Dialysis, Opioids, and Pain Management: Where's the Evidence?

Almost half of all diaylsis patients suffer from chronic pain. However, there are virtually no recommendations for pain management in the dialysis setting. This review presents a practical approach to pain management in this setting.

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According to the 2010 U.S. Census report, life expectancy continues to increase, and those 65 years and older appear to be the greatest beneficiaries of this increased life expectancy, with growth in this group predicted to nearly double by 2030.[1] Treating this growing elderly population presents many challenges. For example, the incidence of chronic kidney disease (CKD) in people ≥65 years old more than doubled from 2000 to 2008, and end-stage renal disease (ESRD) grew by 600% from 1980 to 2009.[2] Mortality rates among patients with ESRD and dialysis peaked in 2001; since then, mortality rates in these patient groups have declined, with the rate among patients undergoing dialysis decreasing to early 1980s numbers.[2] Increased survival for ESRD and dialysis patients requires a paradigm shift in the treatment approach of many difficult but common comorbid disease states that threaten their quality of life, in particular chronic pain.

A decade ago, it was found that 50% of long-term dialysis patients reported suffering from chronic pain.[3] Musculoskeletal pain is the most common type of pain reported, but neuropathy and peripheral vascular pain also is quite common.[3,4] Approximately 75% of patients on dialysis describe their pain management as inadequate, with 55% reporting a severe pain episode during the last 24 hours.[3]

Unfortunately, there is an absence of pain management recommendations for dialysis patients. There are no published clinical practice guidelines addressing medications for chronic pain specifically for patients with ESRD or requiring dialysis. Nephrologists often are forced to address analgesic needs for their patients with ESRD or dialysis because primary care providers often feel uncomfortable prescribing analgesics and other therapies in this specialized population. This has become a catch-22, because neither provider is an expert at pain management. Likewise, certified pain clinicians who focus on interventional therapy often feel equally inadequate prescribing medications to this unique population.

In our experience, most ESRD patients seek analgesic help from their nephrologist who they may see several times per week compared to a primary care provider who they may see once or twice a year. Experts and pain societies acknowledge this deficiency, but point out that even if they were to assemble an expert panel to review the evidence, the dearth of quality studies would leave them with nothing to review.

The purpose of this commentary is to suggest adaptation of current guidelines, address common misconceptions, highlight deficient areas for research, and capitalize on available scientific evidence to promote a practical approach that can maximize therapeutic outcomes while maintaining safety in this vulnerable population.

Guidelines Simplified

Pain patients suffering from chronic conditions can be notoriously persistent and demand that prescribers intervene.[5,6] Considering the pitfalls of nonsteroidal anti-inflammatory drug (NSAID) therapy for a CKD patient in whom comorbid conditions are expected, providers often feel enormous pressure to prescribe opioids to alleviate suffering. Unfortunately, time constraints and patient demands likely contribute to practitioners ignoring certain minimum recommended standards from published pain guidelines, which can be disastrous. At a minimum, providers should perform a combined physical and pain assessment, attempting to determine the cause and mechanism of the patient's pain complaint (neuropathic or musculoskeletal) to guide therapy.

It also is crucial to obtain a patient's previous medical history to identify a history of substance abuse, serious mental illness, previous medication trials, documented pharmacy records from all sources, and/or an established pain care plan, if it exists. Any of these considerations can impact a provider's decision to initiate medication management. Prior to issuing a prescription for opioids, providers need to explain to patients appropriate expectations and risk versus potential benefit, as well as discuss the goals of care.[7,8]

Misconceptions

In clinical practice, it often is presumed that increased half-life of opioids in dialysis patients translates into increased analgesia or, in other words, "short-acting agents become long-acting" in this setting. This idea has become so pervasive that, in the authors' experience, it is rare to see an extended-release opioid prescribed to dialysis patients. However, there is not a shred of scientific evidence on which to base this presumption. The half-life referenced here is elimination half-life, which is increased because of the body's inability to excrete the more hydrophilic metabolized drug products that accumulate with renal dysfunction and failure. In most cases, however, the metabolites that have accumulated are inactive and no longer contribute to analgesia or toxicity in any meaningful way.[9]

Only delayed hepatic metabolism of the active parent drug, theoretically, would lead to increased duration of action for opioid analgesics, which appears only marginally increased in dialysis patients.[9-11] While studies have shown that there is a marginal delay of hepatic metabolism in dialysis patients, mostly affecting cytochrome P 450 (CYP450) metabolism, it is unclear if this is some compensatory mechanism to divert drug metabolism to an unobstructed pathway (similar to methadone in dialysis patients) or whether this may have any tangible effect on duration of analgesia. Clearly, this is an area where additional studies would be useful in guiding appropriate drug therapy.

