

A Narrative Review of Management Strategies for Common Symptoms in Advanced CKD



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Patients with advanced chronic kidney disease (CKD) experience multiple bothersome symptoms, undermining their quality of life (QOL). With growing attention to the importance of symptom management in advanced CKD, the evidence regarding symptoms is increasing. In this review, we briefly summarize the current evidence of effective pharmacologic and nonpharmacologic interventions to improve symptoms and QOL in patients with advanced CKD, including those on dialysis. We focused on symptoms that are commonly experienced by patients, such as pain, fatigue, sleep disturbances, itching, nausea and vomiting, cognitive impairment, and anxiety and depression. We noted that research in symptom science focused on improving symptom management in CKD is still very limited. In addition to the lack of clinical practice guidelines to address those common symptoms, the major gaps in the current literature include the evidence regarding mechanistic pathways to inform the development of effective symptom management for CKD populations, the evidence to confirm effective pharmacologic interventions in other populations for CKD populations, and research on how to incorporate effective symptom management approaches into clinical care. Although improving mortality remains as an important area in the kidney community, there is an urgent need to focus on improving symptom management to improve QOL in advanced CKD.

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Patients with advanced chronic kidney disease (CKD) experience multiple symptoms, such as fatigue, pain, insomnia, depression, and anxiety,^{1,2} often concurrently,³ contributing to symptom distress and compromised quality of life (QOL).^{4–6} Although reports of the number of symptoms experienced by patients with advanced CKD vary depending on the measurement used, up to a median of 9 symptoms has been reported.⁷ The symptoms that are most common and/or bothersome among patients with advanced CKD are pain, fatigue, sleep disturbances, muscle cramps, restless legs, itching, nausea and vomiting, cognitive impairment, and anxiety and depression.^{5,8}

Although such symptom experiences (except uremic symptoms) are rather common in many patients with other advanced chronic illnesses (e.g., cancer, congestive heart failure),⁹ most symptoms in CKD are poorly understood and managed.^{10,11} In part due to a lack of routine symptom assessment, patients on dialysis often resign from communicating their symptoms to care providers and adopt ineffective self-management strategies.^{12,13}

National and international kidney communities^{14–16} have advocated for early integration of palliative care into CKD and dialysis care to improve symptom management and QOL, and research on symptom management has increasingly drawn the attention of investigators and care providers. However, as the extent of the applicability of findings from symptom research in other conditions to CKD populations has yet to be confirmed, especially for drug recommendations, a lack of evidence for symptom management for CKD populations persists.

The purpose of this narrative review^{17,18} is to provide a brief summary of current evidence (e.g., reports

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of clinical trials, systematic reviews of clinical trials, observational studies) regarding effective interventions to address the symptoms most commonly experienced by patients with advanced CKD. In this review, frailty—although a common condition among these patients—was not included as a “symptom” because it is a state of an accumulation of multiple deficits, such as unintended weight loss and weakness,^{19,20} rather than a symptom that is reported by patients. We searched for evidence of both pharmacologic and non-pharmacologic therapies to provide a holistic approach to symptom management. Our review focuses on patients with advanced CKD who are already, or soon will be, on long-term dialysis. We did not review studies of patients undergoing conservative management (without dialysis) because symptom management for those patients is likely more aggressive due to goals of care that directed conservative management in the first place.²¹

Management of Common Symptoms in Advanced CKD

Pain

Pain, defined as “an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage,”²² is reported by up to 70% of patients with advanced CKD and nearly 100% of hospitalized patients with CKD.²³ The origin of pain for the majority of these patients is musculoskeletal,²³ and roughly half rate their pain intensity as moderate to severe.²⁴ Undertreated moderate to severe pain adversely affects QOL and can lead to numerous complications, such as stress, anxiety, depression, and overall reduction in life satisfaction.^{24–26}

The first step toward effective pain management is identifying the type of pain through comprehensive assessment. Nociceptive pain occurs through tissue damage and the stimulation of related receptors.^{23,25} Nociceptive pain is often described as sharp, cramping, or dull.²⁵ Neuropathic pain results from damage to the nervous system. It is commonly associated with diabetes, amyloid, and viral infections.^{23,25} Neuropathic pain is described as shooting, stabbing, or burning.^{24,26,27}

