NNJ NEPHROLOGY NURSING JOURNAL

Approaches to Medication Management in Patients with Kidney Failure Opting for Conservative Management

Katherine H. Cho, PharmD, BCACP, Emily J. Ashjian, PharmD, BCPS, BCACP, Michael Smith, PharmD, BCPS, and Amy Barton Pai, PharmD, MHI

CE 1.5 contact hours | 60 pharmacology minutes

The incidence and prevalence of kidney failure, or end stage kidney disease, continue to rise (United States Renal Data System [USRDS], 2018). In-center hemodialysis remains the most common mode of kidney replacement therapy (KRT) (USRDS, 2018). Hemodialysis is a reasonable treatment choice for a large proportion of patients; however, it is uncertain how beneficial it may be for certain populations, including older adults or those with numerous comorbidities and limited life expectancy (Hussain et al., 2013; Murtagh et al., 2016; Murtagh, Marsh et al., 2007; Verberne et al., 2016). Mortality rates have improved for older patients on dialysis, but the rate is still disproportionately high. Compared to their non-dialysis counterparts, patients on dialysis 75 years or older have a 4-fold greater mortality rate (USRDS, 2018).

Overall hospitalization rates have decreased for patients with kidney failure between 2000 and 2015, but in their final 90 days of life, 83.4% of all Medicare beneficiaries with kidney failure were hospitalized with a median length of stay of 17 days (USRDS, 2018). During this period, nearly two-thirds were admitted to the intensive or coronary care unit, and 39% of these patients died in the hospital (USRDS, 2018). One study of older patients with kidney failure ($n = 584$), with over half currently receiving dialysis, found that only 12% of patients knew about palliative care options despite a poor prognosis (Davison, 2010). Current international guidelines, such as the those from the Kidney Disease: Improving Global Outcomes (KDIGO) Working Group, encourage the incorporation of palliative care principles, including the discussion of conservative management of kidney failure (CM-KF) (Davison et al., 2015). Conservative management has been described as "planned, holistic patient-centered care" for patients with kidney failure, which should include shared decision-making, psychologic support, active symptom management, cultural and spiritual domains of care, as well as detailed

Katherine H. Cho, PharmD, BCACP, is a Pharmacist, Michigan Medicine, Department of Pharmacy Services; and University of Michigan College of Pharmacy, Department of Clinical Pharmacy, Ann Arbor, MI.

Emily J. Ashjian, PharmD, BCPS, BCACP, is a Pharmacist, University of Michigan College of Pharmacy, Department of Clinical Pharmacy; and Michigan Medicine, Pharmacy Innovations and Partnerships, Ann Arbor, MI.

Michael Smith, PharmD, BCPS, is a Pharmacist, Michigan Medicine, Department of Pharmacy Services; and University of Michigan College of Pharmacy, Department of Clinical Pharmacy, Ann Arbor, MI.

Amy Barton Pai, PharmD, MHI, is a Pharmacist, University of Michigan College of Pharmacy, Department of Clinical Pharmacy, Ann Arbor, MI.

Statement of Disclosure: The authors reported no actual or potential conflict of interest in relation to this continuing nursing education activity.

Note: Additional statements of disclosure and instructions for CNE evaluation can be found on page 336.

Cho, K.H., Ashjian, E.J., Smith, M., & Pai, A.B. (2020). Approaches to medication management in patients with kidney failure opting for conservative management. *Nephrology Nursing Journal, 47*(4), 319-335, 371. https://doi.org/10.37526/1526-744X.2020.47.4.319

After consideration of risks and benefits, some patients with kidney failure choose conservative management. Conservative management of kidney failure (CM-KF) does not include dialysis or transplant and utilizes primarily pharmacologic strategies for symptom management, which can be challenging due to the number and complexity of symptoms. Additionally, there are safety concerns regarding altered pharmacokinetics and the adverse effects induced by some of the therapies that may be selected to treat symptoms. This review describes common kidney failure symptoms and provides recommendations for pharmacologic management in CM-KF. Selection of medication should be individualized to the patient and comorbidities, drug interactions, cost, and adverse effects should be carefully considered. Additional studies specifically focused on CM-KF are needed.

Key Words:
End stage renal disease, end stage kidney disease, palliative care, conservative management, symptom, medication management, kidney failure.

communication without the use of dialysis (Murtagh et al., 2016, p. 1910).

Retrospective observational studies comparing patients with kidney failure who choose KRT versus conservative management have generally demonstrated a survival benefit for those who choose dialysis (hemodialysis or peritoneal dialysis); however, the magnitude of benefit diminishes with advanced age (80 years old or older) and with a high number of comorbidities (Hussain et al., 2013; Murtagh, Marsh et al., 2007; Verberne et al., 2016). Patients with kidney failure who select conservative management are more likely to have accessed palliative care resources and may be less likely to die in a hospital (Hussain et al., 2013). Conservative management is also associated with stable or improved symptom control and quality of life (Brown et al., 2015), which further emphasizes the need to weigh risks, benefits, and desires for the individual patient before initiating hemodialysis. For some patients, dialysis may not align with their goals of care, and conservative management without dialysis may be appropriate.

The KDIGO guidelines recognize the lack of consensus regarding conservative management and encourage the provision of collaborative, supportive care for all patients with advanced chronic kidney disease (CKD) for symptom management and for the development and communication of patient care goals (Davison et al., 2015). Interviews of patients with kidney failure and clinic staff demonstrate high interpatient variability in symptom reporting, as well as discordance between staff and patient beliefs regarding spontaneous patient self-reporting of symptoms (Flythe, Hilliard et al., 2018). Clinic staff members believed patients proactively report symptoms, but patients stated they did not report symptoms for a variety of reasons, such as normalization of symptoms, poor understanding of symptoms, and perceived futility. This discordance is unfortunate because the majority of patients experience multiple physical and psychological symptoms related to kidney failure (see Table 1) (Almutary et al., 2013; Murtagh, Addington-Hall, & Higginson, 2007).

Symptom Management and Pharmacology Treatment

The majority of symptoms of patients with CM-KF are managed through pharmacologic treatment. However, medication management can be challenging in CM-KM. Patients electing for CM-KF instead of dialysis tend to be older, have more comorbidities, and have lower functional status based on Karnofsky performance scores (Wongrakpanich et al., 2017), increasing their risk for medication-related problems (Pai et al., 2013). In a survey of primary care physicians, respondents reported their ability to select and adjust medication doses as the second leading barrier to conservative management (Tam-Tham et al., 2016). The purpose of this review is to evaluate pharmacologic treatment options to treat kidney failure symptoms in patients who select conservative management.

Table 1
Weighted Mean Prevalence of Common Symptoms in Kidney Failure

Symptom	%
Fatigue	71%
Pruritus	55%
Constipation	53%
Anorexia	49%
Sleep disturbance	44%
Pain	47%
Anxiety	38%
Nausea	33%
Dyspnea	35%
Restless legs	30%
Depression	27%

Source: Murtagh, Addington-Hall, Edmunds et al., 2007.

Fatigue

Fatigue is one of the most commonly reported symptoms in kidney failure (Murtagh, Addington-Hall, & Higginson, 2007). Patients with kidney failure often have a constellation of kidney disease-related symptoms as well as chronic health conditions that make the evaluation and treatment of fatigue difficult (Jhamb et al., 2008). For example, anemia of CKD may worsen restless legs symptoms, resulting in poor sleep that exacerbates fatigue. While the etiology is likely multi-factorial, underlying conditions and symptoms that contribute to fatigue should be evaluated and addressed for each individual patient (Horigan, 2012). A survey of patients treated with hemodialysis illustrated that of all physical symptoms experienced, fatigue was the most important symptom for which they desired better treatment options (Flythe, Hilliard et al., 2018). Unfortunately, many providers are unaware of the prevalence and severity of symptoms, including fatigue (Weisbord et al., 2007), and there are no validated tools to assess fatigue to guide therapy.

The Standardized Outcomes in Nephrology-Hemodialysis (SONG-HD) Working Group is expected to establish consensus regarding standardized outcomes, including patient-centered outcomes related to fatigue (Ju et al., 2018). The group held an international workshop of patients, caregivers, and health professionals where they discussed their perspectives and were administered a survey to identify specific characteristics of fatigue of high importance to patients on maintenance hemodialysis (Ju et al., 2018; Ju et al., 2020). Based on relative importance, the

survey identified life participation, tiredness, and level of energy as most important. Discussions were transcribed for thematic analysis that will assist in the creation of a validated fatigue assessment that can be applied consistently in future trials to provide meaningful results for patients and providers in identified quantitative and qualitative dimensions. Until such a tool and subsequent symptom management guidelines are available, current strategies rely on limited available data.

Anemia

Anemia is common in kidney failure, and the current anemia management strategy in patients with kidney failure includes iron supplementation and erythropoiesis-stimulating agents (ESAs). However, optimal target hemoglobin (Hgb) concentrations have not been established in CM-KF. Given the goals of conservative management, treatment regimens and Hgb goals should be individualized to maximize improvement in patient symptoms while balancing potential risks of medications (e.g., infusion reactions). Iron products can be administered intravenously or orally, and each route has its own unique benefits and risks. Current guidelines recommend selecting iron therapies based on the severity of iron deficiency as well as the availability of vascular access and potential for adverse effects (Del Vecchio & Locatelli, 2017; KDIGO, 2012).

Iron Replacement

Intravenous (IV) administration circumvents variability in gastrointestinal absorption and produces more rapid repletion of iron stores (Del Vecchio & Locatelli, 2017; KDIGO, 2012). Oral iron is typically poorly absorbed in patients with kidney failure due to increased hepcidin, a master regulator of iron homeostasis that reduces gastrointestinal absorption and mobilization of iron from ferritin to transferrin (Macdougall et al., 2016). However, patients with kidney failure who are conservatively managed may not have easy venous access and traveling to the clinic for an IV iron infusion may be difficult. No studies were found that have been conducted specifically in CM-KF, but IV iron is widely used in patients with CKD and kidney failure. A meta-analysis and systematic review demonstrated that patients with Stage 3-5 CKD who are not on dialysis who received IV iron were 61% more likely to reach greater than 1 mg/dL Hgb increase compared to those receiving oral iron (Shepshelovich et al., 2016). The use of this categorical variable as the outcome may be more clinically meaningful given the lack of consensus regarding a target Hgb level. No differences in Hgb increase were observed between the different iron formulations (Shepshelovich et al., 2016). Several IV iron formulations are available, but sodium ferric gluconate (Ferrlecit®, Sanofi-Aventis, Bridgewater, New Jersey), iron sucrose (Venofer®, American Regent, Shirley, New York), ferumoxytol (Feraheme®, AMAG Pharmaceuticals, Waltham, Massachusetts), and ferric carboxymaltose (Injectafer®, American Regent, Shirley, New York) are the most commonly used in the United States (Auerbach et al., 2020). All IV iron formulations are colloidal suspensions of nanoparticles comprised of iron oxide cores covered with a carbohydrate shell; however, Ferrlecit and Venofer are less stable compared to INFeD®, Injectafer®, and Feraheme® (Auerbach & Macdougall, 2017). This results in faster release following administration, so iron replacement using Ferrlecit® or Venofer® requires smaller, more frequent dosing over a longer period of time in anemia (e.g., 1 gram in 5 divided doses over 2 to 4 weeks) (Charytan et al., 2005; Van Wyck et al., 2005), which may be burdensome for CM-KF. Both Feraheme® and Injectafer® are newer preparations, and their physicochemical properties allow for larger, less frequent doses compared to Ferrlecit® and Venofer® (Auerbach et al., 2020) Iron dextran (INFeD®, Allergan, Madison, New Jersey) is also a large molecular weight formulation. However, iron dextran is associated with hypersensitivity reactions (Watson Pharmaceuticals, 2009). Some institutions may use iron dextran to administer large-dose infusions because of the lower cost of this formulation compared to newer formulations (AMAG Pharmaceuticals, 2018; Sanofi Aventis, 2011; Watson Pharmaceuticals, 2009; Vifor, Inc., 2017; Vifor, Inc., 2018).

In randomized controlled trials of patients with CKD who are not on dialysis and have anemia, Feraheme® demonstrated superiority in increasing Hgb and a greater percentage of patients had a more than 1 mg/dL Hgb increase compared to oral iron (Spinowitz et al., 2008). Feraheme® was also non-inferior to Venofer® in a parallel trial of 162 patients with CKD who are not on dialysis (Macdougall, Strauss et al., 2014). In both trials, Feraheme® was administered as two 510 mg doses within 5 ± 3 days: Venofer® was administered in 5 to 10 infusions of 100 to 200 mg over a period of 5 weeks, and oral iron sulfate was administered twice daily over 3 weeks. Injectafer® efficacy compared to oral iron supplementation in anemia was examined in patients with CKD who are not on dialysis in the FIND-CKD trial (Macdougall, Bock et al., 2014). The trial had pre-specified Injectafer® dosing of 500 to 1,000 mg or 200 mg (with monthly supplemental doses) based on ferritin target levels, and ESAs were not allowed in the first 4 months of the study. Patients treated with Injectafer® targeting higher ferritin levels had faster response, greater proportion reaching an increase of more than 1 g/dL Hgb, and delayed time to need for additional anemia treatment (most commonly ESA use). Results are intriguing because patients could receive a single dose, but very few patients with Stage 5 CKD were included (2% and 3.2% in Injectafer® and oral iron groups, respectively). Based on these studies, providers can consider newer IV iron formulations if financially feasible and IV administration is preferred because they allow for shorter, less frequent administration of iron for anemia management.