Recently, debates surrounding the use of opioids for chronic noncancer pain have highlighted research indicating correlations between morphine equivalent daily dose (MEDD) and adverse outcomes.[12-15] Although, there is a strong correlation between daily dose and adverse outcomes, it is plausible that patients requiring higher doses are sicker to begin with and that they had shorter lifespans due to chronic disease(s), regardless of the MEDD. Therefore, the exact cut-off, or threshold, where this risk is significantly increased is not yet clear.[16] In fact, even if there was expert consensus on what constitutes a MEDD, it still does not account for polymorphic variations in metabolism (which affect metabolite concentrations), drug-drug or drug-disease interactions, and various pharmacokinetic patient variables.

Thus, while there never has been sufficient evidence of analgesic efficacy to recommend extended-release over immediate-release agents, it is becoming clear that strategies to provide improved analgesia with decreased opioid use should become the focus. Maximizing the use of adjunctive agents that appropriately target the underlying mechanism for a patient's pain type is critical. Some patients will continue to require opioids to manage their pain, and switching a patient to an extended-release (ER) agent actually may be preferable and improve outcomes in certain circumstances, or, at the very least, improve tolerability by reducing side effects corresponding to lower serum peak concentrations. For example, if more consistent pain relief can be obtained with a reduced total daily dose using an ER agent, it may be preferable. Also, in most cases, ER agents have advantages in terms of fewer metabolites waiting to be excreted at any given time in comparison to similar doses of immediate-release agents with inherently higher peaks.

Table 1. Physical-Chemical Characteristics of Opioids Impacting Ability to Dialyze

Drug	Volume of Distribution (L/kg)	Plasma Protein Binding, %	Water Solubility[a]	Molecular Weight, g/mole
Methadone HCl	3.8	89	12:1	345.9
Fentanyl HCl	6	80	40:1	528.6
Hydromorphone HCl	1.22	N/A	03:1	321.8
Oxycodone HCl	2.6	45	06:1	405.9
Oxymorphone HCl	N/A	10	1-10:1[b]	337.8
Tapentadol HCl	7.7	20	1-10:1[b]	257.8

[a] Both oxymorphone and tapentadol are listed as "freely soluble" by United States Pharmacopeia and The National Formulary USP 36-Nf 31 2013 (U.S. Pharmacopoeia: National Formulary). Freely soluble is defined by the USP-NF as a range of 1 to 10 parts solvent needed to dissolve 1 part solute.
[b] Based on "USP definition" water solubility is in a ratio of parts solvent needed to dissolve parts of solute; generally using the units of mL of solvent per g of solute.

Based on reference 6 and prescribing information.

Perhaps most importantly, dialysis patients with a history of substance abuse should not be given more abusable analgesics merely because they have ESRD and receive dialysis. Recommending opioids in dialysis patients requires an intimate knowledge of their pharmacology, pharmacokinetics, and pharmacodynamics in this unique population. ESRD and/or dialysis should not be considered a free pass to receiving opioids. Clinicians need to account for all of the same factors we ponder for patients with normal kidney function, considering the added burden of ESRD. In short, opioid prescribing for ESRD requires "universal precautions."[17]

Dialysis Considerations

In ESRD, clinicians should review standard considerations for drug therapy, including metabolism and elimination of the drug to determine if it will accumulate, and exercise caution with agents that have active metabolites that can accumulate and provoke toxicity. There are retrospective reviews that provide some insight, but randomized controlled trials that prospectively evaluate the potential risk and impact of drug accumulation within this specialized population are lacking.[18]

Additionally, clinicians prescribing opioids in dialysis also must determine how likely, and to what extent, they will be dialyzed. Characteristics impacting removal of a drug by dialysis include[19]:

- Molecular weight—Larger compounds will not pass easily through the dialysis filter.
- Protein binding—Compounds that are highly protein bound are not dialyzable because the proteins are too large.
- Volume of distribution (Vd)—A higher Vd indicates the drug is penetrating into bodily tissue rather than circulating within the blood and, therefore, is not available for extraction.
- Water solubility—Compounds that are highly water soluble are more easily filtered through the dialysate.