The World Health Organization’s stepwise approach to pain management may be helpful to guide initiation and use of medications.²⁴ The first-line approach to mild nociceptive pain includes using nonopioid analgesics, such as acetaminophen and short-acting nonsteroidal anti-inflammatory drugs (NSAIDs; Table 1).^{23,24} However, NSAIDs as well as other pharmacologic agents should be used with caution because of altered pharmacokinetics and risk for adverse effects

due to the reduction in renal clearance and potential for accumulation of active metabolites. NSAIDs specifically may contribute to the risk of bleeding and cardiovascular events, as well as renal complications in those with residual function.²⁶

Second-line pharmacologic agents for moderate pain include weak opioids, such as tramadol and oxycodone, and perhaps hydromorphone at low doses. Careful attention to the signs and symptoms of serotonin syndrome is very important when tramadol is used, especially in instances of concurrent therapy with other serotonergic drugs.²³ Third-line interventions are reserved for severe pain that has not responded to optimal use of first- and second-line agents. Higher doses of oxycodone and hydromorphone may be necessary along with close monitoring for accumulation of active metabolites. Long-acting agents, such as fentanyl, buprenorphine, or methadone, are also options to treat severe pain; however, providers may consider referral to specialty palliative care or pain clinic for continued evaluation and management of severe, refractory pain.^{24,26,28}

Generally, neuropathic pain is poorly responsive to NSAIDs and opioids.²⁶ First-line agents for neuropathic pain include gabapentin and pregabalin. Tricyclic antidepressants as well as serotonin and norepinephrine reuptake inhibitors may also be effective, but there are limitations in their use due to the potential for anticholinergic effects and limited safety data.²⁴

Nonpharmacologic therapies, such as exercise, massage, and physical therapy, are vital to management of pain and may be successfully deployed alone or in conjunction with medications. However, as disease progresses and functional status declines, the ability to tolerate exercise and physical therapy may decrease.²⁶ Along with nonpharmacologic therapies, topical anesthetics, such as lidocaine, or analgesics, such as diclofenac, should be considered, but should be used with caution to avoid adverse effects due to systemic absorption.²⁴

Itching

CKD-related pruritus is defined as itching directly related to kidney disease without another comorbid condition to explain itching.²⁹ It is known to affect up to 50% of patients with renal failure but is often underreported and undertreated or untreated.³⁰ Often described as a generalized pattern covering much of the body, itching may be sporadic to constant, mild to intense/severe, and contributes to a complex symptom burden. Itching may occur during the day and/or night, impacting sleep quality, mood, and overall QOL.^{28,31} Patients report feeling obsessed with the sensation of their itching and often hopeless in the midst of ineffective treatment options.³⁰

Table 1. Summary of pharmacologic and nonpharmacologic approaches for common symptoms in advanced CKD

