



Non-Pharmacological Intervention Approaches for Common Symptoms in Advanced CKD patients on haemodialysis: Narrative Review

¹Gulshan Roy Chowdhury and ²Dr. Mrs. Jyoti Sarin

¹Ph.D Scholar of MM (Deemed to be university) & Lecturer, College of Nursing, ABVIMS & Dr. R.M.L.Hospital,

²Director & Dean, MM (Deemed to be university) MM College of Nursing, Mullana, Ambala.
gulshan1410@gmail.com, sarinjyoti@yahoo.com

Abstract

Patients with advanced chronic kidney disease (CKD) experience many bothersome symptoms, affecting their quality of life (QOL). The majority of these patients do not have the opportunity to receive a kidney transplant and need other treatments for these burdensome symptoms in order to improve their QOL and prognosis. With growing attention to the significance of symptom management in advanced CKD on haemodialysis, the evidence regarding symptoms is increasing. In this review, we briefly summarize the current evidence of only non-pharmacologic interventions to improve symptoms and QOL in patients with advanced CKD, 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 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 evidence to how to incorporate effective symptom intervention approaches into clinical care is also rare.

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 on haemodialysis.

Keywords

chronic kidney disease; dialysis; quality of life; symptoms; Fatigue; Pain; Malnutrition; Sleep disorders; Nausea and vomiting; Depression and Anxiety; Non-Pharmacological Intervention approaches;

Introduction

Chronic kidney disease (CKD) is defined as the presence of kidney damage or an estimated glomerular filtration rate (eGFR) less than 60 ml/min/1.73 m², persisting for 3 months or more, irrespective of the cause. The last three decades witnessed considerable growth in the global burden of chronic kidney disease (CKD), accounted for by 77.5% of end-stage kidney disease (ESKD) patients on kidney replacement therapy (KRT), with 43.1% alone provided by dialysis. Hemodialysis (HD) forms 89% of the global treatment for ESKD patients.

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.

QOL declines as the CKD progresses, least at stage 5. Diabetic CKD patients tend to have poorer QOL as compared to other aetiologies of CKD. Correction of anaemia tremendously improves QOL.

The purpose of this narrative review is to provide a brief summary of current evidence (e.g., systematic reviews of clinical trials and observational studies) regarding effective interventions to limelight the symptoms most commonly experienced by patients with advanced CKD on haemodialysis. We searched for evidence of non-pharmacologic therapies to practice a holistic approach to symptom management. Our review focuses on patients with advanced CKD who are already, on long-term dialysis.

Management of Common Symptoms in Advanced CKD on Haemodialysis Pain

Pain, defined as “an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage.”

Pain is the most common symptom of these patients which has a negative impact on the quality of their life. The appearance of chronic pain in dialysis patients is usually in rate 37% to 50%, while 82% of them show a moderate to severe intensity pain. The etiology of pain is multifactorial and may be either due to the process of dialysis (puncture, muscle cramps, headaches) or due to the existence of accompanying systemic diseases and painful syndromes. Pain is the most common symptom - discomfort of patients which causes significantly impaired quality of life. This is because the incidence of chronic pain is associated with the onset of affective disorders (anxiety, depression), social disorders (isolation, negligence) and economic impact (e.g. inability to keep the job).

Bone pain is a common manifestation of renal osteo-dystrophy. Renal osteo-dystrophy is a common problem and a painful syndrome unique to end-stage renal disease, which may develop during a patient's time on dialysis.

The etiology of pain in this group is not restricted to pain related to the haemodialysis treatment alone, but may also be a consequence of primary renal disease (e.g. polycystic kidney disease), renal failure (e.g. renal osteodystrophy, calciphylaxis) or other co morbidities such as diabetes, arthritis or vascular disease. Therefore, routine use of pain assessment tools that evaluate characteristics and severity of pain along with the functional disability caused by pain is crucial in developing effective pain management strategies and to monitor the safety and effectiveness of pain treatments.

