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Opioids in Hemodialysis Patients

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Abstract

Chronic pain and prescription opioid use are prevalent among patients with end-stage kidney disease treated with hemodialysis. Vulnerabilities to complications from opioid use are high in this patient population as demonstrated in many recent well conducted patient-oriented studies. Such studies highlight a need for a balanced approach to pain management in hemodialysis patients that includes careful assessment of the risks and benefits of opioid prescriptions in this population. In this article, we review the available literature and experience regarding opioid prescriptions among hemodialysis patients, discuss clinical implications, and outline ongoing research.

Keywords

Buprenorphine; hemodialysis; hydrocodone; methadone; morphine; opioid; oxycodone; pain

Introduction

Chronic pain and prescription opioid use are prevalent among patients with end-stage kidney disease (ESKD) treated with hemodialysis and represent significant areas of unmet clinical and thus research needs. While data on the prevalence and risks of prescription opioid use in hemodialysis patients is increasing, many uncertainties persist. What is clear is that an approach to pain management that includes careful assessment of the risks and benefits of opioid prescriptions among dialysis patients is prudent. In this feature, we define the available literature on the epidemiology and pharmacology related to chronic pain and opioid prescriptions in hemodialysis patients, outline the clinical implications, and importantly, highlight areas for much-needed future research.

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What is known about the prevalence and etiology of pain in hemodialysis patients?

In the U.S., chronic pain has a prevalence of 11% among adults and was estimated in 2016 to have an annual cost of $635 billion.[1] Chronic pain is even more common among patients undergoing treatment with maintenance hemodialysis.[2–4] Employing tools such as the Brief Pain Inventory and the McGill Pain Questionnaire, early reports showed 50% of dialysis patients endorse some problem with pain and nearly 75% of these patients indicated ineffective pain management.[4] Davison et al. went on to analyze 55 publications from 1992 to 2009, for a total of >7,500 patients with chronic kidney disease (most data came from hemodialysis patients), showing that 58% of the evaluated patients experienced pain and 49% reported pain as moderate to severe.[5] A more recent systematic review included 52 studies for a total of ~7000 hemodialysis patients and reported 33–82% and 21–92% of dialysis patients have acute and chronic pain, respectively, with severe pain in up to 76% of patients.[6]

Common comorbidities (e.g. osteoarthritis, diabetic neuropathy), primary kidney disease (e.g. polycystic kidney disease), and metabolic and other complications (e.g. renal osteodystrophy, gout, peripheral vascular disease) predispose dialysis patients to chronic pain. For example, more than half of hemodialysis patients have diabetes mellitus,[7] often with accompanying painful neuropathy, and ESKD-associated mineral metabolism and vascular disorders such as calciphylaxis predispose to chronic pain.[8] Moreover, among hemodialysis patients, there is a reported fracture risk that is 2- to 4-fold higher than that for the general population[9] and falls are common among hemodialysis patients; recent reports indicate that 25–30% of hemodialysis patients experience at least one fall per year and 57% of these individuals reported multiple falls.[10]

Along with a high burden of co-morbid related pain, the hemodialysis procedure itself (typically administered 3 times per week) can be a source for many recurrent pain episodes due to immobilization during the several hours-long treatments (typically 3–4 hours sitting in a chair), muscle cramping resulting from fluid removal, needle insertion and vascular steal syndrome along with other complications of the hemodialysis vascular access, and a “washed out” feeling with substantial fatigue and headaches in the hours following any given dialysis session. In general, vascular access pain, headache, neuropathic pain, and musculoskeletal pain including cramping are cited as occurring most frequently.[2]

What are the complexities and consequences of pain in hemodialysis patients?

