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Pharmacotherapeutic Management of Neuropathic Pain in End-Stage Renal Disease

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Abstract
Background: Chronic noncancer pain is pervasive throughout the general patient population, transcending all chronic disease states. Patients with end-stage renal disease (ESRD) present a complicated population for which medication management requires careful consideration of the pathogenesis of ESRD and intimate knowledge of pharmacology. The origin of pain must also guide treatment options. As such, the presentation of neuropathic pain in ESRD can present a challenging case. The authors aim to provide a review of available classes of medications and considerations for the treatment of neuropathic pain in ESRD. ***Summary:*** In this narrative review, the authors discuss important strategies and considerations for the treatment of neuropathic pain in ESRD, including the pathogenesis of neuropathic pain, physiological changes for consideration in ESRD patients, and disease-specific consideration for medication selection. Pharmacotherapeutic classes discussed include: anticonvulsants, antiarrhythmics, antidepressants, topicals, and opioids. ***Key Message:*** Pain management in ESRD patients requires careful assessment of drug-specific properties, accumulation, metabolism (presence of active/toxic metabolites), extraction by dialysis, and presence of drug – drug interactions. In the absence of pharmacokinetic data in ESRD patients, therapeutic window and potential risks should be factored in the decision making along with continued monitoring throughout therapy.

Introduction

Chronic noncancer pain affects millions of people daily. The International Association for the Study of Pain classifies chronic pain into 3 categories including nociceptive, neuropathic, and a mixture of the 2 [1, 2]. Specifically, neuropathic pain, including damage or disease to the somatosensory system, has an estimated prevalence between 6.9 and 10% of the general population and has variable causality including nerve-damaging disease states and iatrogenic origin [2, 3]. Patients with end-stage renal disease (ESRD) comprise an important cohort of persons requiring long-term pain management, as this group has a reported chronic pain prevalence of up to

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Table 1. Symptoms of neuropathic pain [64]

Symptom	Description
Dysthesia	Unpleasant sensation
Paresthesia	Abnormal sensation (burning, trickling, tingling, numbness) of the skin
Allodynia	Painful response to a nonpainful stimulus (e.g., touch)
Hyperalgesia	Increased sensitivity to pain
Hyperpathia	Exaggerated response to painful stimuli

92%; of which approximately 35% are of neuropathic origin, and about 90% prevalence of peripheral neuropathy in those on hemodialysis (HD) [3–6]. Unfortunately, due to significant physiochemical changes that occur in patients with ESRD, lack of evidence-based pharmacologic treatment protocols, and inadequate education, this population's pain is often extremely difficult to manage. Moreover, the presence of chronic pain is an important contributor to the overall poor quality of life in patients with ESRD, as these patients report greater levels of depression. Additionally, the presence of chronic pain increases overall probability of hospitalization or death. This review identifies select pathophysiological changes and evaluates literature that has examined neuropathic pain modalities in this population [2].

Neuropathic Pain

Neuropathic pain involves damage to the somatosensory nervous system, and specifically a lesion to afferent pathways must be present for the syndrome to develop [2]. These lesions can cause a cascade of neurogenic pathologies including spontaneous ectopic nerve impulse generation, neuronal membrane excitability caused by upregulation of voltage-gated sodium channels, ectopic activity resulting in development of central sensitization, and enhanced release of excitatory amino acids and neuropeptides throughout peripheral afferent fibers [2, 7–10]. Those excitatory amino acids lead to excitation of several receptors including N-methyl-D-aspartate and alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic. These varying pathologies evolve to diverse signs and symptoms of neuropathic pain, including common descriptors such as burning, numbness, tingling, and electrical-type pain, medically differentiated as dysesthesia, parasthesia, allodynia, hyperalgesia, and hyperpathia, all of which are defined in Table 1. Importantly, neuropathic pain differs significantly from nociceptive pain, which refers to direct tissue injury (somatic or visceral). A careful differential diagnosis can help guide targeted and individualized pharmacotherapeutic selection, as many of these pain pathologies can overlap in patients with ESRD and may prove difficult to isolate a singular cause.