Potential risks associated with IV iron include hypersensitivity reactions, hypotension, and potential increased

Table 2
Reported Incidence of Adverse Reactions Associated with Various IV Iron Formulations

Drug Name	Manufacturer's Recommended Adult Dosing	Adverse Effect (%)
Sodium ferric gluconate (Ferrlecit®)	• 10 mL (125 mg elemental iron) in 100 mL NS IV over 1-hour period • 1000 mg cumulative dose over 8 dialysis session may be required for repletion • Individual dose >125 mg may be associated with higher adverse event incidence/severity	• Common (≥10%) = nausea, vomiting and/or diarrhea, cramps, hypertension, dizziness, dyspnea, chest pain, leg cramps, and pain. • Clinically significant hypotension (2%) • Hypersensitivity (0.8%)
Iron sucrose* (Venofer®)	• 200 mg (undiluted) IV over 2 to 5 minutes (for CKD-ND) • 1000 mg cumulative dose over 5 sessions within 14-day period	• Nausea (8.6%) • Vomiting (5.0%) • Diarrhea (7.2%) • Dizziness (6.5%) • Dyspnea (5.8%) • Hypertension (6.5%) • Hypotension (2.2%) • Hypersensitivity (N/A)
Ferumoxytol (Feraheme®)	• 510 mg in 50 to 200 mL NS IV over at least 15 minutes • 1080 cumulative dose over 2 sessions separated by 3 to 8 days	• Nausea (3.1%) • Vomiting (1.5%) • Dizziness (2.6%) • Dyspnea (1.0%) • Hypotension (0.2%) • Hypersensitivity (0.2%)
Ferric carboxymaltose (Injectafer®)	• Weight <50 kg: 15 mg/kg (elemental iron) IV • Weight 50 kg or more: 750 mg/kg (elemental iron) IV • Two doses separated by 7 days; infuse over 15 minutes	• Nausea (7.2%) • Vomiting (1.7%) • Dizziness (2.0%) • Hypertension (3.8%) • Hypotension (1.0%) • Hypersensitivity (0.1%)
Iron dextran (INFeD®)	• Please refer to dosage table in package insert. • Administer 0.5 mL IV test dose over 30 minutes before first infusion.	• Nausea, vomiting, diarrhea (N/A) • Dyspnea (N/A) • Chest pain (N/A) • Hypertension, hypotesnion (N/A) • Hypersensitivity (N/A)

*Dosing and incidence are for non-dialysis dependent adult patients with chronic kidney disease; NS = 0.9% sodium chloride; N/A = not available.

Sources: AMAG Pharmaceuticals, 2018; Sanofi Aventis, 2011; Vifor, Inc., 2017; Vifor, Inc., 2018; Watson Pharmaceuticals, 2009.

infection risk (see Table 2) (KDIGO, 2012). Management of hypersensitivity reactions often include an antihistamine and a histamine$_2$-receptor antagonist (H_2RA). Data regarding increased infection risk and IV iron is conflicting, but parenteral iron should be avoided in patients with active infections (Macdougall et al., 2016). Patients with CKD or kidney failure inherently have immune dysfunction and experience higher rates of acute infection compared to those without CKD, but the majority of data have been focused on patients with kidney failure, which may be confounded by dialysis access-related infections (Dalrymple & Go, 2008). Data regarding infection risk in patients with CKD who are not on dialysis are limited but are likely similar to patients receiving CM-KF who do not have risk of dialysis access infections. No difference in infection rates between IV ferric carboxymaltose and oral iron were observed in the 626 patients enrolled in the FIND-CKD study (Macdougall, Bock et al., 2014).

Oral iron therapy may be a viable option for CM-KF, and compared to IV iron, oral iron has its own advantages and challenges. Oral iron is much less time-consuming and invasive to administer than IV formulations, but oral iron therapy is associated with daily administration requirements and gastrointestinal side effects (Tolkien et al., 2015). Previous studies and meta-analyses comparing IV and oral iron have used ferrous sulfate, and oral iron efficacy was inferior compared to intravenous iron (Shepshelovich et al., 2016). However, newer oral iron formulations may have

improved absorption. Ferric citrate (Auryxia®) was first approved as a phosphate binder and is now approved for anemia in patients with CKD who are not on dialysis. In a 16-week, randomized, controlled study, patients with CKD who were not on dialysis were randomized to placebo or ferric citrate 210 mg (1 tablet) three times daily to treat anemia (Fishbane et al., 2017). Ferric citrate doses were increased by three tablets daily at four-week intervals, with an average daily ferric citrate dose of 1,659 mg (7.9 tablets) at study end. The mean increase in hemoglobin in the ferric citrate group was statistically significant at 0.84 g/dL (95% confidence interval, 0.58 to 1.10 g/dL, $p < 0.001$), and a greater proportion of patients treated with ferric citrate had greater than 1 g/dL Hgb increase compared to placebo (52% vs 19.1% respectively, $p < 0.001$). Gastrointestinal adverse effects, including nausea and constipation, were more frequently reported with ferric citrate use than with placebo. However, ferric citrate was also associated with a high incidence of diarrhea (20.5% vs. 16.4% with placebo). Studies directly comparing ferric citrate and IV iron are lacking, and a study comparing ferric citrate and ferrous sulfate in patients with CKD who are not on dialysis is currently underway (ClinicalTrials.gov, 2019). Iron absorption is negligible with the other available iron-based phosphate binder, Velphoro® (sucroferric oxyhydroxide), and therefore, it is not an appropriate choice for iron supplementation. In summary, if an oral agent is selected for anemia management in patients with CM-KF, ferric citrate represents a good option due to the high bioavailability of iron in this formulation compared to traditional oral ferrous sulfate.

ESA Use

Iron supplementation alone may not be sufficient to treat anemia in the setting of decreased erythropoietin (EPO) production with advanced CKD. ESAs reduce fatigue in patients with CKD (Canadian Erythropoietin Study Group, 1990). In a retrospective cohort study of CM-KF in renal palliative care clinics (Chan et al., 2014), ESA use was associated with statistically significant improvements in Hgb and fatigue over a six-month period. Thirty-nine patients received ESA doses according to manufacturer recommendations (see Table 3), with 71% of patients administered methoxy polyethylene glycol-epoetin beta (mean dose 55.8 mcg/month) and the remainder given darbepoetin alfa (mean dose 29.1 mcg/week). Primary endpoints included change in Hgb and the proportion of patients achieving Hgb of 10-12 g/dL. ESA treatment was associated with a statistically significant increase in mean Hgb to 9.4 g/dL by the third month (compared to 7.6 g/dL at baseline), and over half (55.6%) of ESA recipients achieved the Hgb target of 10-12 mg/dL compared to none in the control group. Additional endpoints included number of all-cause hospitalizations, red blood cell transfusions, and fatigue, as measured by the Edmonton Symptom Assessment Scale (ESAS). Treatment, with ESAs was associated with improvement in fatigue, with a mean decrease in ESAS score of 0.6 at the end of six months ($p = 0.017$).

Table 3.
Hypothetical Risks Included in Survey Questions of Patients on Hemodialysis to Quantify Patient Preferences in Anemia Management

Attributes
• Having an allergic reaction because of a blood transfusion
• Having lung damage because of a blood transfusion that makes it hard to breathe
• Getting a serious infection because of a blood transfusion
• Increasing the time you need to wait for a kidney transplant because of a blood transfusion
• Increasing the chance your body will reject a kidney transplant if you get one because of a blood transfusion
• Needing to arrange transportation and spent 1 to 2 hours at a hospital or infusion center to receive a blood transfusion
• Having a 1% risk of dying from a heart attack or stroke because of the anemia medicine

Source: Hauber et al., 2017.

The average number of all-cause hospitalizations was significantly lower in ESA recipients (4.44 vs 9.24, $p = 0.001$), and there was a trend towards fewer transfusions in ESA-treated patients compared to control (mean 0.96 vs 2.76, $p = 0.084$). No serious adverse effects were reported with ESA use, though one patient's ESA dose was decreased in the setting of Hgb greater than 12 g/dL. These results suggest ESA use may be beneficial in CM-KF and may help reduce anemia, fatigue, hospitalization rates, and possibly even the need for transfusions.

Transfusion

Transfusions are effective but are avoided if possible due to the potential for infection and acute lung injury (Macdougall & Obrador, 2013; Tanhehco & Berns, 2012). Their potential benefit in treating anemia should be weighed carefully in CM-KF given the potential additive mortality risks with higher Hgb goals. A survey of patients on hemodialysis was conducted to assess patient preferences relative to anemia and transfusions (Hauber et al., 2017). Patients were presented two hypothetical anemia medications along with three medication-related attributes (see Table 3) and asked to rank attributes as most or least important to them. Ranking of respondent importance of an attribute was determined using the difference between the attribute with the highest and lowest reported preference. Attribute importance levels were then coded as categorical variables. Patients preferred fewer transfusions and reported the most important attribute of transfusion avoidance was lower acute lung injury. However, the evaluation of patient-centered goals necessitates a willingness to exchange risks for benefits. Comparison of patient prefer-

ences demonstrated that patients were willing to choose a hypothetical medication and accept a 4.5% risk of a medication-related stroke or heart attack if it increased the probability of the medication assisting with symptom relief from 25% to 75%. These findings suggest that patients are able and willing to engage in the discussion of risk versus benefit as it relates to the balance of safety and quality of life with anemia treatment options.

Preferences for Anemia Treatments

Preferences of patients with CM-KF in anemia management have not been specifically studied; however, discussion of patient goals can help guide therapeutic decision-making. Although no adverse events were reported in the study of ESAs in CM-KF, the study had a small sample size and short follow up (Chan et al., 2014). Risks associated with ESA therapies and high Hgb concentration (e.g., hypertension, stroke, and increased cardiovascular mortality) (Del Vecchio & Locatelli, 2016) should be explicitly provided to patients during discussions of fatigue management. Similar to IV iron dosing, ESA administration and frequency can be tailored to symptom improvement in addition to patient desires to minimize number of injections or avoid IV infusions (KDIGO, 2012). Subcutaneous ESA administration allowing for home administration and extended dosing intervals (e.g., every 4 weeks) was shown to decrease the frequency and number of office visits compared to in-office administration in a three-month pilot study of patients with Stage 4 and 5 CKD, which was described by one patient as "liberating" and could provide similar benefits for CM-KF (Riley et al., 2017).

Depression

Fatigue can also be a result and a symptom of depression. Estimates of prevalence of depression in patients with CKD vary widely (1.4% to 94.1%) (Palmer et al., 2013), but approximately 25% of adults with CKD are diagnosed with depression, which is 4 to 6 times greater than the general population (Hedayati et al., 2009; Watnick, 2009). In a meta-analysis of cohort studies, depression was associated with increased mortality in kidney failure (Palmer et al., 2013).

Unfortunately, data regarding antidepressant medication use is limited in patients with kidney disease. Medication selection therefore relies heavily on previous medication trials/failures, patient comorbidities, and assessment of side effect profiles to minimize risk of adverse events. Many antidepressants can worsen drowsiness, nausea, vomiting, or hypertension, and these symptoms are often present in patients with CKD and kidney failure due to uremia or fluid overload (DiPiro et al., 2020). Selective serotonin reuptake inhibitors (SSRIs) are generally drugs of choice in CKD due to a more favorable side effect profile with regards to somnolence, anticholinergic effects, seizure risk, and cardiovascular disease (Hedayati et al., 2012; Nagler et al., 2012). However, SSRIs may cause gastrointestinal adverse effects including nausea and vomiting.