Non-pharmacologic therapies that address the whole person in the context of their disease

and personal life are vital in managing chronic pain. These may include physical therapies such as aerobic exercise, stretching, massage, acupressure, and acupuncture; behavioural therapies such as cognitive behavioural therapy, biofeedback, relaxation techniques, counselling, guided imagery, and mindfulness-based stress reduction; as well as interventions such as nerve blocks and trigger point injections.

Fatigue

Fatigue is a feeling of exhaustion, tiredness, weariness, or lack of energy, which is common and potentially debilitating, and often unrecognized in HD patients.

Fatigue has been identified as a priority symptom by the Standardized Outcomes of Nephrology–Hemodialysis. The estimated prevalence is 54% to 66% for patients with advanced CKD and up to 97% in patients on hemodialysis.

Fatigue can be extremely weakening and intrusive both mentally and physically, which makes patients undergoing HD often experience limitations at work, in physical activity and social interaction.

A multidisciplinary health care strategy comprising alternative therapy such as acupressure; mind based therapy such as meditation, deep breathing and yoga; body based therapies such as physical activity, therapeutic exercise, body massage; biological based therapy such as diet and nutrition shall help to reduce the fatigue in dialysis population.

The results of Liu et.al. (2015) suggests that aerobic exercise plays an important role in physical function and decreases depression.

Mini-bike exercise and breathing based leg exercises are safe and effective in the rehabilitation and complementary treatment of patients undergoing hemodialysis.

Several studies have demonstrated that exercise during dialysis not only decreases fatigue, but also increases self-confidence and self-efficacy.

There is a growing body of evidence on the impact of social–psychological, and alternative health practices on fatigue in patients with CKD/ESKD, especially stress management and relaxation techniques.

Similarly, cognitive-behavioural therapy was effective in reducing inflammatory factors, sleep disturbances, and fatigue severity in haemodialysis patients. Other strategies, including acupressure, foot reflexology, foot massage, aromatherapy, and yoga, have been shown to be feasible and effective in reducing fatigue in ESKD.

Muscle Cramps

Muscle cramps are painful, sudden and involuntary muscle contractions that typically occur in lower extremities. Cramps can occur during hemodialysis sessions, in between the sessions, and during sleep also.

Muscle cramps are often experienced by the patients on hemodialysis that result in discomfort, shortened treatment times, and inadequate dialysis dose.

Up to 50% people with chronic renal failure undergoing dialysis suffer from muscle cramps, especially involving the lower limbs. The cramps in this type of patient are linked to depression, a decline in quality of life, and sleep disorders. The etiology of cramps in hemodialysis patients is not clear.

The severe muscle cramps are experienced near the end of the dialysis and persisting for a time after dialysis is often due to dehydration.

A case study by Appanraj.R, et.al (2015) on 20 patients concluded that by assuring the dry weight and monitoring the sodium frequently the episodes of muscle cramps can be controlled.

In a Cochrane review in 2012, Blyton et al. examined some non-pharmacological Interventions to help cramp symptoms. These included: using night splints; avoiding heavy covers on the bed, and making changes to sleeping position, changes to footwear; taking horse chestnut seed extract.

Many studies concluded significantly on the effectiveness of Intra-dialytic stretching exercise on prevention and reduction of muscle cramps among patients undergoing haemodialysis.

There is clearly a need for effective education regarding recognition of individual patient need & appropriate intervention strategies in muscle cramps in dialysis patient & nurses, in partnership with patient, relatives & other health professional can help to empower the individual to manage their cramps.

Nightly stretching before going to sleep reduces the frequency and severity of nocturnal leg cramps in older adults.

Application of Sequential compression devices (SCD) to LE may prevent the generation of LE HD-related cramping in a select group of patients. (SCD) improve venous return (VR).

Intradialytic massage found to be an effective way to address muscle cramping.