General causes of neuropathic pain variously include diabetes, traumatic nerve injuries, autoimmune disorders, genetic disorders, amyloid depositions, and medications [2]. Although diabetes is the leading cause of ESRD worldwide and attributed to neuropathic pain in this population, symptoms may be compounded due to neurological changes that occur directly from kidney failure itself [11, 12]. Central nervous system (CNS) alterations that occur in this population mainly include cognitive impairment, dementia, and stroke which often are attributed to CNS vascular injury, oxidative stress, and buildup of uremic toxins [11, 12]. Peripheral manifestations mainly include peripheral neuropathy, which can be caused by an accumulation of uremic toxins (known as uremic neuropathy) due to their generalized nature of nerve conduction slowing effects, as well as hyperkalemia [11]. Although this review aims to focus on neuropathic pain within ESRD patients, nociceptive pain specific to ESRD can be numerous as well and include tissue damage resulting from peripheral arterial disease, bone pain from severe secondary hyperparathyroidism, or ischemic pain resulting from the presence of an arteriovenous fistula.

Physiological Changes in the ESRD Population

Although there is an abundance of pain management modalities that may be used in the treatment of neuropathic pain, physicochemical changes that occur in the ESRD population can accentuate risks of certain medications and classes of medications all of which elevate the challenge of pharmacotherapeutic considerations. Moreover, this population has been minimally studied in medical clinical trials, thus pain management is generally based on experience with consideration to pharmacokinetic and pharmacodynamic changes that occur in renal failure. Table 2 highlights alterations in pharmacokinetic properties in this setting.

Perhaps the most important manifestation of renal failure when dosing analgesics is decreased overall renal elimination of parent medications and their metabolites, in medications that require renal elimination. While this is an extremely important consideration that will impact the dosing of many medications, there are many other

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Table 2. Changes in pharmacokinetic parameters in patients with chronic kidney disease [14–18, 20]

Pharmacokinetic parameter	Definition	Influenced by	Examples of changes in chronic kidney disease	Impact of those changes
Absorption	A determinant of drug bio-availability, representing the amount of administered dose reaching systemic circulation	– Gastric pH – Gastrointestinal motility – First-pass metabolism	– Increased gastric pH (conversion of high salivary urea concentrations into ammonia by gastric urease) – Delayed gastric emptying in patients with concomitant diabetic gastroparesis – Gastrointestinal edema occurring in patients with concomitant cirrhosis or congestive heart failure	– Impacts the time required to reach maximal plasma concentration – Decreases maximum plasma concentration
Volume of distribution	The extent of drug distribution throughout the body; especially the amount of drug distributed into extravascular tissues	– Plasma protein binding – Tissue binding – Total body water	– Hypoalbuminemia – Increased concentrations of alpha-1-acid glycoprotein – Fluid retention, increasing total body water	– Impacts concentration of free drug available to bind to receptors – Increased volume of distribution for hydrophilic drugs
Elimination	The extent of drug clearance either renally or nonrenally	– Renal: number of functioning nephrons, renal blood flow, glomerular filtration rate, and tubular secretion – Nonrenal: hepatic and extra-hepatic metabolism (cytochrome P450, UGT, and NAT enzymes), and transport pathways	*Renal* – Decreased amount of functioning nephrons – Reduced renal blood flow – Reduced glomerular filtration rate – Reduced tubular secretion *Nonrenal* – Decreased activity of cytochrome P450, UGT, and NAT – Cytochrome P450 3A4 downregulation via direct inhibition by uremic toxins	– Diminished overall elimination leading to overall drug accumulation

Created by Bettinger JJ, Mathew RO, Wegrzyn EL, Fudin J. *Updated November 2016:* With permission, Dr. Jeffrey Fudin http://paindr.com/wp-content/uploads/2018/02/2016Nov-Changes-in-pharmacokinetic-parameters-in-patients-with-CKD-1.pdf. Data compiled from [14–18, 20]. UGT, UDP-glucuronosyltransferase; NAT, N-acetyltransferase.

