by severe cardiovascular diseases, ischemia/infarction, and heart failure due to heart valve calcification. The role of antiresorption therapies, such as bisphosphonates, is still unclear [162] but they could be useful for preventing vascular calcifications [163]. Moreover, osteoporosis is, by itself, the cause of chronic bone pain, caused by the increased density of bone sensory nerve fibers and overexpression of sensitized nociceptors [164]. Therefore, bisphosphonates could also be useful for their analgesic activity on osteoporotic bone.

However, bisphosphonates are cleared by the kidney and their use in patients with ESRD increases the risk of drug accumulation. They should therefore be used with caution in this population. Denosumab is an osteoprotegerin (OPG) mimicker, working on the OPG/RANK/RANK ligand system, but is not cleared by the kidney and there is no risk of accumulation in patients with chronic renal failure. However, severe hypocalcemia is a possible side effect of

denosumab [165], and this side effect has been used to correct high calcium levels in patients with ESRD suffering from immobilization-related hypercalcemia [166].

5 Conclusions

Pain is a common symptom in patients with ESRD, which significantly affects their QoL [5]. Over 40% of HD patients suffer from moderate to severe pain and receive inadequate analgesia [7]. Many barriers have been identified, for both patients and caregivers, for adequate pain management.

Implementation of educational programs is the first step for overcoming these barriers. Medical students receive inadequate formation on pain management topics in their undergraduate curriculum, including the use of potent drugs, such as opioids [167]. Continuous learning sessions should be offered at regular intervals for all healthcare professionals working in HD [168]. Patients should also be educated to self-assess their pain, to use proper language to communicate pain intensity and quality to physicians, and, even more importantly, to avoid hazardous self-administration of potentially dangerous analgesic drugs. Standardization of pain assessment is needed to hit the target of pain relief. Caregivers are commonly unaware of the presence of pain symptoms in their dialysis patients and frequently do not implement analgesic treatments.

Given the high prevalence of chronic pain in HD patients, nephrologists should consider pain specialist referral as an integral part of the therapeutic plan. Multidisciplinary teams should be established to convey the different skills of professionals from a range of disciplines in comprehensive patient care. The multidisciplinary approach ensures many benefits in the management of difficult subjects, particularly those with many comorbidities, such as HD patients. It can help in managing patients with complex pain and in planning advance care, including decision making about the goals of treatment. Nurses, physiotherapists, occupational therapists, psychologists, and health educators (such as diabetes educators) should be allied in the multidisciplinary team. Psychological support could be a key factor to overcome fears and negativity, which are part of the CKD and its course. Depression is strongly associated with pain, and treating depressive symptoms in HD patients could enhance dialysis compliance, reduce healthcare resource utilization, and improve survival [11]. Families should also be involved in helping to manage pain in patients with ESRD, focusing on patient-reported pain descriptors and considering their expectations, socioeconomics, culture, and personality.

Clinical trials are warranted for the evaluation of the efficacy and safety of analgesic techniques in HD patients. In clinical practice, using information from research conducted in other populations would not be prudent; we need improved knowledge in the context of patients with ESRD. Non-pharmacological approaches should be encouraged, but little is currently known about their use in this population. Research should be specifically enhanced in this field of pain treatment, including CAM. Pharmacokinetic studies in HD patients are lacking for most of the available analgesic drugs, precluding their safe use in patients with ESRD. The choice of analgesic drugs should be guided by the following principles. Firstly, the "safety first approach" (according to the philosophy of 'primum non nocere') is a medical priority in HD patients, who are more susceptible to potentially harmful adverse events than the general population. Specifically, considering drug clearance and toxicity is mandatory when selecting analgesics in patient with ESRD. On the other hand, some concerns regarding long-term opioid use in chronic non-cancer pain could be less relevant in patients with reduced life expectancy [169]. Secondly, the 'mechanism-based approach' should be applied in order to use the pharmacological class that better targets the pain physiopathology, i.e. topical patches for localized neuropathic pain; gabapentinoids for neuropathic pain syndromes; and central analgesics, such as paracetamol and opioids, for central sensitization. In selecting the analgesic agent, the etiology of pain and its quality (nociceptive vs. neuropathic) matter as much as its intensity. Finally, possible drug–drug interactions should be taken into account in HD patients who are polymedicated, presenting alterations of the pharmacokinetics related to CKD. The need for specific guidelines to treat pain in ESRD is paramount, given the current inadequate literature and the potential for increased adverse effects discussed above. Future efforts should determine and overcome the patient, provider, and system barriers to pain management in patients with ESRD.

Compliance with Ethical Standards

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