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Fostering Innovation in Symptom Management among Hemodialysis Patients

Paths Forward for Insomnia, Muscle Cramps, and Fatigue

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Abstract

Individuals receiving in-center maintenance hemodialysis bear a high burden of both physical and mood symptoms. More than half of patients on hemodialysis report sleep disturbance, muscle cramps, and fatigue. Patients describe symptoms as having a deleterious effect on their quality of life, suggesting that symptom alleviation may meaningfully improve patient-reported outcomes. Moreover, patients on hemodialysis have identified symptom management as a key area for research and innovation, prioritizing symptom alleviation over other health outcomes such as mortality and biochemical indices. Despite the importance of symptoms to patients, there has been little research explicitly geared toward improving patient symptoms, and therefore minimal innovation in symptom management. In general, the physiologic underpinnings of symptoms are poorly understood, hampering the development of targeted therapies. In fact, there have been few drugs or devices approved by the US Food and Drug Administration for the indication of improving any patient-reported outcomes for patients on hemodialysis. Recognizing this gap in innovation, the Kidney Health Initiative, a public–private partnership between the American Society of Nephrology and US Food and Drug Administration, convened a workgroup to first prioritize symptoms for the development of therapeutic interventions, and then identify near-term actionable research goals for the prioritized physical symptoms of insomnia, muscle cramps, and fatigue. This paper summarizes the pathophysiology of the three prioritized symptoms, identifies key knowledge gaps, acknowledges factors that challenge development of new therapies, and offers the nephrology community actionable research goals for insomnia, muscle cramps, and fatigue.

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Introduction

Individuals receiving in-center maintenance hemodialysis experience exceptionally high rates of morbidity and poor quality of life compared with individuals with other chronic diseases (1,2). A high burden of both physical and mood symptoms is strongly associated with these poor outcomes. More than half of patients on hemodialysis report sleep disturbance, cramping, and fatigue (3). Patients describe symptoms as substantially affecting their quality of life because of interference with social relationships, financial stability, and overall well-being (4,5). These data suggest that symptom alleviation may meaningfully improve patient-reported outcomes.

Moreover, patients on hemodialysis have identified symptom management as a key area for research and innovation, prioritizing symptoms over other health outcomes such as mortality and biochemical indices (6,7). Despite the importance of symptoms to patients, there has been little research geared toward improving patient symptoms, and therefore minimal innovation in symptom management over the years. Additionally, payment models focus largely on biochemical rather than patient-centered outcomes, missing an opportunity to incent symptom-focused care delivery. In general, the physiologic underpinnings of symptoms are poorly understood, hampering the development of targeted therapies. In fact, there have been few drugs or devices approved by the US Food and Drug Administration (FDA) for the indication of improving any patient-reported outcomes for patients on hemodialysis. Innovation in symptom management is essential to meet the needs of individuals receiving maintenance hemodialysis.

Kidney Health Initiative Hemodialysis Symptom Project

Overview

In 2016, the Kidney Health Initiative (KHI), a public–private partnership between the American Society of Nephrology and FDA, assembled an interdisciplinary workgroup to (*1*) conduct a study to prioritize symptoms to target for therapeutic development among

in-center patients on hemodialysis, and (2) convene a stakeholder meeting to identify opportunities for targeted therapeutic development for the prioritized symptoms (Figure 1).

Patient Prioritization of Hemodialysis Symptoms

Results of the workgroup's prioritization study were published in an earlier issue of the *Clinical Journal of the American Society of Nephrology* (8). The study found that the top prioritized physical symptoms were insomnia, muscle cramps, and fatigue, and the top mood symptoms were anxiety, depression, and frustration. Participants endorsed interest in therapies such as exercise, support groups, and medications. Notably, many participants cited challenges with high pill burdens and expressed preferences for nonpharmacologic treatment options.

Stakeholder Meeting

The KHI workgroup then held a stakeholder meeting with the goals of (*1*) reviewing the pathophysiology of the prioritized physical symptoms, (*2*) identifying barriers to the development of new therapies for these symptoms, and (*3*) determining potential opportunities for new or improved treatment and prevention strategies. The meeting focused on physical symptoms because (*1*) physical symptoms are more common than mood symptoms, (*2*) treating physical symptoms may improve mood symptoms (4,8), and (*3*) at least two randomized, controlled trials (RCTs) for depression, the top mood symptom, have been conducted among patients on hemodialysis in the United States (9,10).