The Chronic Kidney Disease Antidepressant Sertraline (CAST) trial examined the efficacy of sertraline on depression, quality of life, and safety in Stage 3-5 CKD-ND patients ($n = 193$) in a 12-week, placebo-controlled, randomized clinical trial (Hedayati et al., 2017). Depression symptom severity, remission, response, and quality of life were assessed using the Quick Inventory of Depressive Symptomatology-Self-Reported (QIDS-SR16), Work and Social Adjustment Scale (WSAS), and the Kidney Disease Quality of Life Survey-Short Form (KDQOL). Patients with Stage 5 CKD accounted for 17% of subjects. Sertraline doses were increased by 50 mg at study visits every three weeks to a maximum tolerated dose or 200 mg/day, with a median dose of 150 mg/day. The study did not show statistically significant differences in depression symptom severity, remission, response, or overall quality of life, and cognitive behavorial therapy (CBT) was not utilized. The only statistically significant change with sertraline treatment was an improvement in sleep (average KDQOL score change 5.0, $p = 0.03$). Regarding safety, there was no difference in severe adverse events (e.g., cardiovascular death, bleeding) or rates of drug discontinuation, but sertraline-treated patients experienced significantly more nausea and diarrhea compared to placebo, though the risk of severe adverse events was similar. These findings suggest that although sertraline induces more nausea and diarrhea, its safety and efficacy is likely similar to placebo. In a 12-week study of 120 patients on hemodialysis, treatment with sertraline titrated up to 200 mg ($n = 60$) was associated with improved depression scores ($P = 0.035$) compared to CBT as measured using a clinician-rated depression scale (QIDS-Clinician-Rated [QIDS-C]). (Mehrotra et al., 2019) However, only 37% of patients were able to be titrated up to the 200 mg dose, and 19% of patients initially assigned to sertraline had discontinued sertraline by study end (Mehrotra et al., 2019). These studies suggest that sertraline is a safe and reasonable first-line choice for depression in patients with kidney disease and in kidney failure.

Antidepressant medications with active metabolites excreted by the kidneys can accumulate and result in adverse effects, and pharmacokinetic parameters must be considered (Hedayati et al., 2012; Nagler et al., 2012). The majority of available pharmacokinetic data comes from small studies in patients on hemodialysis or peritoneal dialysis, often following administration of a single dose. A single-dose, pharmacokinetic study of fluoxetine 40 mg in adult, male volunteers ($n = 25$) with varying levels of renal function found no significant differences in peak fluoxetine or norfluoxetine (active metabolite) concentrations, and no renal dose adjustment is required (Aronoff et al., 1984). Citalopram 20 mg was administered to seven adults with CKD (creatinine clearance [CrCl]) range 10 to 53 mL/min, average CrCl 27 mL/min), and a 35% increase in half-life was observed (Joffe et al., 1998). As a result, citalopram does not require a dose adjustment in mild to moderate renal impairment, but its use is not recommended in patients with an estimated CrCl less than 20 mL/min due

to concerns of adverse effects (e.g., QTc prolongation) (Forest Pharmaceuticals, Inc., 2011). Paroxetine has an increased elimination half-life at CrCl less than 30 mL/min, and due to increased central nervous system depressant effects, less frequent administration and lower doses (e.g., initial 10 mg/day, maximum 40 mg/day) are suggested (Hedayati et al., 2012).

Additional antidepressant medications that are not preferred agents in patients with advanced CKD include bupropion, venlafaxine, and tricyclic antidepressants (Hedayati et al., 2012; Nagler et al., 2012). Bupropion is metabolized to an active metabolite with similar activity that is renally eliminated, resulting in concerns regarding accumulation and increased seizure risk, insomnia, and increased heart rate (DiPiro et al., 2020). These risks may be increased in CM-KF as uremia worsens over time. Following a one-time 150 mg dose of bupropion in 10 subjects with kidney disease with an average estimated glomerular filtration rate (eGFR) of 30.9 mL/min/1.73m^2, a 126% increase in AUC and 140% increase in elimination half-life was observed (Turpeinen et al., 2007). No specific dose adjustments are recommended by the manufacturer, but a maximum daily dose of 150 mg has been suggested (Nagler et al., 2012). Venlafaxine also has an active metabolite and can cause nausea, hypertension, and insomnia. A pharmacokinetic study in patients with renal impairment ($n = 12$, mean CrCl mL/min) showed a greater than 50% increase in elimination half-life compared to patients without renal impairment (Troy et al., 1994), and a dose reduction of at least 50% was subsequently suggested in patients with CrCl less than 30 mL/min. Tricyclic antidepressants, such as amitriptyline and nortriptyline do not require dose adjustments in renal dysfunction, but providers should monitor patients for additive central nervous system effects or worsening fluid status due to increased intake of fluids in response to anticholinergic side effects (Nagler et al., 2012). Due to the lack of data regarding efficacy of antidepressants in renal dysfunction, consideration should be given to individualizing medication selection based on previous patient medication use/failure, comorbidities, and side effects to minimize potential patient harm.

Insomnia

Insomnia contributes to worsening of fatigue, but the underlying cause of insomnia in CKD can be due to a variety of factors, including abnormal levels of endogenous sleep-regulating hormones (e.g., increased orexin, decreased melatonin), uremic pruritus, and restless legs syndrome (RLS) (Lindner et al., 2015). Non-pharmacologic measures, such as optimizing sleep hygiene and cognitive behavioral therapy, should be included, and pharmacologic therapies should be used appropriately with careful attention to drug selection because sleep hygiene may be insufficient, given the complex underlying pathophysiology and limited data in kidney disease.

Sleep Disorders

Decreased concentrations of melatonin have been attributed to the absence of nocturnal rise in melatonin concentration in patients with kidney disease, and previous studies have examined melatonin supplementation (Koch et al., 2009). In a randomized, double-blind, placebo-controlled crossover study of patients on hemodialysis ($n = 20$), Koch and colleagues (2019) examined objective and subjective measures of sleep in patients treated with melatonin 3 mg daily at bedtime. Each study lasted six weeks, and no washout period was included due to the short half-life of melatonin. Objective measures included salivary measurements of melatonin and actigraphy, an established sleep-monitoring method used to interpret periods of sleep and waking. Subjects reported daytime function and subjective sleep experience using a validated sleep disorders questionnaire. Treatment with melatonin increased melatonin levels from a mean baseline of less than 1 pg/mL (i.e., absent) to greater than 4 pg/mL, the accepted level of onset of the evening rise in melatonin compared to placebo. Examination of actometer results demonstrated significant improvements in sleep onset latency, sleep efficiency, actual sleep time, and sleep fragmentation ($P < 0.05$) on nights after daytime dialysis. These findings were corroborated by the results of the patient questionnaires, which demonstrated statistically significant improvements to sleep onset latency, shorter periods of waking during sleep, and longer sleep time. Additionally, though not statistically significant, there was also a trend towards less daytime napping (median 0 minutes vs. 30 minutes in placebo). Results suggested that short-term use of physiologic doses of melatonin in patients on hemodialysis improves sleep, but long-term use in patients on hemodialysis may yield less clear benefit.

Russcher and colleagues (2013) conducted a randomized, placebo-controlled trial of low, physiologic doses of melatonin (3 mg daily) in patients on hemodialysis ($n = 67$) over 12 months. The primary outcome was an improvement of at least 15 points in the vitality score of the Medical Outcomes Study Short Form 36 (MOS SF-36), which measures physical, functional, mental, and social health components of quality of life. Secondary outcomes included objective sleep measures (i.e., sleep onset latency, sleep, efficiency, and sleep time) as measured by actigraphy, as well as salivary melatonin concentrations. At study end, vitality as measured by MOS SF-36 did not change with melatonin, and objective sleep measures were not different from baseline. There was a large percentage of participants lost to follow up (42%) due to transplantation and study withdrawal. No adverse effects were reported. The authors conducted a post-hoc sample size calculation, which estimated that 28 patients would be needed per group to be 80% powered to observe a 20-minute difference in sleep efficiency. This required sample size was only present at month 3 of the study. At three months, sleep efficiency and actual sleep time (difference 49 minutes, 95% CI 2.1-95.9) were improved, and it is possible that the observed lack of

long-term benefit is a result of inadequate study power. Given the burden of insomnia, minimal adverse effects, and anticipated survival in CM-KF, daily administration of low-dose melatonin may be a beneficial and reasonable initial agent to improve sleep onset, efficiency, and time asleep.

Orexin is another hormone with observed disturbances in renal dysfunction. Increased levels, as found in CKD due to lack of inhibition due to blunted nocturnal melatonin increases, are associated with insomnia, and an orexin antagonist, suvorexant (Belsomra®), was approved in 2014 (Merck & Co., Inc., 2014). There are insufficient data to recommend for or against its use in CM-KF; clinical trials excluded frail, elderly patients (Herring et al., 2017). Although no renal dose adjustments exist, suvorexant has a long half-life and notable adverse effects include somnolence, abnormal dreams, and suicidal ideation (Sutton, 2015).

Other commonly used medications used for sleep disorders include the "Z-drugs" (e.g., eszopiclone, zaleplon, zolpidem), benzodiazepines, trazodone, and tricyclic antidepressants (Lindner et al., 2015). However, these medications should be used cautiously due to the potential for accumulation and adverse effects such as dizziness or somnolence (Lindner et al., 2015; Nagler et al., 2012). For initiation of sleep, zaleplon or zolpidem are both short-acting agents that do not require renal dose adjustments (Lindner et al., 2015; Nagler et al., 2012). Both have been examined in patients on hemodialysis. In a short, randomized crossover trial, patients on hemodialysis ($n = 20$) received either zolpidem 5 to 10 mg or clonazepam 1 mg for two-week periods separated by a one-week washout period (Dashti-Khavidaki et al., 2011). Sleep quality was the primary outcome, which was assessed using a patient questionnaire (Pittsburgh Sleep Quality Index) as administered by the research staff. Both medications significantly improved sleep quality scores, and clonazepam improved scores to a greater degree than zolpidem. However, less daytime drowsiness and amnesia was reported with zolpidem than clonazepam. However, neither agent is approved for long-term use in insomnia. The only non-benzodiazepine hypnotic that is FDA-approved for maintenance therapy of insomnia is eszopiclone. Eszopiclone does not require renal dose adjustment (Lindner et al., 2015) but lacks data in kidney disease.

Longer-acting benzodiazepines are preferred to short-acting agents to minimize rebound insomnia; however, monitoring for adverse effects, such as sedation, is recommended due to redistribution due to the lipophilicity of these medications (Arnold, 1991). Lorazepam undergoes glucuronidation in the liver to an inactive metabolite, and dose adjustments in renal dysfunction may not be necessary (Greenblatt, 1991; Morrison et al., 1984). However, due to potential adverse effects, such as somnolence, lorazepam, temazepam, and clonazepam, should be initiated at the lowest possible dose with frequent evaluation for adverse effects if used (Lindner et al., 2015).

Trazodone does not require renal dose adjustment and is undetectable in dialysate (Doweiko et al., 1984), but it has a high incidence of somnolence and should be used cautiously in renal dysfunction and at low doses out of concern for potential accumulation due to active, renally excreted metabolites (Lindner et al., 2015).

Mirtazapine is a sedating antidepressant often used for sleep. It has not been extensively studied in renal dysfunction, but the elimination half-life was unchanged even in Stage 5 CKD, suggesting no accumulation, and patients can be started on a low dose (e.g., 7.5 to 15 mg/day) with slow adjustments accompanied by monitoring for side effects (Nagler et al., 2012). It should be noted that mirtazapine is associated with somnolence, constipation, and increased appetite (which may be beneficial for some patients), so fluid status, potassium, and phosphorus should continue to be monitored in CM-KF receiving mirtazapine (Merck & Co, Inc., 1996).

Tricyclic antidepressants (TCAs), such as amitriptyline and nortriptyline, owe their sedative properties to the ability to enhance histaminergic activity (DiPiro et al., 2020). TCAs also have significant anticholinergic activity, and if used, TCAs should be used at the lowest possible dose with added monitoring of fluid status due to potential increase to fluid intake in response to anticholinergic side effects (Nagler et al., 2012). Additionally, TCAs may be used in some patients for pain management, which is discussed below. The cumulative lack of robust evidence for pharmacologic treatments for insomnia in end stage kidney disease, and the risk for adverse drug events require careful consideration of both the drug and the dose used, which should be used in conjunction with non-drug measures (Lindner et al., 2015). In a recent stakeholder focus group meeting from the Kidney Health Initiative, patients reported in rank order that they desired exercise, support groups, then followed by medication to address mood symptoms, including depression. This suggests a more holistic approach should be considered for symptom management in insomnia and depression in kidney failure, with an emphasized need for additional research and open communication (Flythe, Hilliard et al., 2018).

Restless Legs Syndrome

Restless legs syndrome (RLS) affects an estimated 3% to 58% of patients using CM-KF (Murtagh, Addington-Hall, & Higginson, 2007), with a severe impact on sleep and quality of life. Kidney failure-related RLS may have multiple etiologies, though the exact pathophysiology is uncertain. Causes of RLS in kidney failure include dopaminergic dysfunction, anemia, and uremia; therefore, the most studied pharmacologic options in renal dysfunction include gabapentin, levodopa, ropinirole, and iron dextran (Gopaluni et al., 2016).