Restless Leg Syndrome (RLS)

RLS refers to complaints of an unpleasant sensation in the legs accompanied by an irresistible urge to move them. This syndrome's symptoms are circadian and usually begin in the evening. RLS symptoms worsen during periods of inactivity and rest and are transiently relieved by movement.

A decrease in haemoglobin levels causing a decrease in the levels of iron, have been implicated as the primary cause of RLS (Restless Leg Syndrome) and is directly linked to CKD and dialysis.

Maintaining good sleep hygiene, decreasing tobacco, alcohol, and caffeine use, increasing exercise, and discontinuing any medications that may exacerbate RLS are some of the

approaches to take care of RLS. In addition, transcranial stimulation, pneumatic compression, vibrating pads, and acupuncture are emerging as interventions to study RLS.

Itching

Dermatologic disorders have a negative impact on patient's physical and mental health, rendering them a low quality of life. Proper evaluation and management of these dermatologic disorders may reduce the associated morbidity and improve the quality of life in these patients.

In a cross-sectional study by Deshmukh SP (2013) in a tertiary care hospital for a period of 2 years, Xerosis, pallor, dyspigmentation, and pruritus were the commonest cutaneous manifestations observed in patients of CRF on haemodialysis. Of these, xerosis was extensive in diabetes mellitus patients and acquired perforating dermatosis too affected them. Uremic fetor affected patients having blood urea levels more than 200 mg/dl.

Pruritus was the commonest and most bothersome symptom observed, affecting 65.71% patients. Nail changes were more prevalent in patients who received haemodialysis for longer period of time.

Intervention development has been challenged by a lack of understanding of the mechanisms responsible for pruritus in CKD. 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.

Sleep disorders

For overall physical and mental well-being sleep is important. Sleep disturbances can include irregularity in sleeping habits, difficulty falling asleep, early morning awakening, and frequent awakening at night, sleep apnea and restless leg syndrome.

Approximately 50%-75% of patients experience symptoms of insomnia. Chronic pain, Stress, older age, dialysis shift, melatonin, duration of dialysis therapy, high levels of urea And/or creatinine, disability and somatic complaints such as pruritus and bone pain and high PTH, all contributes in the development of insomnia in ESRD patients, although the mechanisms are yet fully not known.

The prevalence of sleep disorders continues to rise among persons with CKD and has almost doubled over the past 10 years.

Many studies concluded that vitamin D deficiency might be directly linked to sleep disorders in HD patients.

Interventions to increase physical activity should be considered alongside current strategies as a possible approach to managing fatigue and insomnia.

According to the American College of Physicians, cognitive behavioural therapy for insomnia (CBT-I) is the first line of treatment and pharmacological intervention as an adjunct

or secondary treatment for insomnia. The four core components of CBT-I are stimulus control, sleep restriction and consolidation, cognitive restructuring and sleep hygiene.

Stimulus control refers to techniques that are designed to re-establish the association between bed and sleep. These recommendations may include using the bedroom only for sleep or sex, sleeping only in the bedroom and leaving the bed when not able to sleep. The goal of sleep restriction and consolidation is to get efficient sleep where total sleep time matches the time in bed. Patients are encouraged to establish and maintain a fixed sleep–wake schedule to help get them into a healthy sleep rhythm. Cognitive restructuring challenges dysfunctional patient beliefs and attitudes about sleep that can contribute to cognitive hyperarousal at night. Sleep hygiene focuses on a broad set of ‘good sleep habits’ that include exercising regularly, avoiding excessive liquids, caffeine, nicotine and alcohol in the evening, ensuring that the bedroom is comfortable and noise-free, and adjusting the timing of meals and snacks relative to bedtime.

Two studies (Burrai F, 2019 & Scherer, 2017) 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 colleagues (2019) 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.

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.

The reported rates of nausea and vomiting in patients with CKD range from 30% to 43%. The aetiology 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.