Meeting participants ($n=23$) included nephrologists, researchers with symptom expertise, clinical pharmacists, dialysis organization representatives, payers, patients, and care partners (Supplemental Table 1). The event consisted of large and small group meetings designed to spur interaction and yield specific, actionable recommendations to inform future research direction (Supplemental Figure 1). In symptom-specific small groups, participants reviewed existing treatment strategies (Table 1), discussed plausible symptom pathophysiology, and identified critical knowledge gaps and challenges (Table 2). Participants then collaboratively developed action plans with three specific, measurable, achievable, results-focused, and time-bound (S.M.A.R.T.) research goals for each symptom (Table 3). In generating and prioritizing research goals, participants weighed the available evidence, as well as the feasibility, acceptability, and immediacy of the candidate interventions.

Key Targets for Improving Management of All Symptoms

Meeting participants identified three overarching recommendations for spurring innovation in symptom therapeutics that transcended symptom type. First, participants recognized dialysis care delivery system aspects, such as communication, care team support, and clinic environment, as relevant to symptom management. Data from patients with advanced cancer have shown a link between symptom reporting and better patient-reported and health outcomes (11). However, data suggest that patients on dialysis may under-report their symptoms to care teams (4). To improve symptom management, clinicians must routinely address symptoms with their patients. Developing standardized care processes that foster patient–care team communication and facilitate symptom-related discussions, such as clinician rounding tools, may enhance communication. Patient support groups and mentoring programs are also potential strategies for improving symptom management and coping.

Second, participants recognized a role for payment reform, suggesting incorporation of symptom management into the definition of "quality" dialysis care. Existing quality measures focus largely on biochemical indices rather than patient-prioritized symptoms (7). Despite a lack of evidence-based interventions for many symptoms, focusing clinical interactions on symptoms may produce better outcomes (11). Payment incentives for documentation of such symptom-based interactions would promote more individualized, patient-centered rounding. The Centers for Medicare and Medicaid Services, an integral partner in payment reform efforts, convened an ESKD Patient-Reported Outcomes Technical Expert Panel in May 2017, marking an important step in efforts to align payment incentives with patient-prioritized outcomes (12).

Third, participants recommended development of standardized approaches to symptom data collection, recognizing inadequate data as a barrier to innovation. In clinical practice, the mostly commonly used symptom assessment tool is the Kidney Disease Quality of Life symptom subscale, a scale that captures degree of bother of 12 physical symptoms over the past 4 weeks. However, clinics typically administer the Kidney Disease Quality of Life annually, limiting its utility in week-to-week management decisions. Although symptom-specific patient-reported outcome measures (PROMs) such as the Insomnia Severity Index and Functional Assessment of Chronic Illness Therapy, Fatigue exist, they are used in research settings only. Efforts to develop a short, valid, dialysis-specific PROM for fatigue are underway (13). There is no existing PROM for muscle cramps among patients on dialysis. Such limitations in symptom data lead to knowledge gaps about the association of symptoms with potentially modifiable aspects of hemodialysis treatment (*e.g.*, modality, schedule, and dialysate composition). Moreover, development of symptom-specific PROMs would facilitate testing symptom responsiveness to intervention in future research.

Symptom-Specific Gaps, Potential Solutions, and Research Goals

Insomnia

Existing data indicate that 40%–85% of patients on hemodialysis experience significant sleep disturbance (3,14,15). In a study of over 1600 patients on dialysis, 50% had trouble falling sleep, 50% woke up at night, and 49% had early morning awakening; over half reported one or more of these sleep-related symptoms all or most of the time (15). Moreover, insomnia is associated with worse quality of life and higher mortality among patients on hemodialysis (16,17).