Opioids that are heavily extracted during dialysis may precipitate withdrawal symptoms in patients, and studies exploring the effect of supplemental dosing during or after dialysis are noticeably absent. The physical-chemical properties of commonly used opioids are listed in Table 1.

Monitoring in Dialysis Patients

Monitoring for treatment compliance is a necessary and significant challenge for practitioners treating dialysis patients. For most, a urine drug screen is not practical. There are alternative options, including a serum drug screen (SDS), which by immunoassay returns a quick result for a basic panel of illicit and prescription drugs. This of course is far less accurate compared to definitive testing by gas or liquid chromatography mass spectrometry. However, since an SDS can be performed easily in conjunction with dialysis, there is no additional burden on the patient.

In addition to screening for compliance, monitoring includes follow-up assessments for efficacy, tolerability, and progress towards treatment goals. Prescribers should consider initiation of opioids on a trial basis, identifying a threshold at which they are no longer comfortable proceeding with chronic opioid treatment, with a predetermined escape strategy to withdraw opioid therapy or refer to a pain specialist who can collaboratively manage this complex patient population. Patients must understand the benefits and risks of such therapy and that continued use

Table 2. Accumulation, Metabolism, and Elimination of Opioids in ESRD

Drug Name	Hepatic metabolism[A]	Elimination: Renal/Hepatic (R/H)[a]	Phase of Hepatic Metabolism	CYP450 Hepatic Enzymes[b]	Primary Metabolites
Methadone[3,4,6-9]	Yes	R=20-50%[c] H=balance unknown	Phase I	CYP3A4 CYP2B6 CYP2C8 CYP2C19 CYP2C9 CYP2D6	EDDP (2-ethyl-1,5-dimethyl-3,-3-diphenylpyrrolinium) EMDP (2-ethyl-5-methyl-3,3-diphenylpyraline)
Fentanyl[2-4,6-8]	Yes	R=75%[c] 10% unchanged H=9%	Phase I	CYP3A4	Norfentanyl (>99%)
Hydromorphone[5,6,8,10]	Yes	R=balance unknown H=balance unknown	Phase II: via UGT2B7	N/A	Hydromorphone-3-glucuronide (H3G; 36.8%)
Oxycodone[6,8,11]	Yes	R=72±19%[c] H=balance unknown	Phase I	CYP3A4 CYP2D6	Noroxycodone Oxymorphone
Oxymorphone[49-52]	Yes	R=>40% H=balance unknown	Phase II: via UGT2B7	N/A	Oxymorphone-3-glucuronide (O3G; 38%)
Tapentadol[53,54]	Yes	R= 99% H= ~1%	Phase II	CYP2C9 CYP2C19	Tapentadol-O-Glucuronide (55%) Tapentadol-O-Sulfate (15%)

of opioids is contingent on compliance, response, activity level, and absence of aberrant behaviors. For example, if the patient reports unchanged daily function and pain levels despite adjunct medications and dose adjustments, then reassessment is warranted and may indicate the necessity for referral.

Dangers of Current Recommendations

Methadone

The Centers for Disease Control and Prevention (CDC) reported that methadone prescriptions for pain have more than quadrupled since 1999. Although methadone prescriptions represent only 2% of opioid prescriptions, they account for nearly one-third of all opioid overdose deaths, which is more than double the amount for any other opioid.[20] Pain societies and government agencies agree that methadone should be reserved for pain specialists and practitioners who are intimately familiar with its unique pharmacology, pharmacokinetics, pharmacogenetics, and drug interactions. This is reflected in their published clinical practice guidelines.[21-26]

In ESRD, however, methadone is recommended as first-line therapy, preferred treatment, or even described as safe.[19,27-30] Why has methadone transformed into this pillar of safety in ESRD? It is a dire misconception! These recommendations are based purely on its metabolism, elimination, and lack of extraction during dialysis. Methadone has advantages in ESRD because it is both hepatically metabolized and eliminated, with only an estimated 20% routinely excreted by the kidneys, yet it can compensate in ESRD presumably through increased biliary-fecal excretion.[31] Methadone also is not routinely dialyzed because it's highly protein bound, with high molecular weight, high Vd, and low water solubility.[19]

The combined effect of these advantages is that methadone concentrations in patients with ESRD are similar to those with normal renal function. In other words, the opioid that routinely results in the majority of overdose deaths in patients with normal renal function still remains the most serious risk in the ESRD population for the very same reasons. The advantages discussed above do not take into account the reasons methadone can be dangerous when prescribed by inexperienced practitioners. Methadone's half-life (15-60 h) is much longer than its analgesic duration of action (6-8 h),