Symptom	Pharmacologic approach	Nonpharmacologic approach
Pain	<ul style="list-style-type: none"> Topical anesthetics (e.g., lidocaine or diclofenac)²⁴ Nonopioid analgesics (e.g., acetaminophen) and short-acting nonsteroidal anti-inflammatory drugs^{23,24} For moderate pain, weak opioids (e.g., tramadol and oxycodone and hydromorphone)²³ For severe pain, higher doses of oxycodone and hydromorphone as well as long-acting agents (e.g., fentanyl, buprenorphine or methadone)^{24,25,28} 	<ul style="list-style-type: none"> Exercise, massage, and physical therapy²⁷
Itching	<ul style="list-style-type: none"> Gabapentin 100 mg/day along with continued assessment of symptom experience and titration by a medical provider^{31–33} Difelikefalin at a dose of 0.5 µg per kilogram of body weight³⁶ 	<ul style="list-style-type: none"> Rehydrating emollients, aqueous gels, essential oils, topical capsaicin cream, gamma-linolenic acid ointment, phototherapy, and acupuncture^{31,40}
Nausea and vomiting	<ul style="list-style-type: none"> For first-line intervention for nausea, ondansetron For second-line intervention, metoclopramide 2.5 mg every 4 hours as needed if concern for gastroparesis or constipation For third-line intervention, olanzapine 2.5 mg every 8 hours as needed or haloperidol 0.5 mg every 8 hours as needed For severe, refractory symptoms, haloperidol dosing can be titrated to 1 mg²⁵ 	<ul style="list-style-type: none"> Environmental and dietary modifications as well as complementary and integrative interventions such as massage, guided imagery and music therapy^{25,40,41}
Fatigue	<ul style="list-style-type: none"> Erythropoietin-stimulating agents to treat anemia⁵⁷ 	<ul style="list-style-type: none"> Exercise^{42,63,66} Cognitive-behavioral therapy⁶³ Acupressure^{64,65} Foot reflexology^{66,67} Foot massage⁶⁸ Aromatherapy^{69,70} Yoga⁷¹
Cognitive impairment		<ul style="list-style-type: none"> Management of co-occurring conditions⁷⁹ Medication review to reduce sedation, minimize polypharmacy, and improve sleep^{77,87} Encouragement of physical activity, mental stimulation, and adequate nutrition, and early goals of care discussions^{77,87} Exercise⁸⁹
Sleep disorders	<ul style="list-style-type: none"> Dopamine agonist^{112,113} Correction of anemia¹¹⁴ Benzodiazepines (lorazepam, alprazolam, clonazepam)^{118,119} Non-benzodiazepine-receptor agonists (zolpidem, zaleplon)¹²⁰ Low-dose gabapentin¹¹⁷ Melatonin¹¹⁶ 	<ul style="list-style-type: none"> Address modifiable contributing factors (e.g., pain, itching, and mood disorders) Cognitive-behavioral therapy¹⁰³ Music therapy¹⁰⁸ Acupressure¹⁰⁹ Change of dialysis modality¹⁰³
Anxiety and depression	<ul style="list-style-type: none"> Serotonin reuptake inhibitors (e.g., citalopram, escitalopram, fluoxetine, paroxetine, sertraline)^{139–141} Serotonin–norepinephrine reuptake inhibitors (e.g., venlafaxine, duloxetine, mirtazapine)^{139–141} Atypical antidepressants (e.g., bupropion, trazodone, nefazodone)^{139–141} Tricyclic antidepressants (e.g., amitriptyline)^{139–141} 	<ul style="list-style-type: none"> Address contributing factors (e.g., pain, itching and mood disorders) Psychotherapy and cognitive-behavioral therapy¹³¹ Exercise^{132,133} Acupuncture¹³⁴ Magnesium¹³⁵ Chinese herbal medicine¹³⁶ Electroconvulsive therapy¹³⁷ Social support¹³⁸ Address concerns related to spirituality and religion¹³⁸ Relaxation techniques¹³⁸

Intervention development has been challenged by a lack of understanding of the mechanisms responsible for pruritus in CKD.^{30,31} Various substances, such as parathyroid hormone, histamine, calcium, and magnesium, and pathologies, such as microinflammation, opioid receptor, and other sensory processing derangements, are suspected pruritogens, but causality has not been consistently established. Therefore, current management strategies target 1 or more of these suspected culprits.

Hydrating emollients and other topical analgesics (e.g., aqueous gels, essential oils, optical capsaicin, gamma-linolenic acid ointment, tacrolimus ointment) have been recommended as first-line treatment for uremic pruritus.^{31,32} Escalation of therapy includes systemic agents. Gabapentin (a centrally acting calcium

channel blocker and anticonvulsant) appears to be a stand-alone in the category of agents with a highly significant effect.^{31,33} The exact mechanism of action of gabapentin is not fully understood, but is suspected to be attributable to its multireceptor affinity, potentially altering dopamine, serotonin, and norepinephrine.³² As to the dosing and frequency of gabapentin, there is some consensus suggesting 100 mg/day for CKD patients along with continued assessment of symptom experience and titration of the drug. For end-stage kidney disease (ESKD) patients on dialysis, the minimal effective dose has not been clearly established; however, doses in the range of 100 to 300 mg 3 times per week postdialysis have demonstrated some efficacy in reducing pruritus as well as improving sleep and pruritus-associated depression.³⁴ The exact mechanism

of action of gabapentin is not fully understood; however, it is suspected that it can potentially influence levels of dopamine, serotonin, and/or norepinephrine due to its multireceptor affinity.³²

European guidelines on chronic pruritus bring attention to the antipruritic effects of various agents, such as activated charcoal, gamma-linolenic acid cream, topic capsaicin, thalidomide, and others³⁵; however, these are rather broad guidelines that do not solely focus on interventions in the CKD or ESKD population. The British Association of Dermatologists³⁴ also offer broad guidelines for management of generalized pruritus in adults without underlying skin disorders to include specific commentary on management strategies for uremic pruritus. Difelikefalin, a selective kappa opioid receptor agonist, given by infusion for patients on dialysis with moderate to severe pruritus, has shown clinically meaningful improvement in itch intensity and related QOL as well as sleep.³⁶