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Table 3. Comparison of drug therapy for national and international neuropathic pain guidelines [65–68]

Guidelines:	CPS [65] updated as of November 2014	NeuPSIG/IASP [66] updated as of January 2015	NICE [67] updated as of February 2017	EFNS [68] updated as of April 2010		
Trigeminal neuralgia	First-line: carbamazepine		First-line: carbamazepine Second-line: seek specialist	First-line: carbamazepine, oxcarbazepine Second-line: surgery		
Type of neuropathic pain	All neuropathic pain	All neuropathic pain	All neuropathic pain	Central neuropathic pain	Diabetic neuropathy	Post-herpetic neuralgia
First-line	Gabapentin Pregabalin Duloxetine Venlafaxine TCAs	Gabapentin[A] Pregabalin Duloxetine Venlafaxine TCAs	Gabapentin Pregabalin Duloxetine Amitriptyline	Gabapentin Pregabalin Amitriptyline TCAs	Gabapentin Pregabalin Duloxetine Venlafaxine ER TCAs	Gabapentin Pregabalin TCAs Lidocaine plasters[B]
Second-line	Tramadol CR opioids: Morphine Oxycodone Fentanyl Hydromorphone	Tramadol Capsaicin 8% patches* Lidocaine patches*	If the initial treatment is not effective or is not tolerated, offer one of the remaining 3 drugs above ↑, and consider switching again if the second and third drugs tried are also not effective or not tolerated	Tramadol Opioids	Tramadol[C]	Opioids: Oxycodone Morphine Methadone Topical capsaicin
Third-line	Cannabinoids	Strong opioids: Oxycodone Morphine Botulinum toxin A*	Tramadol: acute only Topical capsaicin*	Opioids	Opioids: Oxycodone	
Fourth-line/last-line	Methadone Tapentadol Lamotrigine Topiramate Valproic acid Citalopram Escitalopram Paroxetine Lacosamide Topical capsaicin Topical lidocaine[D] Botulinum toxin		Specialist setting: Cannabis sativa extract Lacosamide Lamotrigine Levetiracetam Morphine Oxcarbazepine Topiramate Tramadol: long term Venlafaxine	Lamotrigine[E] Cannabinoids[F]		

* For peripheral neuropathy; A, gabapentin immediate release, extended release, and enacarbil; B, topical lidocaine with its excellent tolerability may be considered first line in the elderly, especially if there are concerns regarding the CNS side effects of oral medications; C, tramadol may be considered first line in patients with acute exacerbations of pain especially for the tramadol/acetaminophen combination or in patients with predominant coexisting non-neuropathic pain; D, topical lidocaine may be second-line for postherpetic neuralgia; E, lamotrigine may be considered in CPSP or SCI pain with incomplete cord lesion and brush-induced allodynia; F, for multiple sclerosis. We acknowledge the contribution of Caroline Breen and Kangni Wang in compiling this table in collaboration with authors ELW and JF.

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Tramadol for as needed use is often difficult to tolerate due to serotonin activity. Tapentadol was approved in Europe in 2011[3], EFNS guidelines were last updated in April 2010.

Trigeminal Neuralgia: The reason that we separated out TM is because the EFNS guidelines divides up neuropathy by central neuropathic pain, diabetic neuropathy, post herpetic neuralgia and trigeminal neuralgia. All other guidelines list "all neuropathic pain" indication.

CPSP, central post-stroke pain; CR, controlled release; ER, extended release; SCI, spinal cord injury; TCAs, tricyclic antidepressants; CPS, Canadian Pain Society; NICE, National Institute for Health and Care Excellence; EFNS, European Federation of Neurological Societies; IASP, International Association for the Study of Pain; NeuPSIG, Neuropathic Pain Special Interest Group; CNS, central nervous system.

changes, which may have a broader effect on drug action, that warrant consideration in this population.

