

# Pharmacotherapeutic considerations for chronic pain in chronic kidney and end-stage renal disease

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In hemodialysis (HD) patients, the prevalence of chronic pain can be up to 92%.<sup>1</sup> A survey of HD patients found 55% reported a severe pain episode in the previous 24 hours.<sup>2</sup> Furthermore, ~75% of HD patients report inadequate pain management.<sup>2</sup> Despite these shocking statistics there is no universally accepted guideline for the treatment of pain in HD patients. Nevertheless, poorly managed pain in HD patients promulgates psychological disturbances, impaired sleep, decreased dialysis compliance, and an overall decline in quality of life.<sup>1</sup>

Providers may be hesitant to prescribe analgesics to patients on HD due to the significant differences in pharmacokinetics compared with their healthy counterparts. Pharmacokinetic variations of most drugs are generally well studied in “healthy” patients; however, physiochemical attributes in HD patients are fraught with uncertainty.<sup>3</sup>

Due to decreased renal elimination of medications and metabolites, a common assumption in patients with renal disease is that estimated renal function is the main, and sometimes only, factor to consider when making dose adjustments. Although not entirely false, other physiologic changes must be considered when selecting medications and commensurate dosing. Table 1 demonstrates the various changes that occur to absorption, volume of distribution, and elimination that must be accounted for in this patient population.

The dialysis machine itself must also be considered among the many changes that HD patients undergo when selecting pharmacotherapy. Certain characteristics impact the removal of a drug by dialysis, including molecular weight, protein binding, volume of distribution, and water solubility.<sup>9</sup> The least likely drugs to be removed by dialysis are those with large molecular weights that are highly protein bound, that have high volume of distribution, and with poor water solubility.<sup>9</sup> Given the aforementioned complexities of selecting appropriate medications for patients with chronic kidney disease (CKD), and the potential for adverse events with inappropriate dosing, it is no wonder why providers are so uncomfortable prescribing analgesic therapy to patients with advanced CKD. Nonpharmacologic approaches should be optimized and used in conjunction with any chronic pain patient. If pharmacotherapy is required for adequate pain management, opioids are frequently thought to be first-line therapy when comparing toxicities to alternatives such as nonsteroidal anti-inflammatory drugs (NSAIDs).

There are two basic scenarios a provider will encounter with the treatment of opioids in CKD patients: inheriting the established opioid patient or initiating chronic opioid

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**Table 1** Changes in pharmacokinetic parameters in patients with chronic kidney disease

Pharmacokinetic parameter	Definition	Influenced by	Examples of changes in chronic kidney disease	Impact of those changes
Absorption	A determinant of drug bioavailability, representing the amount of administered dose reaching systemic circulation	<ul style="list-style-type: none"> <li>• Gastric pH</li> <li>• Gastrointestinal motility</li> <li>• First-pass metabolism</li> </ul>	<ul style="list-style-type: none"> <li>• Increased gastric pH (conversion of high salivary urea concentrations into ammonia by gastric urease)</li> <li>• Delayed gastric emptying in patients with concomitant diabetic gastroparesis</li> <li>• Gastrointestinal edema occurring in patients with concomitant cirrhosis or congestive heart failure</li> </ul>	<ul style="list-style-type: none"> <li>• Impacts the time required to reach maximal plasma concentration</li> <li>• Decreases maximum plasma concentration</li> </ul>
Volume of distribution	The extent of drug distribution throughout the body; especially the amount of drug distributed into extravascular tissues	<ul style="list-style-type: none"> <li>• Plasma protein binding</li> <li>• Tissue binding</li> <li>• Total body water</li> </ul>	<ul style="list-style-type: none"> <li>• Hypoalbuminemia</li> <li>• Increased concentrations of alpha-1-acid glycoprotein</li> <li>• Fluid retention, increasing total body water</li> </ul>	<ul style="list-style-type: none"> <li>• Impacts concentration of free drug available to bind to receptors</li> <li>• Increased volume of distribution for hydrophilic drugs</li> </ul>
Elimination	The extent of drug clearance either renally or nonrenally	<ul style="list-style-type: none"> <li>• Renal: number of functioning nephrons, renal blood flow, glomerular filtration rate, and tubular secretion</li> <li>• Nonrenal: hepatic and extrahepatic metabolism (cytochrome P450, UGT, and NAT enzymes), and transport pathways</li> </ul>	<p>Renal</p> <ul style="list-style-type: none"> <li>• Decreased amount of functioning nephrons</li> <li>• Reduced renal blood flow</li> <li>• Reduced glomerular filtration rate</li> <li>• Reduced tubular secretion</li> </ul> <p>Nonrenal</p> <ul style="list-style-type: none"> <li>• Decreased activity of cytochrome P450, UGT, and NAT</li> <li>• Cytochrome P450 3A4 downregulation via direct inhibition by uremic toxins</li> </ul>	<ul style="list-style-type: none"> <li>• Diminished overall elimination leading to overall drug accumulation</li> </ul>

**Note:** Data from Nolin,<sup>3</sup> Gabardi and Abramson,<sup>4</sup> Nolin,<sup>5</sup> Reidenberg and Drayer,<sup>6</sup> St Peter et al,<sup>7</sup> and Yeung et al.<sup>8</sup>

**Abbreviations:** UGT, UDP-glucuronosyltransferase; NAT, N-acetyltransferase.

therapy. Inherited opioid patients should be assessed for risks versus benefits, with an “escape route” in mind if improvement is suboptimal or aberrancy is observed and confirmed.