To determine effective therapies, understanding the origin of nausea and vomiting is critical. The chemoreceptor trigger zone and the vomiting centre are both central mediators responsible for the symptom of emesis.

Although evidence of effective interventions in patients with CKD is largely lacking, non-pharmacologic 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.

Malnutrition

Non-iatrogenic factors such as suboptimal dietary intakes, poor appetite, taste alterations, insulin resistance, and psychosocial factors are also involved in the aetiology of malnutrition. Morbidity arising from malnutrition in these patients severely affects quality of life (QoL).

The global prevalence of malnutrition associated with CKD was found to be 42.7%. Males were predominantly affected with malnutrition as compared to females.

The severity of malnutrition was stratified according to the stages of CKD, and it was found to be higher in progressive stages of CKD among the low-income groups as compared to the high-income groups.

Improving nutritional assessment methods for patients on hemodialysis is highly needed. Findings reveal that risk of malnutrition is associated with multiple factors such as osteoporosis, occupation, walking, ability to ambulate, certain complication during haemodialysis session, and some haemodialysis side effects.

Accurate nutrition knowledge may be particularly important when individuals are ready to make dietary changes.

Nutritional counselling by qualified dietitians should be mandatory in renal units as part of the medical therapy management to the nutritional status of haemodialysis patients.

The intervention by a single dietitian, aimed at providing a personalized dietary prescription should be administered (including energy [25–35 kcal/kg/day] and protein [1 – 1.2 g/kg/day] based on K/DOQI guidelines, 2020).

In the nutrition education sessions, the patients were addressed over protein and energy intake, content of phosphorus and potassium in foods, cooking techniques, and a fourth issue chosen according to the patient's specific needs; for example, content of fat, cholesterol, or sucrose in foods, elaborating an individualised dietary plan

Depression and anxiety

Depression and anxiety are among the challenges that may further complicate the lives of patients with CKD.

Both depression and anxiety may coexist in patients with CKD and have a negative effect on patients' QOL. Fraser and colleagues showed that 31.6% of patients with CKD stage 3 reporting worse QOL measures had anxiety and depression.

To cope with depressive symptoms and improve overall QoL, it becomes imperative to implement a multidimensional approach that includes different intervention strategies.

A study was conducted in 2015 (Moradi M) about effect of acupuncture on the anxiety of patients undergoing the treatment with haemodialysis. The findings of this study indicated that the acupuncture and massage therapy of the right points could reduce overt and covert

anxiety in these patients. In terms of depression and anxiety in haemodialysis patients, CBT (Cognitive behaviour therapy) was also proven to be effective in a few studies. Cognitive behavioural therapy probably increases health-related quality of life.

According to a study, (Lerma et al., 2017) at follow-up, depression, anxiety, and cognitive distortions had decreased, and QoL had increased after the intervention by CBI techniques consisted of positive self-reinforcement, deep breathing, muscle relaxation, and cognitive restructuring.

Several non-pharmacologic approaches have been tried to improve symptoms of depression/anxiety in CKD patients, with variable success. These interventions included exercise intervention.

Intradialytic exercise training programmes have a positive effect on patients' physical and psychological functioning. Moreover, social support from family and social environment, spirituality and religiosity, tele-nursing programmes and participation in network support groups frequently lead to a reduction of anxiety and depressive symptoms in patients on maintenance haemodialysis. Finally, the provision of education and information to dialysis patients by renal professionals and a systematic psychiatric evaluation of these individuals can lead to early diagnosis and treatment of depressive symptoms.