As outlined in Table 2, renal failure can lead to increases in gastric pH, decreases in gastric motility, and changes in first-pass metabolism which all may impact overall absorption (positively or negatively), time required to reach maximum plasma concentration and overall plasma concentration and area under the concentration curve (AUC) [13, 14]. ESRD is also associated with hypoalbuminemia, increases in concentration of alpha-1-acid glycoprotein, and increases in fluid retention which may all impact concentration of free drug available to bind with receptors and cause increased volume of distribution for hydrophilic drugs [14–17].

With renal failure, there is a progressive decrease in the amount of functioning nephrons, reduced renal blood flow, reduced glomerular filtration rate, and reduced tubular secretion, all of which decrease overall renal drug elimination and can result in accumulation of parent drug and metabolites [14, 17]. There have also been reports of nonrenal elimination disturbances associated with kidney failure, including decreased activity of cytochrome P450, UDP-glucuronosyltransferase, and N-acetyltransferase enzymes which could theoretically impact hepatic metabolism of medications [18–20]. The dialysis apparatus itself can significantly impact drug concentrations. Specific chemical characteristics of drugs that increase their removal by dialysis include lower molecular weight, minimal protein binding, lower volumes of distribution, and higher water solubilities [21].

Treatment of Neuropathic Pain

Pharmacotherapeutic options for the treatment of neuropathic pain are as varied as the pathogenesis. For instance, neuropathic pain include may include trigeminal neuralgia, diabetic neuropathy, central post stroke, or combined neuropathies [1–3]. This is evident when comparing various international guidelines for the treatment of neuropathic pain (Table 3). Three main therapeutic classes are widely accepted as first-line options for the treatment of chronic pain: anticonvulsants, serotonin-norepinephrine reuptake inhibitors (SNRIs), and tricyclic antidepressants (TCAs). The anticonvulsants are further subdivided by varied pharmacologic mechanisms, with gabapentinoids acting as stereotypical first-line agents, especially when considering that they are excreted unchanged without active or inactive metabolites.

Traditional opioid agonists are not generally effective in the chronic treatment of neuropathic pain; however, there are several opioids with unique mechanisms that should be considered when all other non-opioid therapies fail. It is also particularly prudent to keep these select opioids in mind for use in patients with ESRD as concomitant comorbid disease states or drug – drug interactions could present contraindications to non-opioid first-line therapies. The unique attributes of these opioids with neuropathic benefits will be discussed later in this section.

Select Anticonvulsants

Gabapentinoids

Gabapentinioids, gabapentin and pregabalin, are anticonvulsants commonly used in diabetic peripheral neuropathy and other neuropathic pain syndromes [22]. Both agents inhibit alpha-2-delta ($\alpha_2\delta$) subunit of N-type voltage-gated calcium channels in the CNS, thereby reducing excitatory neurotransmitter release [23]. Despite sharing the same mechanism of action, there are key pharmacologic differences between the 2 agents. Gabapentin exhibits zero-order saturable absorption, where the bioavailability decreases as the dose increases [24]. Pregabalin has linear absorption, and therefore, more predictable pharmacokinetics. Pregabalin has 6 times higher binding affinity for the $\alpha_2\delta$ receptor than gabapentin.

Gabapentin and pregabalin do not undergo hepatic metabolism and are primarily eliminated unchanged in the urine [24, 25]. Both agents require renal dose adjustments in ESRD due to potential for accumulation. The recommended dosing in ESRD for gabapentin is 300 mg and for pregabalin is 75 mg, administered once a day [25]. The aforementioned dosing recommendations are based on population-based pharmacokinetic data and not on actual clinical trials. HD removes approximately 35% of gabapentin and 50–60% of pregabalin and supplemental doses are generally recommended post-HD [25]. One pharmacokinetic advantage is the absence of hepatic cytochrome P450 related drug – drug interactions given both medications do not undergo hepatic metabolism.