Pathophysiology. Although there are numerous approaches to insomnia management, few have dialysis population-specific evidence supporting them, and key knowledge gaps about the pathophysiology of insomnia in ESKD remain. Existing data reveal alterations in circadian

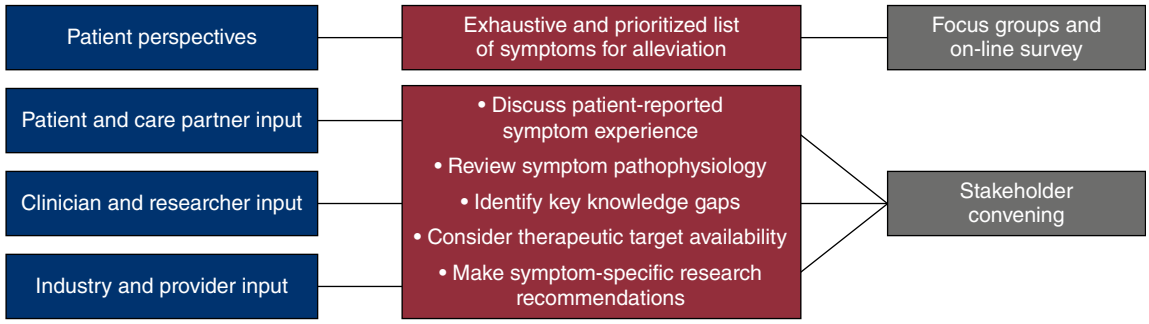

Figure 1. | **KHI project overview.** In 2016, the KHI assembled an interdisciplinary workgroup to (*1*) conduct a study to prioritize symptoms to target for innovation among in-center patients on hemodialysis, and (*2*) convene a diverse stakeholder meeting to identify specific opportunities for targeted therapeutic development for the prioritized symptoms.

rhythm and sleep structure, and attenuation of nocturnal melatonin surge among individuals with kidney failure, mechanisms that offer potential therapeutic targets (18,19). However, other factors also affect sleep and may influence the efficacy of insomnia therapies. Examples include medical conditions (obstructive sleep apnea, restless leg syndrome, mental health disorders, and pain), sequelae of ESKD (extracellular hypervolemia, uremic toxin

Table 1. Current treatment landscape for insomnia, muscle cramps, and fatigue[a]

Intervention Type	Insomnia	Muscle Cramps	Fatigue
Behavioral	Cognitive–behavioral therapy Physical exercise Sleep hygiene training Sleep restriction Relaxation training	Physical exercise	Cognitive–behavioral therapy Physical exercise Stress management Energy conservation
Pharmacologic[b]	Sedative hypnotics Anxiolytics Antipsychotics Antidepressants Antihistamines Melatonin	Vasodilators Neurologic agents Quinine Intradialytic saline, hypertonic saline, glucose, and mannitol Oral rehydration salts	Human growth hormone Anabolic steroids Anxiolytics Antidepressants Psychostimulants Erythropoietics Iron
Dietary supplements		L-carnitine, potassium, magnesium, vitamins E and C, creatinine	L-carnitine, vitamins B-12 and D, essential fatty acids
Dialysis-related	Home dialysis Frequent hemodialysis Shift, schedule Dialysate temperature	Home dialysis Frequent hemodialysis Fluid removal rate Treatment time Ultrafiltration profiling Sodium profiling Dialysate composition Dialysate temperature	Home dialysis Frequent hemodialysis Shift, schedule Fluid removal rate Treatment time Extracellular hypervolemia
Comorbid condition treatment	Restless leg syndrome Obstructive sleep apnea Depression Anxiety	Liver disease Neurologic disease Thyroid dysfunction	Depression Anxiety Sleep disorders Thyroid dysfunction Parathyroid disease Numerous other conditions
Other	Transplantation Circadian rhythm resynchronization Light therapy Acupressure Hypnosis	Transplantation Tonic water Pickle juice Yellow mustard White sugar Chicken broth Salt water	Transplantation Acupressure Hypnosis

[a]Listed therapies are representative and are not exhaustive of all potential symptom-alleviating therapies.
[b]Includes short- and long-term drugs, prescription and over-the-counter drugs, compounds, and hormones.