	Minor Metabolites	Active Metabolites	Accumulation of Parent Compound in ESRD	Accumulation of Active Metabolite in ESRD
	N/A	None	No[f]	No
	Despropionylfentanyl Hydroxyfentanyl Hydroxynorfentanyl (<1%)	None	Unknown	N/A
	Dihydromorphine (0.1%) Dihydroisomorphine (1%)	H3G	Yes[e]	Yes: H3G[e]
	Oxycodyl Oxymorphol Noroxycodyl	Noroxycodone and Oxymorphone[d]	Yes	Yes: Noroxycodone Yes: Oxymorphone[g]
	Oxymorphone-6-gluronide (O6G; 1%)	Oxymorphone-6-gluronide	Yes	Yes: O6G
	N-desmethyl-tapentadol (13%) Hydroxyl tapentadol (2%)	N/A	Unknown	No

[a] Data from subjects with normal hepatic/renal function
[b] Major CYP enzymes are bolded
[c] Percentages are variable based on pharmacogenomics, age, drug-drug interactions, etc
[d] Higher potency than oxycodone but present in extremely low concentrations
[e] Hydromorphone-3-glucuronide accumulates 100 times more than parent molecule in ESRD
[f] Methadone compensates in ESRD exclusively excreting via biliary-fecal route
[g] Oxycodone and noroxycodone concentrations increased by 50% and 20%, respectively in ESRD

ESRD, end-stage renal disease

resulting in accumulation and delayed respiratory depression.[32-34] While this accumulation may not be exacerbated in ESRD, it certainly is not mollified.

Methadone is highly susceptible to drug interactions. It undergoes phase I metabolism via multiple CYP450 oxidative pathways, particularly 3A4, 2B6, 2C8, 2C9, 2C19, while converting methadone into its inactive metabolites.[32,34] This helps explain why methadone has so many documented drug-drug interactions that could increase/decrease efficacy and increase mortality and morbidity. A frequently overlooked liability of methadone is its dependence on p-glycoprotein (pGP) efflux pumps for absorption through the gastrointestinal mucosa and the blood brain barrier, both of which are critically affected by multiple other drugs that are pGP inhibitors or inducers.[35]

Methadone also possesses a significant risk for cardiac toxicity by prolonging the QTc interval and potentially inducing dangerous arrhythmias such as Torsades de pointes, a risk that likely is more prevalent in phenotypical poor 2B6 metabolizers. These factors remain the most challenging aspect of methadone administration and it is, therefore, disingenuous and unsafe to assume that patient selection, careful titration, and ongoing monitoring are somehow less important in patients with ESRD. Thus, although it has some metabolic advantages in dialysis patients, methadone should remain reserved for pain specialists and clinicians experienced with its unique challenges. Continued use of methadone as first-line therapy in ESRD results in unnecessary exposure to serious risks in an already vulnerable patient population (Table 2).

Fentanyl

Fentanyl undergoes phase I metabolism via CYP450, almost exclusively through 3A4 N-dealkylation (99%), into its inactive but major metabolite, norfentanyl. CYP 3A4 is the most used pathway in drug metabolism, with numerous 3A4 inhibitors that could increase fentanyl concentrations to dangerous levels, even at normal doses.[36] This was demonstrated in a study during which patients receiving fentanyl were administered ritonavir, a potent CYP 3A4 inhibitor, which increased overall fentanyl exposure (AUC) by 174%.[37,38]

In addition, there is a mistaken belief that fentanyl is heavily metabolized and eliminated entirely through hepatic mechanisms.[39,40] However, <10% is excreted by hepatic mechanisms, whereas 75% of the fentanyl dose is excreted in the urine with 10%

excreted unchanged.[38] The only randomized controlled trial in ESRD patients undergoing renal transplant found a large variability in fentanyl pharmacokinetics and an inverse relationship between blood urea nitrogen (BUN) and fentanyl clearance. Patients with the highest preoperative BUN also had the lowest fentanyl clearance and the most postoperative respiratory depression requiring mechanical ventilation.[41]

Fentanyl likely is not dialyzed because of its physical-chemical characteristics: large Vd, highly protein bound, low water solubility, and high molecular weight. Based upon these characteristics, it has been assumed that fentanyl generally is safe for use in patients undergoing dialysis and has been recommended as a first-line therapy. However, although it may not be dialyzed in the traditional sense, there are reports of fentanyl being absorbed directly onto dialysis filters.[42] Transdermal fentanyl absorption across the skin is highly variable, and this is reflected in the wide range of morphine equivalents listed for each patch strength.[38] The potency of fentanyl patches also precludes its use as a first-line agent prior to initiation and dose-finding with short-acting opioids that may accumulate, complicating this transition in ESRD. Fentanyl has not been adequately studied in patients with ESRD to measure potential accumulation and the impact of drug interactions— more studies are needed before it can be recommended for routine use.