Adverse effects of particular concern in ESRD patients include sedation, cognitive impairment, and peripheral edema considering comorbid uremia and fluid retention in this population [22, 23]. Myoclonus has been documented in ESRD patients who were taking higher than recommended doses and resolved upon discontinuation. In patients who fail to respond to the maximum recommended renal dosing of gabapentin (assuming tolerability), a trial of pregabalin may be considered due to its

stronger binding affinity for the α2δ receptor. In one study, substitution of gabapentin with pregabalin resulted in 25% additional pain relief in patients with normal renal function [25, 26].

Carbamazepine

Carbamazepine inhibits voltage-gated sodium channels and is the only anticonvulsant with a labeled indication for trigeminal neuralgia [22]. Carbmazepine is a potent enzyme inducer of various CYP450 and p-glycoprotein and is subject to many drug – drug interactions. Since CYP3A4 effects common medications, there is significant concern for drug – drug interactions that lower blood levels of the substrate drug. This is particularly concerning for patients receiving ant-retrovirals and antibiotics due to increased drug resistance, cardiac medications, and many others. Carbamazepine induces its own metabolism where its clearance increases, half-life shortens, and serum levels decrease within 1–3 weeks of initiation. For instance, the half-life for carbamazepine ranges from 10 to 20 h but is decreased by auto-induction to 4–12 h [22]. The active metabolite carbamazepine 10,11-epoxide is produced by CYP3A4 and is thought to account for hepatotoxicity. Carbamazepine promotes secretion of antidiuretic hormone, increasing thirst and water retention, which worsen coexisting fluid overload in ESRD patients [22].

There are no dose adjustments required in ESRD patients as only 1–3% of the drug is excreted unchanged in the urine [22, 27]. Therapeutic drug monitoring is employed for efficacy and safety for epilepsy and mania, an off-label indication, but there are no defined targets for neuropathic pain. Therapeutic levels for epilepsy are 4–12 μg/mL and for mania are 8–12 μg/mL and concentrations above 15 μg/mL are considered toxic [22, 27]. Close monitoring of carbamazepine and the 10,11 epoxide should be employed to mitigate toxicity.

Oxcarbazepine

Oxcarbazepine is a keto-analogue of carbamazepine that also inhibits voltage-gated sodium channels [22]. Oxcarbazepine undergoes rapid reduction to the active metabolite 10-monohydroxy metabolite (MHD). Oxcarbazepine is a weak inducer of CYP3A4 but does not affect other CYP450 enzymes nor induce its own metabolism [22, 28]. Therefore, it has far lower drug – drug interaction potential than carbamazepine.

Oxcarbazepine is primarily eliminated in the urine, 1% as unchanged drug and 27% as the active metabolite MHD [22, 28]. The AUC of MHD is 2–2.5 fold higher in patients with ESRD compared to those with normal renal function. The package insert recommends oxcarbazepine is initiated at 50% of the recommended dose in patients with CrCl <30 mL/min [28]. Furthermore, the immediate release formulation is recommended over the extended release in patients with ESRD [28].

Oxcarbazepine is associated with lower risk of hepatotoxicity than carbamazepine as it does not produce a 10,11 epoxide metabolite [22]. Hepatotoxicity reports with oxcarbazepine were immunologic, manifesting as drug reaction with eosinophilia and systemic symptoms syndrome rather than direct hepatic injury [29]. While oxcarabazepine is associated with lower drug – drug interactions and less hepatoxicity that carbamazepine, the incidences of SIADH and hyponatermia are more common with oxcarbazepine [30].