The consequences of chronic pain are highly invalidating for hemodialysis patients. Chronic pain in hemodialysis patients is associated with psychologic stress, depression, limitations in mobility and work, poor quality of life, sleep disturbances, increased emergency department and hospital visits, and longer hospital stays.[11–14] Moreover, uncontrolled pain in hemodialysis patients may lead to shortened or missed dialysis treatments and withdrawal from dialysis.[15]

The pharmacologic treatment of pain in patients receiving dialysis is challenging because of a unique or exacerbated risk for many types of medications in dialysis (see Table 1). Hemodialysis poses unique risks stemming from reduced clearance of drugs and metabolites

typically eliminated by the kidneys, and from side effects that are of particular significance in the presence of kidney failure (e.g. hypotension which is already a common problem during hemodialysis). Despite limited evidence for efficacy,[16] long-term opioid therapy, defined as ≥ 90 days of opioid analgesics, has emerged as a dominant treatment paradigm for chronic pain, particularly among maintenance hemodialysis patients.[17] Limited appreciation for chronic pain being a multi-dimensional phenomenon comprised of physical and psychosocial components, concerns regarding adverse events of therapeutic alternatives (e.g. loss of residual kidney function with non-steroidal anti-inflammatory agents), and emphasis on aggressive pain treatment may have contributed to high opioid prescription rates among hemodialysis patients. Patients treated with hemodialysis generally have low levels of physical activity and high rates of insomnia and depression,[18] all of which can exacerbate chronic pain, complicate its management, and be potentiated by opioid use.[19]

What is the magnitude of opioid use among hemodialysis patients?

The opioid epidemic in the U.S. has, in part, been ascribed to prescription oversupply and opioid-related harms, and these problems appear common and intensified in the hemodialysis population.[20–22] Generally utilizing data from the US Renal Data System (USRDS), Medicare prescription claims, or data from other large dialysis databases such as The Dialysis Outcomes and Practice Patterns Study (DOPPS), investigators have attempted to fully quantify opioid utilization in the hemodialysis population. A systematic review from 2011 including several well conducted studies (10 total) that described opioid use in dialysis patients showed the prevalence of opioid use in individual studies to be variable ranging from 5% (95% Confidence Intervals [CI], 4.1% to 5.4%) to 36% (95% CI, 27.3% to 45.5%) across unique cohorts dating from 1995 to 2006.[23] More recently, again without considering duration or dose of opioids, a 2014 report documented increased and widespread use (38%–50%) of opioids in the US hemodialysis population (using data from 2008).[24] In comparison, the authors noted previous US studies reported much lower opioid use in the general (17%–18%) and veteran (33%) populations. More granular reports examining opioid prescriptions in hemodialysis patients subsequently showed that ~20% of patients on dialysis received a chronic opioid prescription (≥90 days of filled prescriptions) on an annual basis, which is 3-times as great as the rate of chronic opioid prescription in the general Medicare population.[22,25] Discrete 2012 data from a single healthcare system in Tennessee found 27% met inclusion criteria as long-term opioid recipients.[26] In a prospective cohort of incident hemodialysis patients that we recruited from the New England area between 2011–2017 (n=441), 22% were opioid users at the start of maintenance dialysis.

As the opioid crisis progressed across the U.S., many prescribers stopped initiating opioid therapy resulting in significant declines in multiple metrics of opioid use.[21] While more recent data on opioid use in hemodialysis patients remains scant, reports suggest a similar trend occurred in the dialysis population as well. Recent publications suggest, among hemodialysis patients, overall rates of opioid prescriptions, quantity, days' supply, and total morphine milligram equivalents (MME) peaked between 2010 and 2012, then declined through 2014.[27] Even more updated information is sorely needed on such epidemiology given the myriad established risks associated with opioid use in hemodialysis patients. Moreover, given the unique and complex pain and other symptomology often driving opioid

prescribing in ESKD, specific attention to adequate pain treatment is also critical for this vulnerable population.

What is the morbidity and mortality associated with opioid prescriptions?

In the non-dialysis population, observational data and limited clinical trial data suggest that long-term opioid therapy is associated with potential harms without significant improvements in chronic pain which is often defined by pain-related functional interference (referred to as “pain interference”). In addition to a higher risk of overdose death among long-term opioid recipients,[28] accumulating data show dose-dependent associations with hypogonadism, infection, osteoporosis, falls, fractures, motor vehicle accidents, opioid use disorder (OUD), and intermittent withdrawal symptoms.[29,30] Finally, opioids confer risks of misuse and addiction.[31,32] The estimated total direct and indirect costs of opioid overdose in the U.S. were at least $18 billion in 2009.[33]