Table 2. Knowledge gaps, barriers, and potential solutions by symptom

Symptom	Knowledge Gaps	Barriers	Potential Solutions[a]
Insomnia[b]	• Limited understanding of pathophysiology (*i.e.*, sleep-wake cycle disruption with dialysis schedule, napping during dialysis, restless leg syndrome, extracellular hypervolemia, sleep apnea, uremic toxins)	• Challenges in implementing CBT in dialysis settings	• CBT adapted for dialysis settings
	• Unknown if pathophysiology of insomnia differs by dialysis modality	• Insomnia medications identified as high-risk by payers	• Pharmacological treatments (*e.g.*, sleep aids)
	• Limited knowledge of effect of insomnia on patient-reported and clinical outcomes	• Low adherence to CPAP machines	• Improvement in CPAP technology
	• Lack of PK/PD modeling studies of insomnia drugs among patients with ESKD		• Stimulation to help patients stay awake during dialysis
Muscle cramps[c]	• Limited understanding of pathophysiology (*i.e.*, electrolyte imbalance, muscle fatigue, fluid shifts, hypotension, neurologic).	• Limited data to drive treatment selection	• Intradialytic exercise
	• No single, universally accepted definition of cramping	• Patient reservations about reporting cramps to clinic personnel (personal pride, fear of being labeled as "difficult")	• Spicy substances (*e.g.*, pickle juice, mustard)
	• Limited knowledge of effect of cramping on patient-reported and clinical outcomes	• Lack of objective approaches to dry-weight estimation	• Ultrafiltration rate reduction
			• Pharmacologic treatments (*e.g.*, gabapentin, quinine)
			• Technological advances in dry-weight estimation
Fatigue[d]	• Limited understanding of pathophysiology (*i.e.*, role of sleep disorders, mental health, anemia, ultrafiltration, uremia, comorbid medical conditions, treatment shift, modality)	• Payer-driven dialysis scheduling, limited flexibility	• Pharmacologic treatments (*e.g.*, ESAs, psychostimulants)
	• Lack of standardized approach to medical work-up of fatigue	• Fatigue often multifactorial and may be without clear, modifiable root cause in some individuals	• Physical exercise
	• Limited evidence on medication use for fatigue among patients with ESKD	• Unclear ownership of medical work-up of fatigue (cost and provider barriers to acceptability)	• CBT
		• Lack of objective approaches to dry-weight estimation	• Standardized approach to medical work-up

CBT, cognitive–behavioral therapy; CPAP, continuous positive airway pressure; PK/PD, pharmacokinetic/pharmacodynamic; ESAs, erythropoiesis-stimulating agents.
[a]The overarching recommendations of payment reform, dialysis care delivery system modifications, and standardized symptom data collection as avenues by which to improve symptom management were common to all three symptoms and are excluded from the table.
[b]Insomnia small group ($n=12$) included patients ($n=2$), care partner ($n=1$), nephrologists ($n=3$), researcher content expert ($n=2$), clinical pharmacist ($n=1$), payer representative ($n=1$), industry representative ($n=1$), and dialysis organization representative ($n=1$).
[c]Muscle cramps small group ($n=9$) included patients ($n=2$), nephrologists ($n=5$), clinical pharmacist ($n=1$), and dialysis organization representative ($n=1$).
[d]Fatigue group ($n=23$) included insomnia ($n=12$) and muscle cramps ($n=9$) participants and government representatives ($n=2$).

accumulation, and inflammation), dialysis prescription aspects (modality, shift, and frequency), and sleep hygiene (napping) (17). Research aimed at elucidating the individual roles of factors unique to ESKD in insomnia would inform therapeutic development. Furthermore, it is important to differentiate among sleep disorders in

Table 3. Symptom-specific strategic action plans for top-prioritized research goals