Valproic Acid

Valproic acid inhibits voltage-gated sodium channels and increases gamma-aminobutyric acid levels [22]. Clearance of free valproic acid is reduced by 27% in patients with CrCl <10 mL/min; however, HD removes 15–22% of valproic acid [31]. The package insert recommends that dosage adjustments are not necessary in patients with renal failure [30]. Valproic acid is highly protein bound (90%) where reduced protein binding in ESRD patients may increase free levels, thereby increasing risk for toxicity. Therefore, serum drug monitoring in ESRD patients may be misleading. Patients should be monitored closely for adverse effects and complications. Some adverse effects that may warrant discontinuation include hepatotoxicity, pancreatitis, significant sedation or mental status alterations, ataxia, uncontrolled tremors, or other adverse effects intolerable by the patient. Hyperammonemia has been reported with valproic acid and has been linked to hyperammonemic encephalopathy. In patients who develop unexplained changes in mental status, serum ammonia should be measured, and if elevated, valproic acid should be discontinued [30]. Of important note, the concomitant use of valproic acid with carbamazepine can increase concentrations of the carbamazepine 10,11 epoxide, thereby increasing risk for hepatotoxicity [22, 30].

Topiramate

Topiramate is a sodium channel inhibitor with mild inhibition of carbonic anhydrase [22]. Topiramate is 15–41% protein bound and is predominantly excreted unchanged in the urine (70%) [32]. The typical dosing range for topiramate is 200–800 mg/day in normal renal func-

tion. In patient with CrCl <70 mL/min, the manufacturer recommends 50% dose reduction; however, there are no specific recommendations for ESRD [32]. HD removes 50% of topiramate, and a supplemental dose of 50% of the daily dose is recommended after HD session [22, 32]. The most common adverse effects include paresthesia, weight loss, taste perversion, somnolence, psychomotor slowing, memory impairment, and difficulty with concentration/attention. Topiramate has been associated with acute myopia associated with secondary angle closure glaucoma with symptoms occurring within 1 month of initiation. In patients with glaucoma, topiramate should be avoided. Weight loss may be an appealing (adverse) effect in overweight or obese patients with neuropathic pain.

Select Antidepressants

As identified in the various guidelines above, antidepressants that inhibit the reuptake of serotonin (5-HT) and norepinephrine (NE) have shown to be effective in treating neuropathic pain; with NE being the primary analgesic mediator [33]. The 2 most frequently used classes of antidepressants in neuropathic pain include TCAs and selective SNRIs.

TCAs are the more traditional class that has historically been regarded as first line with regard to neuropathic pain due to the wealth of efficacy data associated with their use. However, the major drawback to their use is related to their relatively complex pharmacology lending to a significant toxic profile. The mechanism of action includes inhibition of histamine, alpha-1 adrenergic, and muscarinic receptors in addition to their effects on 5-HT and NE [34]. This nonselectiveness increases their propensity to cause anticholinergic, cardiac, and other undesired effects, which are even more pronounced in the elderly population in whom TCAs are not recommended based on Beer's Criteria [34, 35]. The elderly also comprise the majority of the renal disease population; therefore, SNRIs generally represent a safer option for these patients as they are more selective for 5-HT and NE reuptake transporters.

Although all SNRIs are renally cleared to a degree and all have dosing adjustments for renal impairment, duloxetine is the only one with recommendations to be avoided if creatinine clearance is <30 mL/min [36, 37]. Lobo et al. [36] specifically found that the AUC was about 2-fold higher in subjects with ESRD compared to those with normal renal function after ingestion of duloxetine. Venlafaxine is primarily metabolized through O-demethylation via CYP2D6 into its active metabolite O-desmethylvenlafaxine and to a lesser extent via CYP3A4 [38, 39]. Although this subjects it to drug – drug interactions with CYP2D6 inhibitors/inducers and pharmacogenomic variability, <5% of venlafaxine and about 30% of O-desmethylvenlafaxine are excreted renally [38]. Despite this, the half-life of both venlafaxine and O-desmethylvenlafaxine has shown to be significantly prolonged in those with renal impairment and in those receiving dialysis [38]. Desvenlafaxine, the commercially available O-desmethyldesvenlafaxine metabolite, is about 45% excreted unchanged in the urine and about 55% metabolized through phase II glucuronidation via UDP-glucuronosyltransferase enzymes [40, 41]. This has also shown to have a prolonged half-life in those with renal impairment [37, 40].