Gabapentin has demonstrated improvement in RLS symptoms in CM-KF (Cheikh Hassan et al., 2015). Cheikh Hassan and colleagues (2015) conducted a retrospective cohort analysis of CM-KF and patients with kidney failure

($n = 34$) managed with hemodialysis to evaluate RLS symptom improvement as demonstrated by change in RLS symptoms score on a validated palliative symptom instrument, the Palliative care Outcome Scale-Symptoms (POS-S) Renal. Patients using CM-KF were those who did not receive (or wish to receive) dialysis or undergo transplant and had attended the renal palliative care clinic at least twice. Patients with non-uremic RLS were excluded. The majority of patients were older and were followed for a median of 27 weeks. Gabapentin was effective for RLS symptoms in nearly 70% of patients (POS-S RLS symptom score ≤ 1, $p = 0.023$). POS-S scores were not different between CM-KF or dialysis groups, nor was there a statistically significant difference in the mean starting, daily, and final doses of gabapentin (50 mg/day, 100 mg/day, and 100 mg/day respectively) between the two groups. However, 47% of patients receiving CM-KF reported a side effect related to gabapentin use (vs. 17% of patients on dialysis), and 17% of patients receiving CM-KF discontinued gabapentin. This suggests that while effective for restless legs, gabapentin should be started at low doses with regular evaluation for adverse effects in patients receiving CM-KF.

Ropinirole was compared to levodopa to evaluate improvement in RLS symptoms by Pellecchia and colleagues (2004) in a 14-week, open-label, randomized crossover trial of patients on hemodialysis ($n = 10$). Subjects were treated with either ropinirole or sustained-release levodopa and symptoms assessed using patient questionnaires (6-item International Restless Legs Study [IRLS] Group, Clinical Global Impression [CGI] Scale) and patient sleep diaries. Levodopa was started at 100 mg/dose with an average study dose of 190 mg/day, and ropinirole was started at 0.25 mg/day with a final mean study dose of 1.45 mg/day. Ropinirole was associated with a larger reduction in IRLS score (12.2 vs 4.6, $p < 0.001$), as well as a larger improvement in CGI score (2.7 vs. 1.3, $p < 0.01$) compared to levodopa. Four subjects receiving ropinirole reported complete disappearance of RLS symptoms compared to none who received levodopa. One subject receiving levodopa withdrew from the study due to severe vomiting, while no adverse events were reported with ropinirole. Clinically significant orthostatic hypotension was not observed with ropinirole treatment. While no studies have examined ropinirole in patients receiving CM-KF, there are no recommended renal dose adjustments. Based on the safety and efficacy of ropinirole in patients on dialysis, ropinirole is likely a reasonable option for RLS with initiation at a low dose of 0.25 mg/day and regular monitoring for adverse effects.

Iron is involved in the rate-limiting step of converting tyrosine to levodopa, which is the hypothesis for decreased dopaminergic activity and increased RLS symptoms associated with low iron levels (Earley et al., 2000). Studies have examined the effect of iron on RLS symptoms, but only one has included patients with kidney failure ($n = 25$) and utilized IV iron dextran (ID). In a four-week, double-blind, placebo-controlled trial, Sloand and colleagues (2004) administered 1,000 mg IV ID at baseline and Weeks 1, 2, and 4, and evaluated RLS symptoms using their own symptom scale. At two weeks, the change in RLS severity was significant (-3 points vs no change, $p = 0.01$), but the change in symptom severity was not significant by study end. A study with ferric carboxymaltose also found beneficial effects on RLS symptoms; however, patients with CKD and anemia (Hgb cutoff of 12 mg/dL or less) were excluded (Cho et al., 2016). Although data regarding efficacy of iron treatment for RLS is limited in kidney failure, the use and safety of IV iron in kidney failure is well established, and IV iron may be reasonable to try for dual management of symptoms of RLS and anemia in patients receiving CM-KF with appropriate monitoring. Newer, more bioavailable iron-based phosphate binders, such as ferric citrate as well as standard oral ferrous sulfate, may also be an option in patients receiving CM-KF if IV access is a barrier.

Uremic Pruritus

Uremic pruritus is another symptom associated with renal dysfunction with significant negative impact on patient quality of life. Unlike dermatological pruritus, uremic pruritus lacks visible skin lesions or other changes to the skin in the absence of excoriations caused by excessive scratching (Mettang & Kremer, 2014). The exact mechanism of uremic pruritus is unknown, but factors that have been associated with uremic pruritus include inadequate dialysis, inflammation, hypercalcemia, hyperphosphatemia, -opioid receptor overexpression, and neuropathy rather than increased histamine levels (Scherer et al., 2017). Currently, pharmacologic options address these various etiologies, but medication selection should also consider characteristics, such as side effect profile and size of the affected area. After eliminating non-uremic causes of pruritus, the cornerstone of therapy should include daily application of topical emollient to keep skin hydrated (Combs et al., 2015; Mettang & Kremer, 2014). In a study by Morton and colleagues (1996), patients on hemodialysis ($n = 72$) had lower stratum corneum hydration levels (i.e., drier skin) as measured by electrical capacitance using a corneometer, and patients were instructed to apply a topical emollient twice daily for one week. Pruritus was also assessed using a visual analog scale (VAS), and 76% of patients with pruritus reported improvement in severity of pruritus. Nearly half reported that pruritus was completely relieved. Given their safety, low cost, and ready availability, as well as limited efficacy data in patients on dialysis, topical emollients should be incorporated as part of a preferred regimen in uremic pruritus in CM-KF.

Other topical agents that may be considered in uremic pruritus include pramoxine, capsaicin, and camphor-menthol-phenol (Sarna®). These agents are anesthetics or counterirritants that have limited available data regarding efficacy in dialysis. Young and colleagues (2009) compared the efficacy of 1% topical pramoxine, as well as control on severity and quality of life in patients on dialysis ($n = 28$)

with moderate to severe uremic pruritus, compared to Cetaphil® emollient lotion following twice daily use for four weeks. Efficacy was assessed using a patient questionnaire and Investigator Global Assessment (IGA) of response to treatment. Severity was evaluated using an individual VAS. Although not statistically significant, a greater decrease in average VAS score (i.e., severity of itching) was observed in pramoxine-treated subjects (61% vs. 12%) at the end of four weeks. There was no difference in IGA or quality of life, and no adverse effects were reported in either group. Results suggest that pramoxine may be effective and demonstrate similar safety compared to a topical emollient for kidney failure-related pruritus. Another study comparing camphor-menthol-phenol (Sarna®) and a topical emollient (Eurax®) found similar results (Tan et al., 1990). Topical capsaicin 0.025% and its efficacy and safety in moderate to severe, hemodialysis-related pruritus was examined in a randomized, placebo-controlled, crossover trial ($n = 17$) (Tarng et al., 1996). Efficacy was reported as number of subjects reporting change in pruritus severity to mild or none, which was measured using a 4-point verbal response scale. At study end, 82% reported improvement using a visual response scale (VRS) in pruritus severity from moderate to severe (VRS = 3, 4, respectively) to mild or none (VRS = 2, 1, respectively), and 29% reported complete symptom resolution. Seventy-five percent of adverse events were reported during capsaicin use, and the most commonly reported events were redness, stinging, and/or local irritation. These data suggest that all three topical options may be effective for uremic pruritus, are generally well-tolerated, and may be reasonable choices for application to small areas of unbroken skin in CM-KF.

Antihistamines, such as hydroxyzine and diphenhydramine, have failed to demonstrate benefit in uremic pruritus and are not preferred agents in kidney disease or in older patients (Combs et al., 2015; Mettang & Kremer, 2014; Simonsen et al., 2017). These medications are also associated with adverse effects, including increased somnolence and dizziness, as well as anticholinergic effects that could lead to inadvertently increased fluid intake due to increased thirst or dry mouth. Diphenhydramine is renally eliminated and has increased elimination half-life in older patients (Simons et al., 1990), which may increase risk of adverse effects, so if use is required in patients receiving CM-KF, lower and less frequent dosing may be appropriate. Additionally, the American Geriatrics Society recommends against routine use of diphenhydramine due to the increased risk of anticholinergic effects and reduced clearance in older patients (Fick et al., 2019).

Systemic agents may be necessary for patients with uremic pruritus affecting large or multiple areas of the body, and the most robust published data have evaluated gabapentin and sertraline, which have both been studied in patients receiving CM-KF. In a study of patients receiving CM-KF by Cheikh Hassan and colleagues (2015) designed to evaluate both RLS and uremic pruritus, gabapentin demonstrated improvement in pruritus for approximately 80% of patients receiving CM-KF at an average dose of 100 mg/day; however, gabapentin was associated with significantly more adverse effects, such as dizziness, drowsiness, and fatigue (Cheikh Hassan et al., 2015). Chan and colleagues (2013) conducted a retrospective review of patients receiving CM-KF ($n = 20$) with antihistamine-refractory uremic pruritus administered sertraline for uremic pruritus. The initial sertraline dose was 25 mg/day, and doses could be increased by 25 mg at monthly intervals as necessary. Pruritus severity was evaluated using a 10-point numerical rating scale (NRS), and the efficacy outcome defined as the time to control (i.e., subjective satisfactory NRS). The effective dosage of sertraline at that time point was also recorded, as were adverse events. Average time to control of uremic pruritus was 5.1 weeks, with mean pre- and post-treatment NRS scores of 7.47 ± 1.61 and 2.47 ± 1.28, respectively. The average effective sertraline dose was 35 mg/day (median 25 mg/day), and three patients discontinued sertraline due to adverse effects, specifically dizziness and fatigue. This study suggests that low-dose sertraline may be an effective option for treating uremic pruritus, though symptom relief may be less immediate. However, a lower percentage of patients receiving CM-KF experienced adverse effects and discontinued the medication compared to patients receiving CM-KF treated with low-dose gabapentin. No direct comparisons of systemic agents in the management of uremic pruritus in patients receiving CM-KF are available, and the extent of symptom relief cannot be truly compared due to the different scales used. Currently available data suggest that either gabapentin or sertraline may be an effective option, and both medications should be initiated at low doses with monitoring for adverse effects. The incidence of adverse effects and associated medication discontinuation appear to be higher with gabapentin, so sertraline may be a reasonable first choice if a systemic agent is warranted.

Dyspnea

Dyspnea has a significant impact on quality of life for the 35% to 60% of patients with kidney failure who experience acute breathing difficulty (Murtagh, Addington-Hall, & Higginson, 2007; Murtagh, Addington-Hall, Edmonds et al., 2007), but the mechanisms of dyspnea are complex. Sodium retention, fluid overload, anemia, inflammation, and congestive heart failure are all possible reasons for worsening dyspnea in kidney disease (Salerno et al., 2017). Additionally, metabolic acidosis secondary to kidney disease can result in compensatory respiratory alkalosis and shortness of breath in patients receiving CM-KF (Raghavan & Holley, 2016). Excess sodium and fluid will not be removed by dialysis; therefore, diuresis using oral medications is the cornerstone of therapy in combination with dietary sodium and fluid restriction (2.3 grams and 1.5 L per day, respectively) for patients with residual urine output (Valika & Peixoto, 2016). However, challenges, such as optimizing loop diuretic pharmacokinetics and decreased

Table 4
Suggested Single Ceiling Doses of Oral Loop Diuretics When Used in Severe Renal Insufficiency (eGFR < 20 mL/min)

Medication	Ceiling Dose (mg)
Furosemide	400 mg
Torsemide	100 mg
Bumetanide	10 mg

Source: Wilcox, 2002.

amounts of filtered sodium available for excretion due to low glomerular filtration rates in kidney failure, can contribute to diuretic resistance (Ellison, 2017). Diuretic resistance is common in CKD where appropriate natriuresis does not occur even at high diuretic doses (Chitturi & Novak, 2018). Mechanisms of diuretic resistance can broadly be characterized in two categories; pharmacokinetic and pharmacodynamic. Pharmacokinetic reasons for altered diuretic responses include reduced amount of drug delivered to the tubular lumen, reduced GFR, decreased bioavailability, and increased volume of distribution. The effective concentration in the lumen may be suboptimal before the next dose is administered, leading to altered pharmacodynamics and rebound sodium reabsorption blunting the overall effect of diuretics. Additionally, long-term diuretic use can lead to chronic distal tubular hypertrophy (Chitturi & Novak, 2018).