The Centers for Disease Control and Prevention (CDC) recommends that providers use caution if increasing opioid doses above 50 morphine milligram equivalents per day (MME/day) and avoid dose escalations to beyond 90 MME/day.[34] For the dialysis patient population, strong data to guide opioid dosing and alternative pain management strategies are lacking.[35] For example, because of its hepatic metabolism and elimination, methadone is a favored opioid in the setting of kidney failure;[36] however, methadone has multiple drug interactions and prolongs the QT interval which may have important implications given the high rates of sudden cardiac death among hemodialysis patients.[37]

It thus became essential to quantify the risks in the hemodialysis population given the known high prevalence of opioid use in this population. Recent and comprehensive reports by Kimmel and colleagues as well as Ishida et al., offer several insights from Medicare claims data, albeit the most recent years investigated were 2010 and 2011, respectively.[22,38] Kimmel et al. discovered that almost two-thirds of examined patients received at least one opioid prescription each year and that over one-fifth received chronic opioid prescriptions annually. Moreover, their study showed that compared with patients who are not prescribed opioids, hemodialysis patients with chronic opioid prescriptions have a significantly higher risk for all-cause mortality, dialysis discontinuation, and hospitalization.[22] Over one-quarter of opioid users received doses exceeding CDC or other recommendations. Prescription patterns were similar to that in the general population, where hydrocodone accounted for 51% and oxycodone accounted for 16% of prescriptions. Notably, this study was limited to filled prescriptions only. Further studies are needed to understand the actual use of prescription opioids, the prevalence of prescription opioid misuse and use disorders, and their relationships with adverse outcomes among patients with ESKD.

Ishida et al. then reported that opioid use is also linked with altered mental status, falls, and fractures among hemodialysis patients.[38] These data highlight a distinct susceptibility of hemodialysis patients to dose-dependent opioid-related complications which may be attributed to multiple comorbidities, polypharmacy, superimposed uremia, and reduced clearance of active drug metabolites.[38] Others have corroborated such findings linking opioid use to increased fracture risk in a dose-dependent fashion.[39] This work also highlights prior work examining risk factors for bone fractures among hemodialysis patients

in the DOPPS that noted narcotics to be a risk factor among many for adverse outcomes.[40] The aforementioned studies support recommendations that generally advise avoidance of morphine and codeine, which are converted to active metabolites that accumulate in the setting of kidney failure and can exacerbate adverse effects such as central nervous system and respiratory depression.[38] However, the other opioids that are more commonly "cautiously" recommended and used (e.g. hydrocodone, oxycodone, and tramadol) were all also associated with risks for the aforementioned adverse outcomes. Also, despite guidance recommending hydromorphone, fentanyl, and methadone, use of these agents was relatively uncommon, and they were also associated with adverse outcomes.

What about complications from co-dispensing opioids with other medications?

As the above reports came forward highlighting significant associations between opioid use and adverse outcomes in ESKD and dialysis, investigators quickly looked to synergistic risks that may be present when opioids are used in conjunction with other non-opioid medications felt to also carry risks for similar adverse outcomes. Muzzale and colleagues recently reported that the codispensing of opioids and short-acting benzodiazepines was common among patients on dialysis and was associated with higher risk of death.[41] Indeed, among nearly 70,000 incident hemodialysis patients (across 2013–2014) in the USRDS and Medicare claims data, 16% were dispensed a short-acting benzodiazepine and 26% of these patients were codispensed opioids. Among those with opioid codispensing, the all-cause mortality risk was 1.90-fold higher than for those without a short-acting benzodiazepine (95% CI, 1.65 to 2.18).[41] Unsurprisingly, others have found this combination of prescriptions increased hospitalization rates of ESKD patients as well.[42]

In a very similar manner, investigators looked at the risks associated with prescription opioids and gabapentinoids finding that concomitant use increased morbidity and mortality among dialysis patients. For example, in adjusted analyses, concomitant prescription of an opioid and gabapentin compared to no prescription of either was associated with increased risk of death (hazard ratio [HR] 1.16, 95% CI 1.12–1.19), dialysis discontinuation (HR 1.14, 95% CI 1.03–1.27), and hospitalization (HR 1.33, 95% CI 1.31–1.36).[43] Notably, a focused study of the risks of concomitant use of these agents did not identify a specific increased hip fracture risk.[39]

What are the pharmacological issues relevant to prescription opioid use among patients treated with hemodialysis?