Two lesser utilized SNRIs, milnacipran and levomilnacipran, are excreted renally by some degree, as about 55% of milnacipran and 58% of levomilnacipran are found unchanged in the urine [42, 43]. Both have also shown to accumulate in those with renal impairment. Milnacipran's half-life in those with renal impairment was found to be about 3 times that of those with normal kidney function [42]. Levomilnacipran has shown to have significantly increased Cmax and AUC, as well as have a prolonged half-life in those with renal insufficiency [43]. One benefit of these, however, is that they are metabolized mainly through glucuronidation via phase II metabolites lessening their risk of drug – drug interactions.

Antiarrhythmic Drugs

Antiarrhythmic drugs with proposed analgesic effects are sodium channel blockers, also known as Class I antiarrhythmic drugs according to Vaughan-Williams classification scheme [44]. These drugs act similar to local anesthetics that inhibit sodium influx (e.g., lidocaine, bupivacaine), and subsequently, block nerve conduction. In this case, these antiarrhythmic drugs are administered systemically with the exception of lidocaine. Lidocaine is available in parenteral and topical formulations and demonstrated efficacy in postherpetic neuropathy and DPN. Mexiletine is an oral lidocaine analogue that was found to be effective in DPN [45]. The efficacy of flecainide (Class Ic) in neuropathic pain has been reported [46]. Mexiletine requires renal dose adjustments, whereas flecainide requires 50% reduction in patients with CrCl <35 mL/min, but no recommendations exist for ESRD patients [47, 48]. Approximately 38–42% of flecainide is eliminated unchanged in the urine, and it is not removed by HD, which makes its pharmacokinetics less predictable in ESRD patients [49]. In our experience, prescribers are of-

ten concerned about initiating antiarrhythmic medications due to their potential proarrhythmic effects. However, other therapies including TCAs and venlafaxine also carry this risk.

Topicals

Topical agents have the potential to deliver the medication to localized area while minimizing systemic exposure [50]. The presence of vascular and cutaneous calcifications in ESRD may interfere with their absorption, and thus hinder their efficacy. However, this will vary among patients and assessing for efficacy will be the most practical approach. Available topical medications for neuropathy include capsaicin (Zostrix) and lidocaine 5% patches (Lidoderm). Capsaicin binds to transient receptor potential cation channel subfamily V member 1 and depletes substance P in the peripheral sensory neurons, which produces its analgesic effect [50]. Lidocaine is a local anesthetic, discussed above, available in cream, ointment, liquid, and patch formulations [44, 50]. Clonidine is α2-adenergic receptor agonist that was originally approved for hypertension. Alpha-2 receptors are also present on nociceptors in the epidermis, and when activated, can downregulate the excitability of the nociceptors [51]. Topical clonidine 0.1% has demonstrated efficacy in treatment of diabetic neuropathy [52]. They are not commercially available topical clonidine product at the time of writing this manuscript, and it can be obtained through compounding pharmacies. However, topical clonidine gel is currently in the pipeline [52].

Opioids

As previously mentioned, opioids are not first line for the treatment of neuropathic pain but can be considered when first-line agents fail, such adjuvants carry a higher risk than opioids, or there are clear medical contraindications to their use. Traditional mu-opioid agonists are not generally beneficial for the long-term treatment of neuropathic pain; therefore, this section will focus on discussing the 4 opioids with unique mechanisms for reducing neuropathic pain: tramadol, tapentadol, methadone, and levorphanol.