Summary of Non Pharmacologic Approaches for common symptoms in Advanced CKD on Haemodialysis

Symptoms	Non Pharmacologic Approaches
Pain	Multimodal Therapy: Physical Therapy: Aerobic exercise, stretching, massage, acupressure, acupuncture Behavioural therapy: Cognitive behaviour therapy, Biofeedback relaxation technique, Counselling, Guided therapy, Mindfulness – Based - Stress Reduction
Itching	Rehydrating emollients, aqueous gels, essential oils, topical capsaicin cream, gamma-linolenic acid ointment, phototherapy, and acupuncture
Nausea and vomiting	Environmental and dietary modifications as well as complementary and integrative interventions such as massage guided imagery and music therapy.

<p>Fatigue</p>	<p>Exercise: The breathing-based leg exercises program comprised abdominal breathing and low-intensity leg exercise, including leg lifts, quadriceps femoris contraction and knee flexion, and lasted for 15 minutes at one time, three times a week for 12 weeks.</p> <p>Alternative therapy such as acupressure; Foot reflexology; Foot massage; Aromatherapy</p> <p>Mind based therapy such as meditation, deep breathing and yoga;</p> <p>Cognitive-behavioral therapy⁶³</p> <p>Body based therapies such as physical activity, therapeutic exercise, body massage;</p> <p>Biological based therapy such as diet and nutrition (Tailored nutritional intervention based on restrictions: Intake of adequate protein and calories, safe levels of sodium, potassium, phosphorous and fluids are important for dialysis patients).</p>
<p>Muscle Cramps</p>	<p>Intra-dialytic stretching exercise</p> <p>intra-dialytic progressive resistance exercise training (PRET)</p> <p>Using night splints: avoiding heavy covers on the bed, and making changes to sleeping position, changes to footwear; taking horse chestnut seed extract.</p> <p>Sequential compression devices (SCD) to LE</p>
<p>Restless Leg Syndrome (RLS)</p>	<p>Good sleep hygiene, decreasing tobacco, alcohol, and caffeine use,</p> <p>Increasing exercise.</p> <p>Transcranial stimulation, pneumatic compression, vibrating pads, and Acupuncture</p>

Sleep disorders	<p>Cognitive behavioural therapy for insomnia (CBT-I)</p> <p>Stimulus control - Using the bedroom only for sleep or sex, sleeping only in the bedroom and leaving the bed when not able to sleep</p> <p>Sleep restriction and consolidation - Establish and maintain a fixed sleep-wake schedule</p> <p>Cognitive restructuring - Recognizing and replacing negative sleep thoughts with more accurate, positive thoughts about sleep</p> <p>Sleep hygiene - Exercising regularly, avoiding excessive liquids, caffeine, nicotine and alcohol in the evening, ensuring that the bedroom is comfortable and noise-free, and adjusting the timing of meals and snacks relative to bedtime.</p>
Nausea & Vomiting	Complementary and integrative interventions: massage, guided imagery, and music therapy
Malnutrition	<p>Improving nutritional assessment methods</p> <p>Nutrition education program & Nutritional counselling related to protein and energy intake, content of phosphorus (Less phosphorus & phosphate binders) and potassium in foods, cooking techniques</p> <p>Personalized dietary prescription</p>
Depression and anxiety	<p>cognitive behaviour therapy</p> <p>Acupressure and massage therapy</p> <p>Intradialytic exercise training programmes</p> <p>Social support from family and social environment, spirituality and religiosity, tele-nursing programmes and participation in network support groups.</p>

Discussion

In this narrative review, we have briefly summarized the current evidence on interventions for symptoms commonly experienced by patients with CKD on haemodialysis. Patients with ESRD on dialysis experience a multitude of unpleasant symptoms and suffer from a remarkable symptom burden, which contributes to poor patient prognosis. Symptom burden should be comprehensively and accurately assessed to carry out scientific and effective symptom interventions. (Li, H, 2018)

Our narrative review has some 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. Nevertheless, increasing evidence supports that symptom burden is the most important predictor of reduced QOL among people with CKD. There is an urgent need for the kidney community to focus on improving symptom management among patients with advanced CKD on haemodialysis to improve their QOL.

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