We refer the readers to an excellent review in this issue of Seminars for a comprehensive discussion of opioid pharmacology in kidney disease (Hawley CE, Hickey E, Triantafylidis LK, Pharmacologic considerations for opioid use in kidney disease). The discussion below focuses on pertinent pharmacological issues for ESKD patients treated with hemodialysis. It is important to highlight that prospective clinical trials that systematically assess the impact of drug accumulation in the context of ESKD or drug elimination with hemodialysis on patient-oriented clinical endpoints are lacking.

The fact that prescription opioid use disorder has reached such a disproportionately high prevalence in the U.S. compared with many other countries, underscores the opportunities to

improve clinical practice patterns.[44] To better understand the pharmacology of opioids and its application to patients with hemodialysis, it is useful to start with a historical perspective.

Historical perspective—The first introduction of opium dates back to 3400 B.C. in lower Mesopotamia where the opium poppy was first cultivated.[44–46] The juice derived from the poppy was demonstrated to have euphoric effects thus sparking human interest in the pharmacological properties of opioids. Hippocrates was among the first to link analgesic properties to opium and speculated on its potential application to treat various diseases that inflicted pain. The superior analgesic potency of parenteral formulations over oral was discovered in the mid-1800s by Dr. Alexander Wood. Unfortunately, parallel to the pharmacological applications of opioids, the issue of dependence was brought to the surface as almost a half-million soldiers from the U.S. Civil War who received morphine to treat pain associated with war injuries, reportedly became addicted to it. In the early 1900s, non-clinical use of opioids was criminalized in the U.S, while by the mid-1900s, many synthetic opioid formulations were developed, significantly increasing the clinicians' armamentarium for prescription opioids. This was followed by the increasing and widespread concerns that pain control was inadequate in routine clinical settings spawning a significant emphasis on considering pain assessment as a "vital sign." These factors likely inadvertently contributed to the "oversupply" of prescription opioid medications and the subsequent epidemic resulting from opioid-related adverse outcomes like those noted above.

The exact timeline of how opioid use trended among ESKD patients treated with hemodialysis and whether this trend paralleled or even exceeded the trend in the general population has not been established. An important early observation was that levels of endogenous opioid peptides are increased among patients with advanced kidney disease.[47,48] The exact impact of these increased endogenous levels on pain and analgesic response or prescription patterns of opioids among hemodialysis patients remains unclear.

Impact of hemodialysis on opioid elimination—Clinicians prescribing opioids among hemodialysis patients should be familiar with the dialytic properties of opioids that are determined by their molecular weight, protein binding, volume of distribution, and water solubility. As described in the review on the pharmacology of opioids, opioid metabolism produces inactive and active metabolites, some more potent than the parent compound (Hawley CE, Hickey E, Triantafylidis LK, Pharmacologic considerations for opioid use in kidney disease). In patients with ESKD, these metabolites can significantly accumulate, exposing patients to a narrow balance between efficacy and harm.[5,12]

A list of preferred and non-preferred opioid analgesics in patients with ESKD treated with hemodialysis and their relevant pharmacological properties are provided in Table 2. Although chronic pain and pharmacological opioid use is prevalent among hemodialysis patients, literature examining the pharmacological implications of hemodialysis therapy on opioid dosing and opioid dose adjustments is limited.

Opioids with significant dialytic clearance may lead to withdrawal symptoms during or post-dialysis. However, in such instances whether and how much the opioid dose should be

supplemented remains unclear and practitioners are encouraged to practice their best clinical judgement and discuss this possibility with patients in advance.

In one study from Italy, investigators assessed the effect of 4-hour hemodialysis sessions on the plasma concentration of oxycodone and its metabolites in 20 patients with ESKD who were stably treated with oral oxycodone.[49] No oxymorphone or noroxymorphone metabolites were detected at any time (concentrations < 0.2 ng/mL) and limited dialyzability of oxycodone and noroxycodone was documented with hemodialysis. The post-dialysis pain increment was limited with no need for opioid compensation.