Due to the risk of respiratory depression and abuse associated with opioids, patients need to be thoroughly evaluated before starting therapy and closely monitored for the duration of treatment. Therapeutic monitoring is complicated by little to no urine output that precludes the ability to perform urine drug monitoring. This should not allow the patient a “free pass” to avoid opioid compliance monitoring. Instead obtaining random serum blood levels should become the standard of care. The Risk Index for Overdose or Serious Opioid-Induced Respiratory Depression (RIOSORD) could be used to assess patients for opioid-induced respiratory depression and qualify these patients for “take home naloxone.”<sup>10</sup>

An obvious barrier for prescribing opioids in this population is the lack of guidance from major pain management organizations, for nearly all aspects of pain management in patients with CKD, which is directly attributable to the lack of evidence-based treatment guidelines.<sup>9,11</sup> Recommendations published in 2007 by Murtagh et al suggested fentanyl, methadone, and tramadol as opioids to be used in advanced CKD patients managed without dialysis.<sup>11</sup> Although these opioids have favorable pharmacokinetic profiles when used in those with renal dysfunction, they still carry their own

heightened risks.<sup>9</sup> Methadone can prolong the QTc interval and increase risk of torsades de pointes; fentanyl has extremely variable absorption characteristics, which lead to variable serum concentrations that are not easily controlled; and both tramadol and methadone are ubiquitously fraught with toxicities and polymorphic variabilities associated with phase I cytochrome metabolism.<sup>9</sup>

Atkinson et al thoroughly reviewed literature on commonly used opioids in the end-stage renal disease (ESRD) setting and ultimately hypothesized that opioids primarily undergoing hepatic phase II metabolism that yields inactive metabolites (such as tapentadol) are highly protein bound, have larger molecular weights, and have higher lipophilicity (to avoid being dialyzed), should be considered first in this population of patients.<sup>9</sup>

NSAIDs have well-documented renal toxicities that can cause acute kidney injury and influence progression of CKD.<sup>12–14</sup> They have been shown to increase sodium retention and edema, cause hyperkalemia through decreased delivery of potassium to the distal tubule, cause acute renal failure through disruption of the renal hemodynamic balance, cause nephrotic syndrome by increasing lymphocyte recruitment and activation, and cause acute and chronic renal papillary necrosis through direct toxicity.<sup>12,14,15</sup> Nonrenal toxicities include increased blood pressure, decreased antihypertensive

effects of several medications, and increased gastrointestinal (GI) bleed risk.<sup>12,14,16</sup>

The totality of these toxicities led the American Society of Nephrology to recommend that all patients with hypertension, heart failure, or CKD of all causes avoid NSAID use, in their “Choosing Wisely” campaign published in 2012.<sup>14</sup> This recommendation should further be extended to patients on dialysis. Residual renal function has proven to be important even after commencement of dialysis, because of its implication on dialysis adequacy.<sup>17</sup> NSAIDs have been shown to negatively impact residual renal function, and dialysis patients are more susceptible to fluid and electrolyte changes, have blood pressures that are more difficult to control, and are at higher risk for GI bleeds; thus dialysis patients may be at an even greater risk of harm from NSAID use than the general population.<sup>12,14,16,17</sup>

Acetaminophen is most commonly used to alleviate mild pain symptoms such as headaches, toothaches, or backaches. The mechanism in which acetaminophen provides analgesia remains unclear; however, it is thought to inhibit prostaglandin synthesis in the hypothalamus and possibly the spinal cord, with minimal effects on the kidneys.<sup>12</sup> The majority of data supports its renal safety when used in lower, intermittent doses, and only few cases have reported acute renal toxicity after ingestion of larger doses.<sup>12,18</sup> Chronic high-dose acetaminophen may cause renal function decline (decrease in glomerular filtration rate of at least 30 mL/min) and has been reported in women who consumed >3,000 g of acetaminophen over 11 years and has also been associated with tubular necrosis with long-term use (OR: 2.04; 95% CI: 1.28–3.24).<sup>18</sup>

Antidepressants that inhibit the reuptake of serotonin (5-HT) and norepinephrine (NE) have been shown to be beneficial in treating neuropathic pain, with NE as the primary analgesic mediator.<sup>19</sup> Tricyclic antidepressants (TCAs) have traditionally been considered first line with regard to treating neuropathic pain; however, these are relatively “sloppy” drugs, as they inhibit histamine, alpha-1 adrenergic, and muscarinic receptors in addition to 5-HT and NE transporters, which may lead to anticholinergic and other undesired side effects.<sup>20</sup> These effects are even more pronounced in elderly patients who comprise the majority of the renal disease population, and in whom TCAs should not be used based on Beer’s Criteria.<sup>20,21</sup> Therefore, the selective serotonin-NE reuptake inhibitors (SNRIs) represent a safer option compared to TCAs for the treatment of neuropathic pain.