Loop diuretics are recommended as the preferred agent in patients with advanced kidney disease (e.g., eGFR less than 30 mL/min/1.73m^2). Torsemide and bumetanide may be preferable to furosemide due to superior bioavailability (Gehr et al., 1994; Wargo & Banta, 2009). These agents can be titrated to effect, and recommended ceiling doses for oral loop diuretics in advanced renal disease are provided in Table 4 (Wilcox, 2002). Loop diuretics may have improved natriuresis in advanced kidney disease when used in conjunction with thiazide diuretics (Dussol et al., 2012). A pilot study included 23 patients with Stage 4 and 5 CKD who were randomized to a fixed-dose, double-blind, crossover trial with furosemide or hydrochlorothiazide or both drugs in combination (Dussol et al., 2012). Subjects participated in three 30-day study periods, with each study period separated by a 30-day washout period. During the study period, participants received either furosemide 60 mg daily, hydrochlorothiazide 25 mg daily, or both medications simultaneously. The average eGFR was 25 ± 10 mL/min/1.73m^2 at study initiation. Twenty-four-hour urine collection was performed, and primary endpoints were fractional excretion of sodium and chloride. Additionally, blood pressure and total body weight were measured. Compared to study baseline, fractional excretion of both sodium and chloride were significantly increased with combination therapy ($P < 0.05$) compared to monotherapy with either drug. A statistically significant decrease in blood pressure was observed following all three periods, though the largest decrease (mean 15 mmHg) was with combination therapy. The difference in body weight was not statistically significant with hydrochlorothiazide alone, but mean reduction in weight was statistically significant compared to baseline for patients receiving furosemide monotherapy, as well as those receiving combination therapy (-4 kg and -3 kg, respectively; $P < 0.05$). This study provides some prospective evidence of the potential for addition of low-dose hydrochlorothiazide in advanced kidney disease. However, the study design used a loop diuretic with poor bioavailability at doses below the maximal ceiling dose. Furthermore, this was a pilot study, and a large percentage of patients discontinued prematurely due to hypotension and pre-renal acute renal failure. These results suggest that combination therapy with a loop and thiazide diuretic may have additive benefits regarding sodium excretion and blood pressure control though their ability to reduce change in weight was smaller and requires close monitoring for potentially serious adverse effects. Thus, to manage fluid-related dyspnea in patients receiving CM-KF with residual urine output, a loop diuretic is preferred. Doses should be titrated to ceiling doses, and if appropriate, to achieve natriuresis and effective diuresis to mitigate volume overload and dyspnea, a thiazide diuretic could be cautiously considered to supplement the activity of the loop diuretic.

Pain

Pain was reported by nearly half of surveyed patients receiving CM-KF (Murtagh, Chai et al., 2007), and pain can have a significant impact on quality of life. The management of musculoskeletal and neuropathic pain will be discussed herein, but neither palliative sedation nor the management of symptoms at end of life (i.e., hours or days) are discussed. More appropriate guidelines are already available, and both medication and dose selection (and titration) requires consideration of the patient, clinical experience, and practical challenges (Douglas et al., 2009).

Similar to the management of other symptoms in patients with CM-KF, medications should be selected and titrated carefully given the potential for increased toxicity in kidney failure due to decreased renal elimination and accumulation of active metabolites (Koncicki et al., 2017). The overall approach to pain management in renal dysfunction should include a comprehensive assessment, a discussion of realistic pain goals and patient expectations, and regular patient follow up for monitoring efficacy and side effects (Koncicki et al., 2017). Patients receiving CM-KF are at greater risk for central nervous system depression, respiratory depression, and worsening constipation than the general population, which may already be present due to uremia and/or fluid overload and can be worsened

by analgesics (Koncicki et al., 2017). Pain management strategies can include non-pharmacologic strategies, such as meditation, acupuncture, or physical therapy, and patients may benefit from referrals and/or co-management with palliative care (Koncicki et al., 2017). The World Health Organization (WHO) analgesic ladder has been suggested for the management of chronic pain in CKD. However, the WHO analgesic ladder was originally designed for use in cancer pain, and the true risks and benefits are uncertain in patients with CM-KF. This ladder advocates for the use of non-opioids with eventual escalation of therapy to include opioids as needed for pain control; however, guidance on analgesic use in advanced kidney disease relies heavily on expert opinion because clinical data are lacking. Pain experienced by patients receiving CM-KF may include both nociceptive and neuropathic pain, and to limit inappropriate opioid use and its corresponding adverse effects, it has been suggested to utilize medications aimed at alleviating neuropathic pain first (Davison, 2019).

Recommended first-line agents for neuropathic pain in the general population include antiepileptics (e.g., gabapentin), serotonin-norepinephrine reuptake inhibitors, and tricyclic antidepressants (Dworkin et al., 2010). Gabapentin is beneficial in neuropathic pain and often used as first-line therapy; its use in kidney disease has been discussed in previous sections. Another antiepileptic, carbamazepine, is effective for the management of neuropathic pain, particularly trigeminal neuralgia, but has not been studied in advanced kidney disease (Wiffen et al., 2014). It undergoes extensive hepatic metabolism by CYP3A4 to an active metabolite with similar efficacy, carbamazepine auto-induces its own metabolism (Asconapé, 2014), and careful monitoring for drug interactions and symptom management is warranted. There is minimal renal elimination of carbamazepine, and experts suggest starting at 100 mg once or twice daily with appropriate dose adjustments (Davison, 2019). Serotonin-norepinephrine reuptake inhibitors (e.g., duloxetine) and tricyclic antidepressant medications (e.g., amitriptyline) may be options for neuropathic pain, and their use in kidney disease has been discussed previously.

In contrast, musculoskeletal or nociceptive pain occurs as a response to damaging stimuli, and preferred pharmacologic treatment options include the use of acetaminophen and nonsteroidal inflammatory drugs (NSAIDs) (DiPiro et al., 2020). Opioid analgesics should be considered only after documented failure of multiple classes of medications for those with chronic pain. Table 5 presents a listing of common pharmacological options used for pain manatement. For mild pain, experts advocate for the use of non-opioid agents, such as acetaminophen and NSAIDs. Acetaminophen is the preferred agent because it does not rely on renal metabolism or excretion (less than 5%) (DiPiro et al., 2020; Wilcock et al., 2017). However, it is recommended to be administered less frequently (i.e., 650 mg every 8 hours vs. every 4 to 6 hours) in patients with kidney failure (Koncicki et al., 2017) due to prolonged half-life as a result of decreased renal elimination (Martin et al., 1993). Systemic NSAIDs should be avoided in kidney dysfunction due to their vasoconstrictive and sodium retentive properties, which can worsen underlying hypertension and kidney function (Wilcock et al., 2017). Topical NSAIDs, such as diclofenac, may be beneficial in treating localized inflammation of the joints, such as in osteoarthritis pain (i.e., knees, hands), and topical NSAIDs are associated with minimal systemic absorption (6%) (Derry et al., 2016; Novartis, 1988); however, adverse events, such as gastrointestinal (GI) adverse events, may still occur. A Cochrane Systematic Review reported fewer GI adverse events with topical NSAIDs compared to oral formulations (17% vs 26%); however, the authors state that too few serious adverse events occurred in the topical administration studies to allow for conclusions to be drawn (Derry et al., 2016). Taken collectively for CM-KF, topical NSAIDs are likely preferable to systemic NSAIDs due to more favorable cardiovascular profile, but patients should be monitored for GI symptoms. Current guidelines suggest concomitant therapy with low-dose daily proton pump inhibitors or histamine-2 receptor antagonists at maximum dose twice daily (e.g., omeprazole 20 mg daily, famotidine 40 mg twice daily) to prevent GI complications in select patients (Lanza et al., 2009).

Opioid analgesics should be selected carefully in advanced kidney disease because benefits may outweigh the risks, which include overdose and addiction, and patient and caregiver education is vital. Medication selection should include a thorough review of potential drug interactions, metabolism, and elimination to avoid toxicity (e.g., CNS depression, respiratory depression), and opioids should be used in conjunction with non-opioid analgesics and stimulant laxatives to prevent worsening constipation (Crockett et al., 2019; Dowell et al., 2016; Murtagh, Chai et al., 2007). Hydromorphone is attractive in the setting of complex medication regimens as it undergoes rapid glucuronidation (rather than metabolism through the CYP enzyme system) to hydromorphone-3-glucoronide, which lacks analgesic activity but may contribute to adverse events (e.g., confusion, neuroexcitation) (Babul et al., 1995). Fentanyl may be considered at reduced doses and may be preferable to morphine given the presence of two active, renally-excreted metabolites with potential accumulation and toxicity (i.e., sedation, respiratory depression) with the latter (Koncicki et al., 2017). Fentanyl is primarily metabolized through the liver to inactive metabolites, but there is significant interpatient variability in analgesic doses, potentially due to variations in CYP3A4 metabolism (Labroo et al., 1997). Additionally, much of the pharmacokinetic data available in kidney failure is drawn from IV administration because the topical patch is not appropriate for management of acute pain in opioid-naïve patients (Koncicki et al., 2017). Transdermal patches may be used once pain is reasonably controlled and patients have met opioid-tolerant criteria. Initially approved for opioid-tolerant patients with

Table 5
Common Pharmacologic Options Used in Pain Management

Medication	Active Metabolite?	Suggested Dose in Stage 5 CKD
Acetaminophen	No	325 to 650 mg every 6 hours
NSAIDs	No	Avoid
Tramadol	Yes	50 mg every 12 hours
Hydrocodone	Yes – Hydromorphone	Avoid
Morphine	Yes – Morphone-3-G glucuronide; morphone-6-G glucoronide	Avoid
Hydromorphone	Yes – Hydromorphone-3-glucoronide	If selected, use cautiously.
Fentanyl	No	Reduce by 25% to 50%. Recommend consulting specialist given wide inter-patient variations.
Methadone	No	Reduce by 50% to 75%. Recommend consulting specialist given wide inter-patient variations.

Sources: Davison, 2019; Koncicki et al., 2017; Labroo et al., 1997; Murtagh, Chai et al., 2007; Wilcock et al., 2017.

cancer pain, some experts suggest subcutaneous or transmucosal fentanyl for acute breakthrough pain at reduced doses (e.g., 50% reduction) in patients with renal impairment with CrCl less than 10 mL/min (Murtagh, Chai et al., 2007). Due to its lipophilicity, methadone results in significant accumulation and is accompanied by significant variability in interpatient response; however, methadone is used cautiously by some experts because it lacks active metabolites and is not dependent on renal function for excretion. As with other opioid medications, doses of methadone should be tailored to the patient through close follow up and slow dose adjustments.

Other opioid agents, such as tramadol, codeine, and hydrocodone, while commonly used in patients without CKD, are not recommended in patients with kidney disease (Koncicki et al., 2017). In a retrospective cohort study of adult patients on hemodialysis ($n = 140{,}899$) conducted by Ishida and colleagues (2018), all opioid analgesics were associated with an increased hazard ratio for altered mental status and certain agents, specifically hydrocodone, oxycodone, tramadol, codeine, and hydromorphone, which were associated with significantly increased risk for fall and fracture. Tramadol exerts analgesic activity through agonism of u-opioid receptors and inhibition of norepinephrine. However, tramadol has a more potent, active metabolite and is renally excreted, leading to prolonged half-life in renal impairment, and if used, should be administered at low doses at increased intervals (e.g., 50 mg every 12 hours) (Murtagh, Chai et al., 2007). However, some experts suggest tramadol may be reasonable for use in moderate pain before escalating therapy to opioids (Murtagh, Chai et al., 2007), and if selected, tramadol should be used cautiously. Hydrocodone is another semisynthetic codeine derivative with active, renally excreted metabolites, and there are limited data in kidney disease and is not preferred (Murtagh, Chai et al., 2007). Due to potential drug interactions and adverse effects, pharmacologic options for pain management are relatively limited for patients receiving CM-KF, and creation of an appropriate treatment regimen requires careful consideration and patient monitoring by knowledgeable prescribers.

Conclusion

In summary, patients with CM-KF experience a high burden of symptoms, and many symptoms are often intertwined with or worsened by underlying comorbidities, which makes medication selection challenging. Given that patients with CM-KF rely heavily on medication strategies for symptom management, medication selection and management require appropriate follow-up and monitoring by all members of the health care team. There is an unmet need for comprehensive medication management in these complex patients, and the need will continue to grow as the prevalence of kidney failure increases and more patients select CM-KF. Nephrology nurses routinely communicate medication changes and provide assessments, and nurses are well positioned to assist the interprofessional team in the provision of quality care for patients receiving CM-KF.

References

Almutary, H., Bonner, A., & Douglas, C. (2013). Symptom burden in chronic kidney disease: A review of recent literature. *Journal of Renal Care*, *39*(30), 140-150.

AMAG Pharmaceuticals. (2018). *Feraheme (ferumoxytol) package insert.* https://www.feraheme.com/dosing-and-administration

Arnold, J. (1991). Determinants of pharmacologic effects and toxicity of benzodiazepine hypnotics: Role of lipophilicity and plasma elimination rates. *Journal of Clinical Psychiatry*, *52*(9, Suppl.), 11-14.