In another study, investigators enrolled 14 hemodialysis patients with chronic pain who were receiving either methadone or hydromorphone for at least 2 weeks before study start.[50] They noted that plasma methadone levels were more stable during hemodialysis compared to hydromorphone: the mean percent change of methadone plasma levels was ~15% compared with ~55% in the hydromorphone group. The average dialytic plasma clearance of hydromorphone was higher by over 85 mL/minute compared with plasma clearance of methadone. Interestingly, methadone therapy was not associated with an increased rate of adverse events, suggesting this could be a preferred opioid among hemodialysis patients. A rigorous study to confirm these findings, however, has been missing.

In a study of 10 patients with ESKD on maintenance hemodialysis who were being treated with transdermal buprenorphine, a partial opioid agonist and antagonist, plasma levels of buprenorphine and its metabolite norbuprenorphine were not elevated with transdermal buprenorphine dosing up to 70 microg/h.[51] Furthermore, the dialytic procedure did not alter buprenorphine plasma levels or pain intensity among these participants.

One of the prevalent clinical misperceptions is that the duration of analgesic effects of opioids is increased in dialysis patients and hence the dosing interval should be increased. While it is important to remember that the elimination half-life of compounds can be prolonged in patients with ESKD, most parent opioid compounds are metabolized primarily in the liver to inactive metabolites that do not have analgesic effects but may introduce toxicity. Thus, patients may be left not only with the re-emergence of pain once the opioid effect wanes but also potentially with a longer duration of exposure to toxic metabolic products. This emphasizes the need to carefully select opioids that are not metabolized to toxic metabolites (see Table 3).

What methods can screen for opioid use disorder in patients treated with hemodialysis?

Prescription opioids have potential euphoric effects and carry the risk of misuse and a chronic relapsing illness of opioid use disorder. Although opioid use disorder can also result from illicitly purchased opioids like heroin, prescription opioids are the most commonly abused opioids in the U.S. Among noninstitutionalized civilian adults who were prescribed opioids, one in eight reported misuse and among those who reported misuse, one in six suffered prescription opioid use disorder.[32,52] Corresponding granular data for ESKD patients and for hemodialysis patients are lacking and are urgently needed.

Nevertheless, we completely agree with the authors of a recent editorial feature published in the Journal of the American Society of Nephrology that recommends active screening for prescription opioid misuse among dialysis patients before initiating and during long-term opioid therapy.[32] Instruments such as the Opioid Risk Tool (ORT) which are recommended to assess the risk for opioid abuse among individuals prescribed opioids for treatment of chronic pain have not been validated for dialysis patients but likely represent a good starting point for clinical care as well as for research. The ORT is a brief, self-report tool that identifies patients at high-risk for future abusive drug-related behavior and can be administered and scored in less than one minute.[53] The tool is accessible at https://www.drugabuse.gov/sites/default/files/opioidrisktool.pdf. The ORT is recommended upon an initial visit prior to beginning opioid therapy for pain management and in our opinion, can potentially also be applied at longitudinal clinical follow-up visits of patients on chronic opioid therapy. A score of 8 or higher indicates a high risk for opioid abuse, a score of 4 to 7 indicates moderate risk, and a score of 3 or lower indicates low risk for future opioid abuse. Patients identified at moderate and high risk should be referred to pain and addiction specialists. Urinary metabolic screens for opioids are routinely administered to assess opioid misuse in non-ESKD individuals. However, among dialysis patients who are frequently anuric, urinary screening poses practical limitations. Moreover, it is important to highlight that routine urinary screens for opioids may result in false positives in patients eating poppy seeds and those treated with quinolones and false negatives for certain opioids like oxycodone, methadone, and buprenorphine (unless a specific screen for these are requested).[54–56] Alternative specimens from a simple observed collection (e.g. saliva) can be considered for anuric dialysis patients. Data on their application are limited and it is important to consider practical challenges including inability to produce an adequate amount of saliva specimen due to dry mouth, another frequent occurrence in dialysis patients.[57] Considering the fragmented clinical care of dialysis patients and high frequency of emergency room and hospital visits in this population, routine application of central prescription drug–monitoring programs is critical to identify patients with prescriptions from various providers, overlapping prescriptions, and/or high-dose prescriptions. However, more data on the effectiveness of such prescription drug–monitoring programs with special focus on vulnerable populations like ESKD patients is needed especially in light of a recent report that found limited evidence to suggest that these programs were associated with decreased prescribing and dispensing.[58]

What are the strategies to improve the safety of opioid prescriptions in patients treated with hemodialysis?