Tramadol

At 6,000 times less the binding affinity for the mu-opioid receptor, compared to morphine, tramadol exhibits weak opioid activity [53]. In addition, however, it also inhibits the reuptake of serotonin and NE similar to SNRIs and TCAs discussed earlier. Tramadol relies heavily on phase I metabolism, notably CYP2D6 for metabolism to O-desmethyl-tramadol (M1) an active metabolite, and for this reason can be considered a prodrug [54]. While tramadol has been recommended by some for individuals with CKD, the high impact of polymorphic variabilities makes it a less than desirable option due to risk for accumulation of the M1 metabolite. This is particularly important to keep in mind as only 7% of tramadol is removed during dialysis [54]. Additional caution must be given as concomitant use of tramadol with another serotonergic drug, such as a SNRI, can dramatically increase the risk for serotonin syndrome and/or lower the seizure threshold in the setting of ESRD [55].

Tapentadol

Tapentadol represents one of the most promising opioids for the treatment of neuropathic pain in ESRD. Categorized in the same chemical class as tramadol, tapentadol offers increased affinity to the mu-opioid receptor (18 times less than morphine) as well as inhibition of NE reuptake [56]. Tapentadol is a full opioid agonist, whereas tramadol is a partial opioid agonist. Despite being structurally similar, tapentadol has not been found to exhibit serotonergic activity compared to its cousin tramadol. While limited research is available on use in dialysis, in a previous publication, Atkinson et al. [21] made a case for use in dialysis patients by examining its metabolic pathway. Tapentadol is predominantly metabolized by phase II and does not have any active metabolites. Atkinson et al. [21] further hypothesized that tapentadol is likely dialyzable; however, further research is needed. When considering tapentadol's metabolism and lack of serotonergic activity that combined allow for decreased drug – drug interactions, it is a very reasonable option in the patient with ESRD.

Methadone

Methadone is an opioid offering a unique quadruple mechanism for chronic pain management as a mu-opioid agonist, NE reuptake inhibitor, N-methyl-D-aspartate antagonist, and kappa antagonist [57]. It also exhibits activity as a serotonin reuptake inhibitor. Methadone has been widely recommended for use in ESRD [58, 59]. This is largely due to its limited dialyzability as well as compensatory excretion through the biliary – fecal route [60]. This can allow for stable pain relief in ESRD patients without a precipitous trough following dialysis. While

mechanistically an ideal drug for ESRD, methadone has many potential drug – drug interactions through phase I CYP metabolism, which makes it a very dangerous option when starting or stopping other medications that inhibit or induce CYP enzymes. Even in patients with normal renal function, the half-life is highly variable based on phenotype and can range from 1 to 30, and up to 150 h [61]. It can also substantially prolong the QTc interval, increasing the risk for torsades de pointes and sudden death. A baseline electrocardiogram should be obtained prior to initiation and monitored throughout therapy and avoidance of concomitant QTc prolonging drugs is recommended [62].

Levorphanol

Levorphanol is mechanistically identical to methadone excluding activity on 5-HT and offers similar benefits for neuropathic pain [62]. Fortunately, levorphanol avoids concerns for QTc prolongation found with methadone and has minimal drug – drug interactions as it undergoes phase II metabolism only. However, it is metabolized to the active metabolite levorphanol-3-glucuronide, which is renally excreted [63]. Similar to methadone, it has a high volume of distribution and is highly protein bound, but it has a predictable half-life in nondialysis patients of 1–17 h, thus is likely to be minimally affected by dialysis [61].

Conclusion

Neuropathic pain is a frequent complication within the ESRD population. Management of neuropathic pain is complex, and this is compounded by an absence of evidence-based recommendations due to a lack of high-quality studies in ESRD population. Pain management in this population requires careful assessment of drug-specific properties, accumulation, metabolism (presence of active/toxic metabolites), extraction by dialysis, and presence of drug – drug interactions. In the absence of pharmacokinetic data in ESRD patients, therapeutic window and potential risks should be factored in the decision making along with continued monitoring throughout therapy. Due to unpredicted pharmacokinetics, assessing for analgesic and adverse effects along with laboratory monitoring when indicated is important to promote efficacy and safety.

Disclosure Statement

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