Phototherapy, acupuncture, emollients, and other topical analgesics and systemic agents have received attention in the literature. Although the antipruritic effect of phototherapy in ESKD is not completely understood, it was thought to interfere with the structures and mediators that contribute to the induction and perception of pruritus when repeated broadband ultraviolet light therapy was delivered 2 or 3 times weekly.^{35,37}

Nausea and vomiting

Nausea, “the unpleasant sensation of being about to vomit,” can occur alone or can accompany vomiting (the forceful expulsion of gastric contents), dyspepsia, or other gastrointestinal symptoms.³⁸ The reported rates of nausea and vomiting in patients with CKD range from 30% to 43%.³⁹ The etiology of nausea and vomiting is multifactorial and may be related to metabolic or gastrointestinal disturbances as well as medication side effect, all of which are common as kidney disease progresses to the later stages.^{25,39}

Understanding the origin of nausea and vomiting is critical to determine effective therapies. The chemoreceptor trigger zone and the vomiting center are both central mediators responsible for the symptom of emesis.³⁹ Unlike the mechanisms underlying emesis, those involved in the sensation of nausea are not entirely understood. Nonetheless, nausea and vomiting are thought to be most problematic and prominent as renal disease progresses and, as such, the presentation or progression of this symptom burden may signal the need for renal replacement therapy.³⁹

Although evidence of effective interventions in patients with CKD is largely lacking, nonpharmacologic therapies, such as environmental and dietary

modifications, as well as complementary and integrative interventions, such as massage, guided imagery, and music therapy, are recommended due to the side effects associated with common pharmacologic agents.^{25,40,41} However, potentially reversible causes of nausea and vomiting should be first evaluated and treated.³⁹

Ondansetron is recommended as first line for nausea at a dose range of 4 to 8 mg every 8 hours as needed. Second-line intervention may include metoclopramide 2.5 mg every 4 hours as needed if there is concern over gastrointestinal disturbances, such as gastroparesis or constipation (Table 1). Third-line intervention includes olanzapine 2.5 mg every 8 hours as needed or haloperidol 0.5 mg every 8 hours as needed. In the event of severe, refractory symptoms, haloperidol dosing can be titrated to 1 mg.²⁵ Caution is needed as these dopamine antagonists may cause extrapyramidal symptoms.²⁵

Fatigue

Fatigue is a multidimensional symptom characterized by feelings of exhaustion with a vicious and debilitating cycle.^{42–44} Fatigue has been identified as a priority symptom by the Standardized Outcomes of Nephrology–Hemodialysis.⁴³ The estimated prevalence is 54% to 66% for patients with advanced CKD,^{45,46} and up to 97% in patients on hemodialysis.⁴⁷

The exact mechanisms responsible for fatigue in advanced CKD remain poorly understood, but several factors have been described, including lower tryptophan and higher kynurenine levels,⁴⁸ co-occurring chronic illness conditions,⁴⁶ sedentary behavior,⁴⁹ loneliness,⁵⁰ depression,⁴² functional disability,⁵⁰ disordered sleep, muscle weakness,⁴⁴ medication side effects,⁴⁶ and cognitive-behavioral factors, such as high distress levels and maladaptive behaviors (e.g., fear of physical activities).⁵¹ In nondialysis patients, fatigue has also been associated with uremia, pruritus, anemia, and chronic inflammation.^{42,49,52} In patients on hemodialysis, osmotic disequilibrium, blood pressure fluctuations, ultrafiltration diffusion,⁵³ and higher tumor necrosis factor-alpha levels have been associated with fatigue,⁴² but causal relationships have yet to be established.