Aronoff, G.R., Bergstrom, R.F., Pottratz, S.T., Sloan, R.S., Wolen, R.L., & Lemberger, L. (1984). Fluoxetine kinetics and protein binding in normal and impaired renal function. *Clinical Pharmacology and Therapeutics*, *36*(1), 138-144. https://doi.org/10.1038/clpt.1984.152

Asconapé, J.J. (2014). Use of antiepileptic drugs in hepatic and renal disease. *Handbook of Clinical Neurology*, *119*, 417-432. https://doi.org/10.1016/B978-0-7020-4086-3.00027-8

Auerbach, M., Gafter-Gvili, A., & Macdougall, I.C. (2020). Intravenous iron: A framework for changing the management of iron deficiency. *The Lancet Haematology*, *7*(4). https://doi.org/10.1016/s2352-3026(19)30264-9

Auerbach, M., & Macdougall, I. (2017). The available intravenous iron formulations: History, efficacy, and toxicology. *Hemodialysis International*, *21*, S83-S92. https://doi.org/10.1111/hdi.12560

Babul, N., Darke, A.C., & Hagen, N. (1995). Hydromorphone metabolite accumulation in renal failure. *Journal of Pain and Symptom Management*, *10*(3), 184-186. https://doi.org/10.1016/0885-3924(94)00121-Z

Brown, M.A., Collett, G.K., Josland, E.A., Foote, C., Li, Q., & Brennan, F.P. (2015). CKD in elderly patients managed without dialysis: Survival, symptoms, and quality of life. *Clinical Journal of the American Society of Nephrology*, *10*(2), 260-268. https://doi.org/10.2215/CJN.03330414

Canadian Erythropoietin Study Group. (1990). Association between recombinant human erythropoietin and quality of life and exercise capacity of patients receiving haemodialysis. Canadian Erythropoietin Study Group. *BMJ*, *300*(6724), 573-578. https://doi.org/10.1136/bmj.300.6724.573

Chan, K.Y., Li, C.W., Wong, H., Yip, T., Chan, M.L., Cheng, H.W., & Sham, M.K. (2013). Use of sertraline for antihistamine-refractory uremic pruritus in renal palliative care patients. *Journal of Palliative Medicine*, *16*(8), 966-970. https://doi.org/10.1089/jpm.2012.0504

Chan, K.Y., Li, C.W., Wong, H., Yip, T., Sham, M.K., Cheng, H.W., Teo, K.C., Kwok, W.G., & Chan, T.M. (2014). Effect of erythropoiesis-stimulating agents on hemoglobin level, fatigue and hospitalization rate in renal palliative care patients. *International Urology and Nephrology*, *46*(3), 653-657. https://doi.org/10.1007/s11255-014-0661-x

Charytan, C., Qunibi, W., & Bailie, G.R. (2005). Comparison of intravenous iron sucrose to oral iron in the treatment of anemic patients with chronic kidney disease not on dialysis. *Nephron – Clinical Practice*, *100*(3). https://doi.org/10.1159/000085049

Cheikh Hassan, H.I., Brennan, F., Collett, G., Josland, E.A., & Brown, M.A. (2015). Efficacy and safety of gabapentin for uremic pruritus and restless legs syndrome in conservatively managed patients with chronic kidney disease. *Journal of Pain and Symptom Management*, *49*(4), 782-789. https://doi.org/10.1016/j.jpainsymman.2014.08.010

Chitturi, C., & Novak, J.E. (2018a). Diuretics in the management of cardiorenal syndrome. *Advances in Chronic Kidney Disease*, *25*(5), 425-433. https://doi.org/10.1053/j.ackd.2018.08.008

Cho, Y.W., Allen, R.P., & Earley, C.J. (2016). Clinical efficacy of ferric carboxymaltose treatment in patients with restless legs syndrome. *Sleep Medicine*, *25*, 16-23. https://doi.org/10.1016/j.sleep.2016.06.021

ClinicalTrials.gov. (2019). *Impact of ferric citrate vs ferrous sulfate on iron parameters and hemoglobin in individuals with CKD and iron deficiency.* https://clinicaltrials.gov/ct2/show/NCT02888171

Combs, S.A., Teixeira, J.P., & Germain, M.J. (2015). Pruritus in kidney disease. *Seminars in Nephrology*, *35*(4), 383-391. https://doi.org/10.1016/j.semnephrol.2015.06.009

Crockett, S.D., Greer, K.B., Heidelbaugh, J.J., Falck-Ytter, Y., Hanson, B.J., & Sultan, S. (2019). American Gastroenterological Association Institute guideline on the medical management of opioid-induced constipation. *Gastroenterology*, *156*(1), 218-226. https://doi.org/10.1053/j.gastro.2018.07.016

Dalrymple, L.S., & Go, A.S. (2008). Epidemiology of acute infections among patients with chronic kidney disease. *Clinical Journal of the American Society of Nephrology*, *3*(5), 1487-1493. https://doi.org/10.2215/CJN.01290308

Dashti-Khavidaki, S., Chaman, N., Hossein, K., Talasaz, A.H., Amadi, F., Lessan-Pezeshki, M., Ghaeli, P., Dalili, S., & Alimadadi, A. (2011). Comparing effects of clonazepam and zolpidem on sleep quality of patients on maintenance hemodialysis. *Iranian Journal of Kidney Diseases*, *5*(6), 404-409.

Davison, S.N. (2010). End-of-life care preferences and needs: Perceptions of patients with chronic kidney disease. *Clinical Journal of the American Society of Nephrology*, *5*(2), 195-204. https://doi.org/10.2215/CJN.05960809

Davison, S.N. (2019). Clinical pharmacology considerations in pain management in patients with advanced kidney failure. *Clinical Journal of the American Society of Nephrology*, *14*(6), 917-931. https://doi.org/10.2215/CJN.05180418

Davison, S.N., Levin, A., Moss, A.H., Jha, V., Brown, E.A., Brennan, F., Murtagh, F.E.M., Naicker, S., Germain, M.J., O'Donoghue, D.J., Morton, R.L., & Obrador, G.T. (2015). Executive summary of the KDIGO Controversies Conference on Supportive Care in Chronic Kidney Disease: Developing a roadmap to improving quality care. *Kidney International*, *88*(3), 447-459. https://doi.org/10.1038/ki.2015.110

Del Vecchio, L., & Locatelli, F. (2016). An overview on safety issues related to erythropoiesis-stimulating agents for the treatment of anaemia in patients with chronic kidney disease. *Expert Opinion on Drug Safety*, *15*(8), 1021-1030. https://doi.org/10.1080/14740338.2016.1182494

Del Vecchio, L., & Locatelli, F. (2017). Clinical practice guidelines on iron therapy: A critical evaluation. *Hemodialysis International*, *21*. https://doi.org/10.1111/hdi.12562

Derry, S., Conaghan, P., Da Silva, J.A.P., Wiffen, P.J., & Moore, R.A. (2016). Topical NSAIDs for chronic musculoskeletal pain in adults. *Cochrane Database of Systematic Reviews.* https://doi.org/10.1002/14651858.cd007400.pub3

DiPiro, J.T., Talbert, R.L., Yee, G.C., Matzke, G.R., Wells, B.G., & Posey, L.M. (2020). *Pharmacotherapy: A pathophysiologic approach.* McGraw Hill Medical.

Douglas, C., Murtagh, F.E.M., Chambers, E.J., Howse, M., & Ellershaw, J. (2009). Symptom management for the adult patient dying with advanced chronic kidney disease: A review of the literature and development of evidence-based

guidelines by a United Kingdom Expert Consensus Group. *Palliative Medicine*, *23*(2), 103-110. https://doi.org/10.1177/0269216308100247

Doweiko, J., Fogel, B., & Goldberg, R. (1984). Trazodone and hemodialysis. *Journal of Clinical Psychiatry*, *45*(8), 361.

Dowell, D., Haegerich, T.M., & Chou, R. (2016). CDC guideline for prescribing opioids for chronic pain – United States, 2016. *Journal of the American Medical Association*, *315*(15), 1624. https://doi.org/10.1001/jama.2016.1464

Dussol, B., Moussi-Frances, J., Morange, S., Somma-Delpero, C., Mundler, O., & Berland, Y. (2012). A pilot study comparing furosemide and hydrochlorothiazide in patients with hypertension and stage 4 or 5 chronic kidney disease. *Journal of Clinical Hypertension*, *14*(1), 32-37. https://doi.org/10.1111/j.1751-7176.2011.00564.x

Dworkin, R.H., O'Connor, A.B., Audette, J., Baron, R., Gourlay, G.K., Haanpää, M.L., Kent, J.L., Krane, E.J., LeBel, A.A., Levy, R.M., Mackey, S.C., Mayer, J., Miaskowski, C., Raja, S.N., Rice, A.S.C., Schmader, K.E., Stacey, B., Stanos, S., Treede, R.D., … Wells, C.D. (2010). Recommendations for the pharmacological management of neuropathic pain: An overview and literature update. *Mayo Clinic Proceedings*, *85*(3), S3-S14. https://doi.org/10.4065/mcp.2009.0649

Earley, C.J., Allen, R.P., Beard, J.L., & Connor, J.R. (2000). Insight into the pathophysiology of restless legs syndrome. *Journal of Neuroscience Research*, *62*(5), 623-628.

Ellison, D.H. (2017). Treatment of disorders of sodium balance in chronic kidney disease. *Advances in Chronic Kidney Disease*, *24*(5), 332-341. https://doi.org/10.1053/j.ackd.2017.07.003

Fick, D.M., Semla, T.P., Steinman, M., Beizer, J., Brandt, N., Dombrowski, R., DuBeau, C.E., Pezzullo, L., Epplin, J.J., Flanagan, N., Morden, E., Hanlon, J., Hollmann, P., Laird, R., Linnebur, S., & Sandhu, S. (2019). American Geriatrics Society 2019 Updated AGS Beers Criteria® for potentially inappropriate medication use in older adults. *Journal of the American Geriatrics Society*, *67*(4), 674-694. https://doi.org/10.1111/jgs.15767

Fishbane, S., Block, G.A., Loram, L., Neylan, J., Pergola, P.E., Uhlig, K., & Chertow, G.M. (2017). Effects of ferric citrate in patients with nondialysis-dependent CKD and iron deficiency anemia. *Journal of the American Society of Nephrology*, *28*(6), 1851-1858. https://doi.org/10.1681/ASN.2016101053

Flythe, J.E., Dorough, A., Narendra, J.H., Forfang, D., Hartwell, L., & Abdel-Rahman, E. (2018). Perspectives on symptom experiences and symptom reporting among individuals on hemodialysis. *Nephrology Dialysis Transplantation*, *33*(10), 1842-1852. https://doi.org/10.1093/ndt/gfy069

Flythe, J.E., Hilliard, T., Castillo, G., Ikeler, K., Orazi, J., Abdel-Rahman, E., Pai, A.M., Rivara, M.B., St. Peter, W.L., Weisbord, S.D., Wilkie, C., & Mehrotra, R. (2018). Symptom prioritization among adults receiving in-center hemodialysis: A mixed methods study. *Clinical Journal of the American Society of Nephrology*, *13*(5), 735-745. https://doi.org/10.2215/CJN.10850917

Forest Pharmaceuticals, Inc. (2011). *Celexa® (citalopram hydrobromide)*. https://www.accessdata.fda.gov/drugsatfda_docs/label/2012/020822s042,021046s019lbl.pdf

Gehr, T.W., Rudy, D.W., Matzke, G.R., Kramer, W.G., Sica, D.A., & Brater, D.C. (1994). The pharmacokinetics of intravenous and oral torsemide in patients with chronic renal insufficiency. *Clinical Pharmacology and Therapeutics*, *56*(1), 31-38.

Gopaluni, S., Sherif, M., & Ahmadouk, N.A. (2016). Interventions for chronic kidney disease-associated restless legs syndrome. *Cochrane Database of Systematic Reviews*. https://doi.org/10.1002/14651858.CD010690.pub2

Greenblatt, D.J. (1991). Benzodiazepine hypnotics: Sorting the pharmacokinetic facts. *Journal of Clinical Psychiatry*, *52*(9, Suppl.), 4-10.