Hydromorphone

Hydromorphone has been fairly well studied in patients with ESRD and CKD. Hydromorphone undergoes phase II metabolism, yielding hydromorphone-3-glucuronide (H3G), its active metabolite. Both have been shown to accumulate in patients with ESRD.[39] In normal renal function, H3G accumulates 27 times faster than hydromorphone; both H3G and hydromorphone exposure (AUC) are nearly quadrupled in patients with severe renal dysfunction (creatinine clearance <30 mL/min).[19,43] Despite significant accumulation of H3G, there are few reports of neuroexcitation characterized by tremor, myoclonus, agitation, and cognitive dysfunction but no reports of neurotoxicity.[18]

Hydromorphone appears to be significantly removed during dialysis. One study found 40% reductions in post-dialysis concentrations of hydromorphone compared to predialysis levels.[19,28] Several factors contribute to hydromorphone being easily dialyzed, including low molecular weight, high water solubility, low protein binding, and small Vd.[19] Sudden decreases in opioid concentrations may result in withdrawal symptoms, but, unlike with many drugs that require supplemental dosing post-dialysis, this has not been studied adequately with hydromorphone. With phase II metabolism, the risk of drug interactions is low, but accumulation of both the parent drug and the active metabolite could result in opioid toxicity at standard doses. For this reason, hydromorphone should be in the "reduce dose and use with caution" category.

The package insert recommends reducing the dose by 50% in moderate renal impairment and 75% in severe renal impairment, but these dosing guidelines should be evaluated in clinical trials.[44] Clinicians continue to use hydromorphone, presumably because of available evidence for use that is sorely lacking with alternative opioids in this same population.

Oxycodone

Oxycodone has not been well studied in patients with ESRD or CKD. Oxycodone is metabolized primarily by phase I CYP450 enzymes; the predominant pathway is 3A4 N-demethylation to its major metabolite, noroxycodone, which displays weak opioid activity.[45] Oxymorphone is the minor active metabolite of oxycodone formed via 2D6 O-demethylation, but it is formed at rates 6 times slower than noroxycodone.[46] Oxycodone's affinity for the mu-opioid receptor is 4 times greater than that of noroxycodone but 40 times less than that of oxymorphone. Despite this, oxymorphone is formed in concentrations insufficient to effectively contribute to oxycodone's therapeutic effect (<10%).[46,47]

In patients with renal failure who were given oxycodone, concentrations of oxycodone and noroxycodone were increased by 50% and 20%, respectively. However, no critical accumulation of an active metabolite that produces adverse events were found.[39] Oxycodone is not highly protein bound, has higher water solubility, intermediate molecular weight, and medium Vd. There is little data to support this, but the above data suggest that it likely is dialyzable to a large extent. The minor active metabolite (oxymorphone) is produced in small amounts but has been shown to accumulate (along with the parent drug) in patients with renal failure.[19] However, one also must consider the impact of pharmacogenetics, such that an ultrarapid 2D6 metabolizer will convert oxycodone to oxymorphone more readily.[47] If this same patient were placed on a drug such as clarithromycin, a potent inhibitor of 3A4—the only remaining metabolic pathway would convert oxycodone to oxymorphone—this could lead to considerable morbidity and mortality.

Oxymorphone

Oxymorphone, the minor active metabolite of oxycodone, has 2 to 5 times higher affinity than oxycodone for the mu-opioid receptor.[48,49] Oxymorphone

undergoes extensive hepatic metabolism by phase II pathways to form the major, but inactive, metabolite oxymorphone-3-glucuronide (O3G), which accounts for roughly 38% of administered dose but achieves 90 times the concentration of its parent compound and is primarily excreted in urine. Its active metabolite is 6-hydroxy-oxymorphone, which accounts for <1% of the administered dose and is metabolized via the same pathway as the parent molecule. This decreases the likelihood that it will accumulate disproportionately in patients with ESRD.[39] Due to reduced clearance, steady-state concentrations are 40% higher in patients over age 65, and bioavailability increases by as much as 65% in severe renal dysfunction.[50,51] The extent to which oxymorphone may be extracted in dialysis is unclear, but based upon low protein binding, lower molecular weight, and high water solubility, it likely is extracted well.[51,52] No studies have evaluated the efficacy of oxymorphone in patients with ESRD or the potentially toxic effects of its inactive metabolite (O3G) after accumulation. The increased potency in the elderly and those with renal dysfunction necessitate dosage reduction, but its lack of drug interactions makes it an appealing option. More studies are required before oxymorphone can be safely recommended for use in patients with ESRD.