Because fatigue is a multidimensional experience with numerous associated factors, clinical diagnosis can be resource-intensive and requires consideration of distinct features, such as timing, precipitants, presence of libido, sleep quality, exercise capacity, and sedation, as this symptom is often vague. Furthermore, fatigue has dimensions of affect and tolerability. Anticipatory anxiety and the tendency to avoid a stressful encounter or a lack of motivation may be explained in words that sound like a complaint of fatigue.⁵⁴ Thus, differential

diagnosis is needed. Recommended measures for assessing fatigue in the clinical setting include the Ecological Momentary Assessment,⁵⁵ the Piper Fatigue Scale Short Form,^{42,52} the Fatigue Severity Scale, and the Functional Assessment of Chronic Illness Therapy—Fatigue.⁵⁶ However, routine screening for fatigue in this population is rare.⁴³

Developing interventions to improve fatigue has been hindered by a poor understanding of the mechanisms causing fatigue. Thus, managing fatigue centers around targeting factors associated with fatigue. The most tested pharmacologic therapy involves erythropoietin-stimulating agents (ESAs) to treat anemia. A systematic review⁵⁷ of 10 studies in which ESAs were used to reduce fatigue in patients with CKD indicated that, in ESA-naïve patients with CKD and previously untreated anemia, a partial correction of hemoglobin levels to >10 g/dl yielded the most significant change in fatigue scores. Correcting to hemoglobin levels >12 g/dl did not yield clinically meaningful improvements. Although iron therapy is recommended and often used to treat iron deficiency, further empirical testing is warranted to establish its effects on fatigue.

Exercise or physical activity is the most commonly tested nonpharmacologic strategy in patients with CKD. Multiple reviews^{16,42,58} support incorporating exercise into the management of patients with CKD. Interventions including exercise and another strategy, such as music, imagery,⁵⁹ or motivational interviewing/coaching,⁶⁰ demonstrated positive effects on participants' health-related quality of life or fatigue. Ironically, in trials involving exercise, fatigue is often cited as a barrier to participation (Table 1).⁶¹

There is a growing body of evidence on the impact of social–psychological, and alternative health practices on fatigue in patients with CKD/ESKD,⁶² especially stress management and relaxation techniques. Similarly, cognitive-behavioral therapy was effective in reducing inflammatory factors, sleep disturbances, and fatigue severity in hemodialysis patients.⁶³ Other strategies, including acupressure,^{64,65} foot reflexology,^{66,67} foot massage,⁶⁸ aromatherapy,^{69,70} and yoga,⁷¹ have been shown to be feasible and effective in reducing fatigue in ESKD. More research is needed to support and extend these findings. Finally, several studies examining the impact of dialysis modifications reported that more frequent dialysis⁷² or lowering dialysate temperatures⁷³ reduced patient fatigue.

Cognitive impairment

Cognitive impairment (CI) is a deficit in 1 or more brain functions, such as memory, learning, concentration, and decision-making.⁷⁴ The reported prevalence of CI varies from 16% to 70%.^{75,76} People with advanced

CKD exhibit an earlier onset,⁷⁷ faster rate of cognitive decline,^{76,78} and more fluctuations in cognitive function⁴ when compared with the general population. CI in advanced CKD is rarely improved by dialysis,⁷⁹ and has been associated with: diminished functional status,^{76,80} increased mortality, and frequent and longer hospital stays^{76,80}; a decreased likelihood of being referred for palliative care consultations, or patient inclusion in treatment-related decision-making^{75,80–82}; and increased caregiver strain.^{81,83}

CKD is strongly associated with cardiovascular disease, including a high incidence of stroke, arterial stiffness, and central pressure,⁸⁴ all of which may signify a subcortical contribution to changes in cognitive function.⁸⁰ In addition, patients with ESKD demonstrate diminished brain and subcortical volume and higher levels of white-matter disease.⁸⁵ Relationships among sleep-disordered breathing, depression, and CI remain controversial.^{86,87}

Because empirically tested interventions for managing CI in advanced CKD are limited, recommendations are based on clinical expertise and evidence from non-CKD populations. Strategies are aimed at identifying at-risk patients, addressing factors associated with CI, and preserving cognitive function. Routine assessment of cognitive function may facilitate the diagnosis of conditions that may be interfering with cognitive function, and may provide opportunities to engage in advance care planning discussions, refer patients for additional supportive services,^{75,76,80,81} and identify caregivers who may be experiencing high levels of burden and distress.⁸³ Among the several tools to assess cognitive function, the Montreal Cognitive Assessment is recommended for use in clinical settings.^{80,88}

To address factors contributing to CI, comprehensive, team-based care is recommended, including optimal management of co-occurring conditions (Table 1)⁷⁷; medication review to reduce sedation, minimize polypharmacy, and improve sleep^{77,87}; encouragement of physical activity, mental stimulation, and adequate nutrition; and early and frequent goals-of-care discussions.^{77,87} Exercise and cognitive training, effective in preserving cognitive function in healthy, older adults,⁸⁹ has recently been examined in patients with CKD. In a multisite randomized, controlled trial (RCT), dialysis patient participants randomized to the home-based walking intervention demonstrated greater improvements in self-reported cognitive function scores on the Kidney Disease Quality of Life Short Form compared with those in the control group.⁹⁰ Similarly, McAdams-DeMarco and colleagues⁹¹ reported preliminary positive effects of exercise on global cognitive function, psychomotor speed, and executive function in a pilot RCT.