As summarized in prior sections, it is important to appreciate that common prescription opioid analgesics may have altered pharmacokinetics and have toxic metabolites that accumulate, impacting their safety profile considerably. Opioids, in dialysis patients, should only be reserved for moderate to severe pain that is not controlled by non-opioid analgesics. Moreover, their use should aim to be limited to short-term duration with an active plan to quickly transition them to non-opioid analgesics when possible. Equally important is the consideration of non-pharmacological options for pain management as highlighted in another review in this feature. (Brintz CE et al., Non-pharmacological treatments for opioid reduction in patients with advanced chronic kidney disease) Although data are currently

lacking, buprenorphine holds promise as a potentially safer drug for the treatment of pain in dialysis patients relative to full agonist opioid medications. Goal setting via shared decision making is critical for successful outcomes and patient satisfaction.

What role can family members providing care to patients treated with hemodialysis play?

Although research on family caregiving and the role of family members providing care to hemodialysis patients is limited, the broader caregiving literature for patients with chronic illness, including those with chronic pain, has consistently found family caregivers to play important roles in both illness management and symptom management, leading to better patient outcomes. Reasons for these better outcomes include greater adherence to treatment and programs when a family caregiver is involved, the role of the family caregiver in reporting patient symptoms (particularly pain) and the positive role of social support when patients do not manage illness or pain alone.[59–66] Thus, there are several key ways that involving family caregivers could support the effective and safe management of opioids in hemodialysis patients. First, family caregivers could be involved in the screening process and could also complete the ORT to provide their appraisal of the patient's opioid use. This appraisal would complement the ORT provided by the patient and be used in tandem as additional information to identify those at-risk. Second, family caregiver perspectives of the patient's chronic pain (and particularly pain interference) would provide additional information for clinicians and potentially highlight situations where there is large disagreement between patient and caregiver that would flag follow-up. Finally, with some minimal education regarding pain management, family caregivers would be empowered to support better quality care and illness management strategies, in collaboration with the patient, including greater patient adherence and appropriate use of prescribed opioids and more appropriate help-seeking behaviors. Specific research is needed to fully understand the role family caregivers may play in opioid use by hemodialysis patients, but the broader literature suggests they have a unique perspective and role that should be acknowledged and leveraged to optimize goals of care and patient outcomes.

Conclusions and future directions

Pain is reported to be among the most common and burdensome symptoms in hemodialysis patients, with the majority of patients describing their pain as moderate or severe. The causes and types of pain in this patient population are unique and numerous, and medical management is complicated by altered pharmacokinetic and pharmacodynamic properties of analgesic agents in the setting of kidney failure. Due to both the high prevalence of pain and the limited treatment options, opioid medications are extremely common in the ESKD population. Among hemodialysis patients, long-term opioid use is associated with increased rates of falls, hospitalizations, dialysis withdrawal, and death. The unique pharmacokinetic and pharmacodynamic aspects of opioid analgesics in hemodialysis patients coupled with strong epidemiological association studies signaling morbidity and mortality risks from prescription opioid exposure in ESKD, underscore the critical need for ongoing research to inform the best approach to pain management in this population.

The most recent available studies of opioid use in hemodialysis patients suggest a decrease similar to what has been observed in the general population, though the use is still substantially greater than in the general population. More updated data is needed given rapidly changing prescription opioid trends. Non-pharmacologic approaches such as cognitive behavioral therapy, have demonstrated efficacy for chronic pain in the general population, but have not been well studied in patients with ESKD. Buprenorphine, a partial opioid agonist with an improved safety profile compared to other opioids, may be an effective option for reducing opioid use among patients treated with hemodialysis, but there is limited experience with this drug in the ESKD population. Currently, part of the National Institute of Health's "Helping End Addiction Long-term" (HEAL) initiative, the Hemodialysis Opioid Prescription Effort (HOPE) consortium is conducting a clinical trial to address the burden of pain and prescription opioid medications in the hemodialysis population. The HOPE randomized clinical trial will evaluate approaches to reducing pain and opioid use among patients with chronic pain who are receiving maintenance hemodialysis for ESKD. The study's hypothesis is that a pain coping skills training program (similar to cognitive behavioral therapy) will be effective at reducing pain and opioid use, and that buprenorphine may provide an alternative to full agonist opioids that is acceptable and well tolerated by this patient population. Such efforts carry the promise to both reduce harmful opioid exposure while simultaneously treat and reduce chronic pain in a vulnerable population. While such studies carry great promise, it is clear that many additional efforts and innovations will be needed to ultimately address this critical need for our hemodialysis patients.