Hauber, B., Caloyeras, J., Posner, J., Brommage, D., Belozeroff, V., & Cooper, K. (2017). Hemodialysis patients' preferences for the management of anemia. *BMC Nephrology*, *18*(1), 1-9. https://doi.org/10.1186/s12882-017-0665-8

Hedayati, S.S., Gregg, L.P., Carmody, T., Jain, N., Toups, M., Rush, A.J., Toto, R.D., & Trivedi, M.H. (2017). Effect of sertraline on depressive symptoms in patients with chronic kidney disease without dialysis dependence: The CAST randomized clinical trial. *JAMA*, *318*(19), 1876-1890. https://doi.org/10.1001/jama.2017.17131

Hedayati, S.S., Minhajuddin, A.T., Toto, R.D., Morris, D.W., & Rush, A.J. (2009). Prevalence of major depressive episode in CKD. *American Journal of Kidney Diseases*, *54*(3), 424-432. https://doi.org/10.1053/j.ajkd.2009.03.017

Hedayati, S.S., Yalamanchili, V., & Finkelstein, F.O. (2012). A practical approach to the treatment of depression in patients with chronic kidney disease and end-stage renal disease. *Kidney International*, *81*(3), 247-255. https://doi.org/10.1038/ki.2011.358

Herring, W.J., Connor, K.M., Snyder, E., Snavely, D.B., Zhang, Y., Hutzelmann, J., Matzura-Wolfe, D., Benca, R.M., Krystal, A.D., Walsh, J.K., Lines, C., Roth, T., & Michelson, D. (2017). Suvorexant in elderly patients with insomnia: pooled analyses of data from Phase III randomized controlled clinical trials. *American Journal of Geriatric Psychiatry*, *25*(7), 791-802. https://doi.org/10.1016/j.jagp.2017.03.004

Horigan, A.E. (2012). Fatigue in hemodialysis patients: A review of current knowledge. *Journal of Pain and Symptom Management*, *44*(5), 715-724. https://doi.org/10.1016/j.jpainsymman.2011.10.015

Hussain, J.A., Mooney, A., & Russon, L. (2013). Comparison of survival analysis and palliative care involvement in patients aged over 70 years choosing conservative management or renal replacement therapy in advanced chronic kidney disease. *Palliative Medicine*, *27*(9), 829-839. https://doi.org/10.1177/0269216313484380

Ishida, J.H., McCulloch, C.E., Steinman, M.A., Grimes, B., & Johansen, K.L. (2018). Opioid analgesics and adverse outcomes among hemodialysis patients. *Clinical Journal of the American Society of Nephrology*, *13*(5), 746-753. https://doi.org/10.2215/CJN.09910917

Jhamb, M., Weisbord, S.D., Steel, J.L., & Unruh, M. (2008). Fatigue in patients receiving maintenance dialysis: A review of definitions, measures, and contributing factors. *American Journal of Kidney Diseases*, *52*(2), 353-365. https://doi.org/10.1053/j.ajkd.2008.05.005

Joffe, P., Larsen, F.S., Pedersen, V., Ring-Larsen, H., Aaes-Jørgensen, T., & Sidhu, J. (1998). Single-dose pharmacokinetics of citalopram in patients with moderate renal insufficiency or hepatic cirrhosis compared with healthy subjects. *European Journal of Clinical Pharmacology*, *54*(3), 237-242. https://doi.org/10.1007/s002280050452

Ju, A. Unruh, M. Davison, S. Dapueto, J., Dew, M.A., Fluck, R., Germain, M., Jassal, S.V., Obrador, G., O'Donoghue, D., Josephson, M.A., Craig, J.C., Viecelli, A., O'Lone, E., Hanson, C.S., Manns, B., Sautenet, B., Howell, M., Reddy, B., … Tong,, A. (2018). Establishing a core outcome measure for fatigue in patients on hemodialysis: a standardized out-

comes in nephrology-hemodialysis (SONG-HD) consensus workshop report. *American Journal of Kidney Diseases*, *72*(1), 104-112.

Ju, A., Unruh, M., Davison, S.N, Dapueto, J., Dew, M.A., Fluck, R., Germain, M., JAssal, S.V., Obrador, G., O'Donoghue, D., Howell, M., O'Lone, E., Shen, J.I., Craig, J.C., & Tong, A. (2020). Identifying dimensions of fatigue in haemodialysis important to patients, caregivers, and health professionals: An international survey. *Nephrology*, *25*(3), 239-247.

Kidney Disease Improving Global Outcomes (KDIGO). (2012). KDIGO clinical practice guideline for anemia in chronic kidney disease. *Kidney International*, *2*(4). https://kdigo.org/wp-content/uploads/2016/10/KDIGO-2012-Anemia-Guideline-English.pdf

Koch, B.C.P., Nagtegaal, J.E., Hagen, E.C., Van Der Westerlaken, M.M.L., Boringa, J.B.S., Kerkhof, G.A., & Ter Wee, P.M. (2009). The effects of melatonin on sleep-wake rhythm of daytime haemodialysis patients: A randomized, placebo-controlled, cross-over study (EMSCAP study). *British Journal of Clinical Pharmacology*, *67*(1), 68-75. https://doi.org/10.1111/j.1365-2125.2008.03320.x

Koncicki, H.M., Unruh, M., & Schell, J.O. (2017). In practice pain management in CKD: A guide for nephrology providers. *American Journal of Kidney Diseases*, *69*(3), 451-460. https://doi.org/10.1053/j.ajkd.2016.08.039

Labroo, R.B., Paine, M.F., Thummel, K.E., & Kharasch E.D. (1997). Fentanyl metabolism by human hepatic and intestinal cytochrome P450 3A4: Implications for interindividual variability in disposition, efficacy, and drug interactions. *Drug Metabolism and Disposition 25*(9), 1072-1080.

Lanza, F.L., Chan, F.K.L., & Quigley, E.M.M. (2009). Guidelines for prevention of NSAID-related ulcer complications. *American Journal of Gastroenterology*, *104*(3), 728-738.

Lindner, A.V., Novak, M., Bohra, M., & Mucsi, I. (2015). Insomnia in patients with chronic kidney disease. *Seminars in Nephrology*, *35*(4), 359-372. https://doi.org/10.1016/j.semnephrol.2015.06.007

Macdougall, I.C., Bircher, A.J., Eckardt, K.U., Obrador, G.T., Pollock, C.A., Stenvinkel, P., Swinkels, D.W., Wanner, C., Weiss, G., & Chertow, G.M. (2016). Iron management in chronic kidney disease: Conclusions from a "Kidney Disease: Improving Global Outcomes" (KDIGO) Controversies Conference. *Kidney International*, *89*(1), 28-39. https://doi.org/10.1016/j.kint.2015.10.002

Macdougall, I.C., Bock, A.H., Carrera, F., Eckardt, K.U., Gaillard, C., Van Wyck, D., Roubert, B., Nolen, J.G., & Roger, S.D. (2014). FIND-CKD: A randomized trial of intravenous ferric carboxymaltose versus oral iron in patients with chronic kidney disease and iron deficiency anaemia. *Nephrology Dialysis Transplantation*, *29*(11), 2075-2084. https://doi.org/10.1093/ndt/gfu201

Macdougall, I.C., & Obrador, G.T. (2013). How important is transfusion avoidance in 2013? *Nephrology Dialysis Transplantation*, *28*(5), 1092-1099.

Macdougall, I.C., Strauss, W.E., McLaughlin, J., Li, Z., Dellanna, F., & Hertel, J. (2014). A randomized comparison of ferumoxytol and iron sucrose for treating iron deficiency anemia in patients with CKD. *Clinical Journal of the American Society of Nephrology*, *9*(4), 705-712. https://doi.org/10.2215/CJN.05320513

Martin, U., Temple, R.M., Winney, R.J., & Prescott, L.F. (1993). The disposition of paracetamol and its conjugates during multiple dosing in patients with end-stage renal failure maintained on haemodialysis. *European Journal of Clinical Pharmacology*, *45*(2), 141-145. https://doi.org/10.1007/BF00315495

Mehrotra, R., Cukor, D., Unruh, M., Rue, T., Heagerty, P., Cohen, S.D., Dember, L.M., Diaz-Linhart, Y., Dubovsky, A., Greene, T., Grote, N., Kutner, N., Trivedi, M.H., Quinn, D.K., Ver Halen, N., Weisbord, S.T., Young, B.A., Kimmel, P.L., & Hedayati, S.S. (2019). Comparative efficacy of therapies for treatment of depression for patients undergoing maintenance hemodialysis. *Annals of Internal Medicine*, *170*(6), 369-379.

Merck & Co., Inc. (1996). *Remeron® (mirtazapine) prescribing information*. https://www.merck.com/product/usa/pi_circulars/r/remeron/remeron_tablets_mg.pdf

Merck & Co., Inc. (2014). *Belsomra® (suvorexant) prescribing information*. https://www.accessdata.fda.gov/drugsatfda_docs/label/2014/204569s000lbledt.pdf

Mettang, T., & Kremer, A.E. (2014). Uremic pruritus. *Kidney International*, *87*(4), 685-691. https://doi.org/10.1038/ki.2013.454

Morrison, G., Chiang, S.T., Koepke, H.H., & Walker, B.R. (1984). Effect of renal impairment and hemodialysis on lorazepam kinetics. *Clinical Pharmacology & Therapeutics*, *35*(5), 646-652. https://doi.org/10.1038/clpt.1984.89

Morton, C.A., Lafferty, M., Hau, C., Henderson, I., Jones, M., & Lowe, J.G. (1996). Pruritus and skin hydration during dialysis. *Nephrology Dialysis Transplantation*, *11*(10), 2031-2036.

Murtagh, F.E.M., Addington-Hall, J., & Higginson, I.J. (2007). The prevalence of symptoms in end-stage renal disease: A systematic review. *Advances in Chronic Kidney Disease*, *14*(1), 82-99. https://doi.org/10.1053/j.ackd.2006.10.001

Murtagh, F.E.M., Addington-Hall, J.M., Edmonds, P.M., Donohoe, P., Carey, I., Jenkins, K., & Higginson, I.J. (2007). Symptoms in advanced renal disease: A cross-sectional survey of symptom prevalence in Stage 5 chronic kidney disease managed without dialysis. *Journal of Palliative Medicine*, *10*(6), 1266-1276. https://doi.org/10.1089/jpm.2007.0017

Murtagh, F.E.M., Burns, A., Moranne, O., Morton, R.L., & Naicker, S. (2016). Supportive care: Comprehensive conservative care in end-stage kidney disease. *Clinical Journal of the American Society of Nephrology*, *11*(10), 1909-1914. https://doi.org/10.2215/CJN.04840516

Murtagh, F.E.M., Chai, M., Donohoe, P., Edmonds, P.M., & Higginson, I.J. (2007). The use of opioid analgesia in end-stage renal disease patients managed without dialysis: Recommendations for practice. *Journal of Pain & Palliative Care Pharmacotherapy*, *21*(2), 5-16.

Murtagh, F.E.M., Marsh, J.E., Donohoe, P., Ekbal, N.J., Sheerin, N.S., & Harris, F.E. (2007). Dialysis or not? A comparative survival study of patients over 75 years with chronic kidney disease stage 5. *Nephrology Dialysis Transplantation*, *22*(7), 1955-1962. https://doi.org/10.1093/ndt/gfm153

Nagler, E.V., Webster, A.C., Vanholder, R., & Zoccali, C. (2012). Antidepressants for depression in stage 3-5 chronic kidney disease: A systematic review of pharmacokinetics, efficacy and safety with recommendations by European Renal Best Practice (ERBP). *Nephrology Dialysis Transplantation*, *27*(10), 3736-3745. https://doi.org/10.1093/ndt/gfs295

Novartis. (1988). *Voltaren gel (diclofenac sodium topical gel) prescribing information*. https://www.accessdata.fda.gov/drugsatfda_docs/label/2009/022122s006lbl.pdf

Pai, A.B., Cardone, K.E., Manley, H.J., St. Peter, W.L., Shaffer, R., Somers, M., & Mehrotra, R. (2013). Medication reconcil-

iation and therapy management in dialysis-dependent patients: Need for a systematic approach. *Clinical Journal of the American Society of Nephrology*, *8*(11), 1988-1999. https://doi.org/10.2215/CJN.01420213

Palmer, S., Vecchio, M., Craig, J.C., Tonelli, M., Johnson, D.W., Nicolucci, A., Pellegrini, F., Saglimbene, V., Logroscino, G., Fishbane, S., & Strippoli, G.F.M. (2013). Prevalence of depression in chronic kidney disease: Systematic review and meta-analysis of observational studies. *Kidney International*, *84*(1), 179-191. https://doi.org/10.1038/ki.2013.77

Pellecchia, M.T., Vitale, C., Sabatini, M., Longo, K., Amboni, M., Bonavita, V., & Paolo, B. (2004). Ropinirole as a treatment of restless legs syndrome in patients on chronic hemodialysis. *Clinical Neuropharmacology*, *27*(4), 178-181. https://doi.org/10.1097/01.wnf.0000135480.78529.06

Raghavan, D., & Holley, J.L. (2016). Conservative care of the elderly CKD patient: A practical guide. *Advances in Chronic Kidney Disease*, *23*(1), 51-56. https://doi.org/10.1053/j.ackd.2015.08.003

Riley, M.V., Vess, J., & Dumas, B.P. (2017). Home therapy to reduce office visits for patients with chronic kidney disease and anemia. *Nephrology Nursing Journal, 44*(1), 29-33.