Tapentadol

Tapentadol is one of the least studied opioids in patients with ESRD. It is a mu-opioid receptor agonist with selective norepinephrine reuptake inhibition, which makes it particularly useful for complex pain syndromes involving a neuropathic component. Tapentadol is metabolized almost exclusively via phase II conjugation reactions yielding inactive metabolites, with less than 13% entering the CYP450 system and only 3% excreted unchanged.[53] As a result, tapentadol has a very low risk for drug interactions. Tapentadol is excreted primarily by the kidneys (99%), and studies are needed to verify that the accumulation of inactive metabolites will not result in toxicity.[54] Tapentadol's extraction ratio in dialysis is unknown, but it is likely dialyzed to some extent due to low protein binding, low molecular weight, and average water solubility, although it is widely distributed.[53-55]

At the very least, until that data exists, patients with ESRD who are receiving chronic opioid therapy should be carefully titrated. In addition, universal precautions should be employed for patients with CKD and ESRD, similar to those that are employed for patients with normal kidney function, to counter risks of opioid therapy.

Discussion

Evidence for efficacy should guide therapy, not convenience or educated guesses. Accumulation is not a contraindication for therapy in patients with ESRD, unless that accumulation results in increased adverse effects. Accumulation is particularly risky if it can potentially result in toxicity from active metabolites or drug interactions. Typically, drugs that undergo phase II metabolism through glucuronidation have fewer drug interactions because this is a high-capacity/low-affinity system.[56-59]

The common prodrugs codeine and tramadol, which were not appreciably discussed in this article, could present inherent dangers for ESRD patients because both significantly depend on 2D6 metabolism for conversion to their most active forms of morphine and O-desmethyl-tramadol (the M1 metabolite), respectively. Codeine's ultimate degradation to inactive forms is dependent on CYP3A4/ UGT2B7 (codeine to norcodeine, and morphine to corresponding 3- and 6- glucuronides). Tramadol's M1 metabolite occurs by N-demethylation to N-desmethyltramadol (M2), which is ultimately catalyzed by CYP2B6 and CYP3A4.[39,49]

The authors believe that opioids metabolized primarily through phase II mechanisms with inactive metabolites may be the most appropriate options in patients with ESRD. Unfortunately, there are no studies to provide the evidence necessary to justify this assertion.

Similarly, extraction during dialysis is not a contraindication but simply a

concern that blood levels may decrease precipitously. This would result in lack of efficacy and, in the case of opioid therapy, a potential to induce withdrawal. Numerous medications are heavily extracted during dialysis, but supplemental doses are able to quickly replace them. For example, gabapentin and pregabalin are 2 medications that are easily extracted during dialysis. In many ways they are potentially more dangerous because they are excreted entirely unchanged; when accumulated in patients with ESRD, it is the active forms of these 2 drugs that accumulate, unlike with most opioids. However, because many studies have explored the appropriate dosing of the gabapentinoids in both CKD and ESRD populations, both medications can be reduced appropriately and replaced after dialysis. Similar studies with opioids would be of enormous value in guiding pain management recommendations.

Conclusion

Evidenced-based recommendations for opioid therapy in the dialysis setting are virtually nonexistent and heretofore have been based on conjecture, with consideration given only to possible accumulation, metabolism, or the potential for dialysis extraction. Recommendations should acknowledge all facets of drug therapy, including pharmacokinetics, pharmacogenetics, clinical chemistry, and in vivo systematically guided studies, none of which are extensively available at this time. These studies are needed to develop clinical practice guidelines and ensure appropriate pain management in this unique, growing, and vulnerable population. At the very least, until that data exists, patients with ESRD who are receiving chronic opioid therapy should be carefully titrated. In addition, universal precautions should be employed for patients with CKD and ESRD, similar to those that are employed for patients with normal kidney function, to counter risks of opioid therapy. ■

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