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Table 1.

Limitations of various medication classes used to treat pain in hemodialysis patients

Class	Limitations
Non-steroidal anti-inflammatory drugs (NSAIDS)	May accelerate loss of important residual kidney function in some patients
COX-2 Inhibitors	May accelerate loss of residual kidney function; pro-thrombotic
Acetaminophen	Often insufficient pain control
Tricyclic antidepressants	Anticholinergic adverse effects, particularly in the elderly
Selective serotonin reuptake inhibitors / serotonin-nor-epinephrine reuptake inhibitors	Dosing considerations for some agents; may worsen restless leg syndrome; QT prolongation with some agents
Gabapentin / Pregabalin	High toxicity risk including mental status changes, somnolence, and hypotension
Opioids	Increasing epidemiological evidence of increased risk for adverse outcomes with opioid use in ESKD. Addiction potential; constipation, mental status changes, somnolence, respiratory depression; lack of evidence of efficacy for chronic pain

Table 2.

Opioid analgesics that are preferred among hemodialysis patients when they are medically indicated

Analgesic	Pharmacological characteristics	Comments
Hydromorphone	Molecular weight: 285 g/mol (low) Protein binding: ~15% (low) Volume of distribution: 1 L/kg (low) Water solubility: high	Initiate with 25% of the usual starting dose. More potent analgesic than morphine and less pruritus, sedation, and nausea than morphine. Hydromorphone- 3-glucuronide is the principal metabolite which can accumulate between dialysis sessions and may lead to hyperalgesia, cognitive impairment, myoclonus, ataxia, and convulsions. Significantly removed during dialysis-- 40% reductions in post-dialysis concentrations of hydromorphone compared to predialysis levels. Whether supplemental doses are indicated post-dialysis has not been well-studied.
Fentanyl	Molecular weight: 337 g/mol (high) Protein binding: ~79% (high) Volume of distribution: 2–5 L/kg (high) Water solubility: low	Initiate with 50% of the usual starting dose. Not recommended for opioid naïve patient. Administered as a transdermal patch which has an advantage of not increasing pill burden. More potent analgesic than morphine and less toxicity than morphine. Norfentanyl is the principal metabolite but it is pharmacologically inert. No significant dialytic removal. However, may get absorbed directly onto dialysis filters.
Methadone	Molecular weight: 310 g/mol (high) Protein binding: ~70% (high) Volume of distribution: 4–6 L/kg (high) Water solubility: low	Recommended to start with a low dose and slowly titrate upwards. Analgesic half-life is shorter than elimination half-life. Thus, there is a concern for toxicity even after analgesic effect has worn off. QTc prolongation is one of the serious concerns. No significant dialytic removal.
Buprenorphine	Molecular weight: 467 g/mol (high) Protein binding: ~95% (high) Volume of distribution: higher than physiological volume with parenteral administration Water solubility: high	Partial opioid agonist and antagonist Administered either via a buccal preparation or a transdermal patch. Oral bioavailability is poor. Limited renal excretion as major metabolites are eliminated via fecal route No significant dialytic removal.

Table 3.

Examples of opioid analgesics to be avoided among hemodialysis patients

Analgesic	Reason for avoidance
Codeine	Codeine and its metabolites are excreted by the kidneys and accumulate in patients with end-stage kidney disease. If prescribed, dose should be 50% of dose typically used in a non-dialysis patient.
Tramadol	Excreted primarily in urine (~30% as unchanged drug and 60% as metabolites). Risk of unpredictable dosing and serotonin syndrome.
Morphine	Metabolites with toxicity (M3G and M6G) accumulate in patients with end-stage kidney disease.
Hydrocodone	Unpredictable risk of overdosing and underdosing.
Oxycodone	Unpredictable risk of overdosing and underdosing.