Russcher, M., Koch, B.C.P., Nagtegaal, J.E., van Ittersum, F.J., Pasker-de Jong, P.C.M., Hagen, E.C., van Dorp, W.T., Gabreels, B., Wildbergh, T.X., van der Westerlaken, M.M.L., Gaillard, C.A.J.M., & ter Wee, P.M. (2013). Long-term effects of melatonin on quality of life and sleep in haemodialysis patients (Melody study): A randomized controlled trial. *British Journal of Clinical Pharmacology*, *76*(5), 668-679. https://doi.org/10.1111/bcp.12093

Salerno, F.R., Parraga, G., & McIntyre, C.W. (2017). Why is your patient still short of breath? Understanding the complex pathophysiology of dyspnea in chronic kidney disease. *Seminars in Dialysis*. https://doi.org/10.1111/sdi.12548

Sanofi Aventis. (2011). *Ferrlecit (sodium ferric gluconate) package insert*. https://www.accessdata.fda.gov/drugsatfda_docs/label/2011/020955s013s015lbl.pdf

Scherer, J.S., Combs, S.A., & Brennan, F. (2017). Sleep disorders, restless legs syndrome, and uremic pruritus: Diagnosis and treatment of common symptoms in dialysis patients. *American Journal of Kidney Diseases*, *69*(1), 117-128. https://doi.org/10.1053/j.ajkd.2016.07.031

Shepshelovich, D., Rozen-Zvi, B., Avni, T., Gafter, U., & Gafter-Gvili, A. (2016). Intravenous versus oral iron supplementation for the treatment of anemia in CKD: An updated systematic review and meta-analysis. *American Journal of Kidney Diseases*, *68*(5), 677-690. https://doi.org/10.1053/j.ajkd.2016.04.018

Simons, K.J., Watson, W.T.A., Martin, T.J., Chen, X.Y., & Simons, F.E.R. (1990). Diphenhydramine : and pharmacodynamics in elderly adults, young adults, and children. *The Journal of Clinical Pharmacology, 3,* 665-671. https://doi.org/10.1002/j.1552-4604.1990.tb01871.x

Simonsen, E., Komenda, P., Lerner, B., Askin, N., Bohm, C., Shaw, J., Tangri, N., & Rigatto, C. (2017). Treatment of uremic pruritus: A systematic review. *American Journal of Kidney Diseases*, *70*(5), 638-655. https://doi.org/10.1053/j.ajkd.2017.05.018

Sloand, J.A., Shelly, M.A., Feigin, A., Bernstein, P., & Monk, R.D. (2004). A double-blind, placebo-controlled trial of intravenous iron dextran therapy in patients with ESRD and restless legs syndrome. *American Journal of Kidney Diseases*, *43*(4), 663-670.

Spinowitz, B.S., Kausz, A.T., Baptista, J., Noble, S.D., Sothinathan, R., Bernardo, M.V., Brenner, L., & Pereira, B.J.G. (2008). Ferumoxytol for treating iron deficiency anemia in CKD. *Journal of the American Society of Nephrology*, *19*(8), 1599-1605. https://doi.org/10.1681/ASN.2007101156

Sutton, E.L. (2015). Profile of suvorexant in the management of insomnia. *Drug Design, Development and Therapy*, *9*, 6035. https://doi.org/10.2147/DDDT.S73224

Tam-Tham, H., King-Shier, K.M., Thomas, C.M., Quinn, R.R., Fruetel, K., Davison, S.N., & Hemmelgarn, B.R. (2016). Prevalence of barriers and facilitators to enhancing conservative kidney management for older adults in the primary care setting. *Clinical Journal of the American Society of Nephrology*, *11*(11), 2012-2021. https://doi.org/10.2215/CJN.04510416

Tan, C.C., Wong, K.S., Thirumoorthy, T., Lee, E., & Woo, K.T. (1990). A randomized, crossover trial of Sarna and Eurax lotions in the treatment of haemodialysis patients with uraemic pruritus. *Journal of Dermatological Treatment*, *1*(5), 235-238. https://doi.org/10.3109/09546639009086741

Tanhehco, Y.C., & Berns, J.S. (2012). Red blood cell transfusion risks in patients with end-stage renal disease. *Seminars in Dialysis*, *25*(5), 539-544. https://doi.org/10.1111/j.1525-139X.2012.01089.x

Tarng, D.C., Cho, Y.L., Liu, H.N., & Huang, T.P. (1996). Hemodialysis-related pruritus : A double-blind, placebo-controlled, crossover study of capsaicin 0.025% cream. *Nephron*, *72*, 617-622. https://doi.org/10.1159/000188949

Tolkien, Z., Stecher, L., Mander, A.P., Pereira, D.I.A., & Powell, J.J. (2015). Ferrous sulfate Supplementation causes significant gastrointestinal side-effects in adults: A systematic review and meta-Analysis. *PLoS One*, *10*(2), 1-20. https://doi.org/10.1371/journal.pone.0117383

Troy, S.M., Schultz, R.W., Parker, V.D., Chiang, S.T., & Blum, R.A. (1994). The effect of renal disease on the disposition of venlafaxine. *Clinical Pharmacology & Therapeutics*, *56*(1), 14-21. https://doi.org/10.1038/clpt.1994.95

Turpeinen, M., Koivuviita, N., Tolonen, A., Reponen, P., Lundgren, S., Miettunen, J., Metsarinne, K., Rane, A., Pelkonen, O., & Laine, K. (2007). Effect of renal impairment on the pharmacokinetics of bupropion and its metabolites. *British Journal of Clinical Pharmacology*, *64*(2), 165-173. https://doi.org/10.1111/j.1365-2125.2007.02866.x

United States Renal Data System (USRDS). (2018). *2018 USRDS annual data report: Epidemiology of kidney disease in the United States*. National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases. https://www.usrds.org/annual-data-report/previous-adrs/

Valika, A., & Peixoto, A.J. (2016). Hypertension management in transition: From CKD to ESRD. *Advances in Chronic Kidney Disease*, *23*(4), 255-261. https://doi.org/10.1053/j.ackd.2016.02.002

Van Wyck, D.B., Roppolo, M., Martinez, C.O., Mazey, R.M., & McMurray, S. (2005). A randomized, controlled trial comparing IV iron sucrose to oral iron in anemic patients with nondialysis-dependent CKD. *Kidney International*, *68*(6), 2846-2856. https://doi.org/10.1111/j.1523-1755.2005.00758.x

Verberne, W.R., Tom Geers, A.B.M., Jellema, W.T., Vincent, H.H., van Delden, J.J.M., & Bos, W.J.W. (2016). Comparative survival among older adults with advanced kidney disease managed conservatively versus with dialysis. *Clinical Journal of the American Society of Nephrology*, *11*(4), 633-640. https://doi.org/10.2215/CJN.07510715

continued on page 371

Medication Management

continued from page 335

Vifor, Inc. (2017). *Vénofer (iron sucrose) package insert.* https://www.accessdata.fda.gov/drugsatfda_docs/label/2007/021135s017lbl.pdf

Vifor, Inc. (2018). *Injectafer (ferric carboxy maltose) package insert.* https://injectafer.com/prescribing-information-portlet/getDocument?product=IF&inline=true

Wargo, K.A., & Banta, W.M. (2009). A comprehensive review of the loop diuretics: Should furosemide be first line? *Annals of Pharmacotherapy*, *43*(11), 1836-1847. https://doi.org/10.1345/aph.1M177

Watnick, S. (2009). Quality of life and depression in CKD: Improving hope and health. *American Journal of Kidney Diseases*, *54*(3), 399-402. https://doi.org/10.1053/j.ajkd.2009.06.009

Watson Pharmaceuticals (2009). *Infed (iron dextran) package insert.* https://www.accessdata.fda.gov/drugsatfda_docs/label/2009/017441s171lbl.pdf

Weisbord, S.D., Fried, L.F., Mor, M.K., Resnick, A.L., Unruh, M.L., Palevsky, P.M., Lavenson, D.J., Cooksey, S.H., Fine, M.J., Kimmel, P.L., & Arnold, R.M. (2007). Renal provider recognition of symptoms in patients on maintenance hemodialysis. *Clinical Journal of the American Society of Nephrology*, *2*(5), 960-967. https://doi.org/10.2215/CJN.00990207

Wiffen, P.J., Derry, S., Moore, R.A., & Kalso, E.A. (2014). Carbamazepine for chronic neuropathic pain and fibromyalgia in adults. *Cochrane Database of Systematic Reviews*, 4, CD005451. https://doi.org/10.1002/14651858.CD005451

Wilcock, A., Charlesworth, S., Twycross, R., Waddington, A., Worthington, O., Murtagh, F.E.M., Beavis, J., King, S., Mihalyo, M., & Kotlinska-Lemieszek, A. (2017). Prescribing non-opioid drugs in end-stage kidney disease. *Journal of Pain and Symptom Management*, *54*(5), 776-787. https://doi.org/10.1016/j.jpainsymman.2017.08.014

Wilcox, C.S. (2002). New insights into diuretic use in patients with chronic renal disease. *Journal of the American Society of Nephrology: 13*(3), 798-805.

Wongrakpanich, S., Susantitaphong, P., Isaranuwatchai, S., Chenbhanich, J., Eiam-Ong, S., & Jaber, B.L. (2017). Dialysis therapy and conservative management of advanced chronic kidney disease in the elderly: A systematic review. *Nephron*, *137*(3), 178-189. https://doi.org/10.1159/000477361

Young, T.A., Patel, T.S., Camacho, F., Clark, A., Freedman, B.I., Kaur, M., Fountain, J., Williams, L.L., Yosipovitch, G., & Fleischer, A.B., Jr. (2009). A pramoxine-based anti-itch lotion is more effective than a control lotion for the treatment of uremic pruritus in adult hemodialysis patients. *Journal of Dermatological Treatment*, *20*(2), 76-81. https://doi.org/10.1080/09546630802441218

CE EVALUATION FORM – 1.5 Contact Hours 60 Pharmacology Minutes – Expires: August 31, 2022 ANNJ2020

Approaches to Medication Management in Patients with Kidney Failure Opting for Conservative Management

https://doi.org/10.37526/1526-744X.2020.47.4.319

Complete the Following (please print)

Name: _____

Address: _____

City: _____

Telephone: _____ Email: _____

ANNA Member: ☐ Yes ☐ No Member #_____

Payment: ☐ Check Enclosed ☐ American Express ☐ Visa ☐ MasterCard

Total Amount Submitted: _____

Credit Card Number: _____ Exp. Date: _____

Name as it Appears on the Card: _____

Note: If you wish to keep the journal intact, you may photocopy the answer sheet or access this activity at *www.annanurse.org/journal*

SUBMISSION INSTRUCTIONS

Online Submission

Articles are free to ANNA members
Regular Article Price: $15
CNE Evaluation Price: $15

Online submissions of this CNE evaluation form are available at annanurse.org/library. CNE certificates will be available immediately upon successful completion of the evaluation.

Mail/Fax Submission

ANNA Member Price: $15
Regular Price: $25

- Send this page to the ANNA National Office; East Holly Avenue/Box 56; Pitman, NJ 08071-0056, or fax this form to (856) 589-7463.
- Enclose a check or money order payable to ANNA. Fees listed in payment section.
- A certificate for the contact hours will be awarded by ANNA.
- Please allow 2-3 weeks for processing.
- You may submit multiple answer forms in one mailing; however, because of various processing procedures for each answer form, you may not receive all of your certificates returned in one mailing.

Learning Outcome

After completing this learning activity, the learner will be able to describe potential pharmacologic treatment options for symptom management in conservatively managed kidney failure.

Evaluation Form (*ALL questions must be answered to complete the learning activity. Longer answers to open-ended questions may be typed on a separate page.*)

1. I verify I have completed this education activity. ☐ Yes ☐ No

_____
SIGNATURE

		Strongly Disagree	(Circle one)			Strongly Agree
2.	The learning outcome could be achieved using the content provided.	1	2	3	4	5
3.	The authors stimulated my desire to learn, and demonstrated knowledge and expertise in the content areas.	1	2	3	4	5
4.	I am more confident in my abilities since completing this education activity.	1	2	3	4	5
5.	The content was relevant to my practice.	1	2	3	4	5

6. Commitment to change practice (select one):
   a. I will make a change to my current practice as the result of this education activity.
   b. I am considering a change to my current practice.
   c. This education activity confirms my current practice.
   d. I am not yet convinced that any change in practice is warranted.
   e. I perceive there may be barriers to changing my current practice.
7. What do you plan to do differently in your practice as a result of completing this educational activity?

   _____

   _____
8. What information from this education activity do you plan to share with a professional colleague?

   _____

   _____
9. This education activity was free of bias, product promotion, and commercial interest influence. ☐ Yes ☐ No

   If no, please explain: _____

* Commercial interest – any entity either producing, marketing, reselling, or distributing healthcare goods or services consumed by or used on patients or an entity that is owned or controlled by an entity that produces, markets, resells, or distributes healthcare goods or services consumed by or used on patients. Exceptions are non-profits, government and non-healthcare related companies.

Nephrology Nursing Journal Editorial Board Statements of Disclosure

In accordance with ANCC governing rules *Nephrology Nursing Journal* Editorial Board statements of disclosure are published with each CNE offering. The statements of disclosure for this offering are published below.

Paula Dutka, MSN, RN, CNN, disclosed that she is a coordinator of Clinical Trials for the following sponsors: Amgen, Rockwell Medical, Keryx Biopharmaceuticals, Akebia Therapeutics, and Dynavax Technologies.

All other members of the Editorial Board had no actual or potential conflict of interest in relation to this continuing nursing education activity.

This article was reviewed and formatted for contact hour credit by Beth Ulrich, EdD, RN, FACHE, FAONL, FAAN, *Nephrology Nursing Journal* Editor-in-Chief, and Sally Russell, MN, CMSRN, CNE, ANNA Education Director.

American Nephrology Nurses Association – Provider is accredited with distinction as a provider of nursing continuing professional development by the American Nurses Credentialing Center's Commission on Accreditation.

ANNA is a provider approved by the California Board of Registered Nursing, provider number CEP17499.

This CNE article meets the Nephrology Nursing Certification Commission's (NNCC's) continuing nursing education requirements for certification and recertification.