Sleep disorders

Sleep disorders, including insomnia, restless leg syndrome (RLS), obstructive sleep apnea (OSA), central sleep apnea, sleep-disordered breathing, and other forms of sleep disturbances, are common in patients with CKD/ESKD.^{92–96} A common form of sleep disorder identified by kidney patients among their major symptomatic burden is insomnia.⁴³ Insomnia is defined “a repeated difficulty with sleep initiation, duration, consolidation, or quality that occurs despite adequate opportunity and circumstances for sleep, and results in some form of daytime impairment.”⁹⁷ Sleep disorders may be present even in the early stages of CKD,⁹⁸ ranging from 31% to 43% in predialysis CKD to 45% to 80% in patients with ESKD.⁹⁹ Unfortunately, the prevalence of sleep disorders continues to rise among persons with CKD and has almost doubled over the past 10 years.¹⁰⁰

Several factors, including fluid overload,¹⁰¹ contribute to sleep disorders in patients with CKD/ESKD, such as disruption in evening melatonin levels, presence of inflammatory factors, malnutrition, anemia, and iron deficiency known to predispose to RLS, pruritus, pain, and dyspnea, and co-occurring conditions, such as congestive heart failure and mood disorders.^{102,103} Sleep disorders, in turn, are associated with increased morbidity and mortality, fatigue, lower cognitive scores, depression, an impaired immune system, and poor QOL.^{49,104–106}

The first step in managing sleep disturbances is to identify the cause of the sleep disturbance and modifiable factors and work to alleviate them. This involves adequate history-taking, laboratory tests, and polysomnography.¹⁰⁷ On the other hand, patients with OSA may benefit from being referred to sleep medicine specialists for expert assessment and polysomnography.

Trial of nonpharmacologic approaches should be attempted before resorting to a pharmacologic approach. Yang and colleagues¹⁰⁸ identified 13 trials studying nonpharmacologic approaches used to improve sleep disorders in patients on dialysis. Interventions used in these studies included cognitive-behavioral therapy (CBT), acupressure, physical exercise, and change of dialysis modality (Table 1). They concluded that CBT is helpful for insomnia in patients on hemodialysis. Losso and colleagues¹⁰⁹ noted that patients on hemodialysis experience less OSA than patients managed by peritoneal dialysis. Two studies^{102,110} showed that listening to live music was associated with reduced cramps, anxiety and depression, pain, and itching, by which sleep quality could be improved. Natale and colleagues¹¹¹ reviewed 36 studies and noted that, although relaxation techniques and exercise had uncertain effects on sleep outcomes, acupuncture was shown to have a modest impact on sleep outcomes.

Pharmacologic approaches are aimed mostly at addressing factors that likely negatively affect sleep quality. For example, treating RLS with dopamine agonists^{112,113} or correcting anemia and iron deficiency, which may worsen RLS and dyspnea,¹¹⁴ may mitigate the adverse impact of RLS on sleep. Melatonin can be used to treat sleep disorders by reducing sleep onset latency as well as exerting a regulatory effect on the sleep–wake cycle.^{115,116} Treating peripheral neuropathies or pruritus with low-dose gabapentin¹¹⁷ may be beneficial. Medications such as benzodiazepines^{118,119} and non-benzodiazepine-receptor agonists,¹²⁰ used to treat insomnia in general, have shown mixed results in patients with CKD.