As a whole, all SNRIs are renally cleared and have associated dosing adjustments in CKD; however, it is only

recommended that duloxetine should be avoided in patients with creatinine clearance <30 mL/min, primarily due to an ~2-fold higher area under the curve in those with ESRD.<sup>22,23</sup> Venlafaxine is primarily metabolized by CYP2D6 into its active metabolite O-desmethyldesvenlafaxine, and to a lesser extent by CYP3A4.<sup>24</sup> This elevates the risk for drug interactions with CYP2D6 inhibitors/inducers and variable efficacy in those with 2D6 polymorphisms, but both the parent and active compounds are cleared renally and have shown to have prolonged half-lives in those with renal impairment.<sup>22,24</sup> Desvenlafaxine, which is the commercially available O-desmethyldesvenlafaxine, has also demonstrated a prolonged half-life in patients with renal impairment, as ~45% of it is excreted unchanged in urine.<sup>22,25</sup> Fortunately, this is primarily metabolized by the UGT system of enzymes, and only a small percent by CYP3A4, decreasing the likelihood of drug–drug interactions.<sup>25</sup>

Both milnacipran and levomilnacipran, two additional SNRIs, have also shown a prolonged half-life in patients with altered renal function, as 55% of milnacipran and 58% of levomilnacipran are excreted unchanged renally.<sup>22,26,27</sup> Both medications are primarily metabolized through conjugation, avoiding the Cytochrome P450 system, and only levomilnacipran yields an active metabolite (N-desethyl levomilnacipran) that is excreted in the urine.<sup>26,27</sup>

Anticonvulsants play a role in alleviating neuropathic pain largely through the mediation of spontaneous electrical discharge. The two most commonly used are gabapentin and pregabalin, which bind to the alpha-2-delta subunit of voltage-gated calcium channels, resulting in an increase of gamma-aminobutyric acid (GABA) without direct activity on GABA itself.<sup>28,29</sup> The gabapentinoids are generally well tolerated with a relatively low side effect profile and few drug–drug interactions. They both are eliminated renally and excreted largely unchanged. Dosing in CKD is reduced based on creatinine clearance to avoid dangerous accumulation.<sup>30,31</sup> Once a patient with ESRD begins HD, supplemental doses are recommended following each dialysis session as both gabapentin and pregabalin are readily dialyzed.

Other anticonvulsants commonly used for neuropathic pain include carbamazepine, oxcarbazepine, valproic acid, lamotrigine, and topiramate. Carbamazepine, a voltage-gated sodium channel inhibitor, is the only anticonvulsant that has a labeled indication for trigeminal neuralgia.<sup>32</sup> The high side effect profile and required laboratory monitoring make it a more burdensome therapeutic option.<sup>29</sup> Carbamazepine is highly protein bound, therefore, little is removed during HD.<sup>32</sup> CYP3A4 is responsible for metabolism to the

active metabolite carbamazepine-10,11-epoxide.<sup>32</sup> Carbamazepine is also a potent CYP450 inducer; therefore, caution must be exercised for many drug–drug interactions.<sup>33</sup> Concomitant use of valproic acid with carbamazepine can cause a dangerous elevation in the serum 10,11-epoxide levels.<sup>34</sup> Serum elevation of this active metabolite could be missed if only monitoring for plasma levels of the parent drug. Oxcarbazepine the keto-analog of carbamazepine also inhibits sodium channels, can be used as an alternative when carbamazepine is contraindicated, not tolerated, or off label for refractory trigeminal neuralgia.<sup>24,29,33</sup> As the keto-analog, oxcarbazepine is a safer option as it does not involve the CYP system and is not metabolized to the 10,11-epoxide.<sup>35</sup> As a result, it does not have as many drug–drug interactions nor require frequent monitoring. Package labeling recommends initiating oxcarbazepine at half the normal starting dose for a CrCl <30 mL/min; however, there are no specific HD recommendations.<sup>36</sup>

With the high prevalence of pain in CKD patients undergoing HD, providers must not be idle in the care of these patients, with resultant poor pain management outcomes. Undoubtedly, pain management in this population is complicated and requires the assessment of many components including alterations in pharmacokinetics, specific drug properties, comorbid disease states, physical impact of dialysis on the drug administered, and drug–drug interactions. Utilization of drugs metabolized through hepatic phase II metabolism may offer a much safer option; however, clinical trials are lacking. In the absence of evidence-based guidelines, one must use the known pharmacology to design the safest and most efficacious patient-centered treatment plan.

## Disclosure

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