Other interventions, such as oxygen therapy and continuous positive airway pressure for patients with OSA,^{121,122} are associated with improved sleep in patients with OSA and CKD. Last, modifying dialysis modality or intensity has shown modest benefit in some patients.¹²³

Depression and anxiety

Depression and anxiety are among the challenges that may further complicate the lives of patients with CKD.⁴³ Both depression and anxiety may coexist in patients with CKD and have a negative effect on patients' QOL. Fraser and colleagues¹²⁴ showed that 31.6% of patients with CKD stage 3 reporting worse QOL measures had anxiety and depression. On the other hand, anxiety is defined as a subjective sense of unease, intense fear, uncertainty, and dread from the anticipation of a threatening situation that lasts ≥ 6 months.⁷⁴ Anxiety is underrecognized in CKD patients with the exact prevalence of anxiety disorders remaining unclear, but reported estimates range from 12% to 52%.¹²⁵ Depression and/or anxiety have been associated with increased mortality,¹²⁶ suicidal ideation,¹²⁷ decreased adherence to treatment,¹²⁸ hospitalization,¹²⁹ and somatization of symptoms such as pain and fatigue¹³⁰ in patients with CKD.

The diagnosis of a major depression episode requires >5 psychological, somatic, or behavioral symptoms to be present within a 2-week period.⁷⁴ These symptoms may include either a depressed mood, appetite or weight changes, sleep difficulties, psychomotor agitation or retardation, loss of energy, diminished ability to think or concentrate, feelings of worthlessness or excessive guilt, and suicidality.⁷⁴

Optimal management of depression and anxiety in adult patients with CKD remains a challenge. In addition to correcting modifiable risks, a holistic approach that includes both nonpharmacologic and pharmacologic components may be required.¹⁰⁸ Several nonpharmacologic approaches have been tried to improve symptoms of depression/anxiety in CKD patients, with variable success. These interventions included

psychotherapy and CBT,¹³¹ exercise intervention,^{132,133} acupuncture,¹³⁴ magnesium,¹³⁵ and Chinese herbal medicine (Table 1).¹³⁶ Electroconvulsive therapy is usually reserved for treatment of major depression that is nonresponsive to all other modalities of treatment and is particularly useful in treating very severe cases of depression.¹³⁷ Other nonpharmacologic approaches have been used to manage depression and anxiety, with variable success.¹³⁸

Drug pharmacokinetics are altered in CKD, with decreased rates of clearance of some medications and their metabolites, making their half-life unpredictable. This may necessitate dose adjustment. Nagler and colleagues¹³⁸ reviewed 28 studies aiming to evaluate pharmacokinetic parameters in CKD for 24 antidepressants, and recommended dose reduction in CKD stages 3 to 5 for specific antidepressants. Medications used to treat depression/anxiety in patients with CKD include selective serotonin reuptake inhibitors, tricyclic antidepressants, serotonin–norepinephrine reuptake inhibitors, and atypical antidepressants.^{139–141}

Discussion

In this narrative review, we have briefly summarized the current evidence on interventions for symptoms commonly experienced by patients with CKD, including ESKD. We found that research in symptom science focused on improving symptom management in CKD is, although increasing, very limited. In particular, evidence regarding mechanistic pathways to inform the development of effective symptom management for CKD population is seriously lacking. For example, despite the fact that muscle cramps and restless legs are commonly experienced by patients with CKD, including those on dialysis, the pathophysiology is still uncertain and we could not identify sufficient evidence-based strategies (i.e., interventions that have peer-reviewed documented empirical evidence of effectiveness)¹⁴² to manage these debilitating symptoms.

In addition to the lack of evidence regarding the efficacy of interventions to improve symptoms, research on how to incorporate effective symptom management into clinical care is another significant gap in the literature. Experts in the field have promoted several care models (e.g., early integration of kidney palliative care, comprehensive and personalized care, patient-centered medical home)^{14,143–148} to improve symptom management and QOL in patients with advanced CKD. Experts also suggest that ideal models of care for this population should include partnerships with primary care providers and advanced practitioners, as patients with CKD are a large high-risk population for whom nephrologists alone cannot effectively address their complex illness management.^{149,150} However, trials to demonstrate the

effectiveness of system-level interventions on patient outcomes are extremely rare. Recognizing these gaps, the Kidney Health Initiative has recently called for innovation in symptom research to alleviate symptom burden and improve QOL in patients with advanced CKD.¹⁶

Our narrative review has limitations as it did not involve quality assessment of the included study reports. Given the limited empirical studies testing interventions for symptoms in CKD populations, we included a variety of empirical evidence levels, such as RCTs with small to large samples, observational studies, and systematic reviews of RCTs. Nonetheless, increasing evidence supports that symptom burden is the most important predictor of reduced QOL among people with CKD.^{1,3} There is an urgent need for the kidney community to focus on improving symptom management among patients with advanced CKD to improve their QOL.

DISCLOSURE

All the authors declared no competing interests.

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