Goals	Actions	Potential Challenges[a]	Solutions	Timeframe, yr
Insomnia				
Test CBT and explore integration of exercise with CBT	• Conduct clinical trial	• CBT adaptation to dialysis setting	• Expert, interdisciplinary clinical team	4–5
		• Provider buy-in	• Provider outreach to facilitate implementation and promote sustainability	
		• Exercising in dialysis clinic	• Patient outreach, local champions	
		• Exercising at home		
Test effectiveness of site-specific insomnia protocols including online CBT and CBT adapted for dialysis	• Perform provider outreach	• Health literacy of patients	• Simple, accessible protocols that incorporate patient input	3–5
	• Develop algorithms	• Internet access, tablet availability	• Patient outreach, local champions	
	• Develop infrastructure for treatment delivery	• Patient adherence	• Dialysis organization outreach	
	• Test online CBT for hemodialysis	• Dialysis personnel and provider buy-in	• Tablet manufacturer outreach	
Test safety and efficacy of at least one drug for insomnia in patients on dialysis	• Select drug	• Business risk to pharmaceutical companies	• Pharmaceutical industry-independent funding	2–3
	• Conduct clinical trial	• Contraindications to drugs	• Industry outreach	
		• Unknown patient preferences	• Patient outreach, local champions	
Muscle cramps				
Measure frequency, duration and severity of cramps to characterize problem	• Investigate measures from other clinical settings	• Lack of existing data	• Potential KHI proposal	1
	• Develop and pilot test an assessment tool for cramping	• Language, cultural differences	• Include non-English-speaking patients and patients from different cultural backgrounds	
Test acceptability of available, low-risk interventions (*e.g.*, pickle juice, mustard)	• Conduct pilot tests	• Unknown patient preferences	• Patient outreach, local champions	3
		• Dialysis personnel buy-in	• Dialysis organization outreach	
		• Lack of experience with agent	• Industry partnership	
Test effectiveness of treatments	• Select most promising interventions from pilot testing for pragmatic clinical trial	• Lack of existing data	• Patient outreach, local champions	5–7
	• Conduct smaller clinical trials that incorporate physiologic measures	• Dialysis personnel buy-in	• Dialysis organization outreach	

Table 3. (Continued)

Goals	Actions	Potential Challenges[a]	Solutions	Timeframe, yr
Fatigue				
Develop a standardized checklist for medical workup	• Develop checklist	• Need for balancing completeness and feasibility • High number of potential conditions for screening • Cost of work-up • Potential for duplicative testing • Ownership of findings and subsequent management	• Engage multidisciplinary partners • Modify evidence-based algorithms from other disciplines • Dialysis organization outreach	1
Test efficacy of standard of care versus exercise versus exercise plus CBT	• Identify exercise approach • Develop protocol with patient engagement (consider patient preferences and acceptance) • Conduct clinical trial	• Implementation • Sustainability • Facility workflows • Legal	• Align with existing social work and CBT programs at partnered dialysis organizations • Early involvement of stakeholders to facilitate implementation and promote sustainability • Expert, interdisciplinary clinical team	3–4
Explore psychostimulants and assess associated patient preferences and risk tolerance	• Develop protocol for PK/PD modeling study • Develop protocol for study assessing patient risk–benefit, tolerance, and preferences	• Lack of existing data • Potential harm • Contraindications to drugs • Lack of interest from pharmaceutical companies • Negative effect on sleep	• Pharmaceutical industry-independent funding • Industry outreach • Patient preference and risk tolerance assessment	1

CBT, cognitive–behavioral therapy; KHI, Kidney Health Initiative, PK/PD, pharmacokinetic/pharmacodynamic.
[a]Funding and recruitment challenges were common to all three symptoms and are excluded from the table.

both research and clinical practice, recognizing that different sleep-related disturbances (*e.g.*, insomnia, sleepiness, and poor sleep quality) require different therapeutic approaches.

Therapeutic Strategies. Patients have expressed interest in nonpharmacologic strategies for symptom management (8), rendering cognitive–behavioral therapy (CBT) an attractive insomnia treatment for patients on hemodialysis. CBT is the first-line therapy for insomnia in the general population. This therapy rests on several core principles, including the principle that psychologic problems stem, in part, from unhelpful ways of thinking or patterns of

unhelpful behavior. CBT focuses on solutions, encouraging patients to challenge faulty thinking and change destructive patterns of behavior (20). It has been shown to improve sleep latency, efficiency, and quality in nondialysis populations (21,22). Challenges to administering CBT to patients on dialysis include lack of trained therapists, low patient adherence, and cost of scaling to large populations. Delivery of CBT by telehealth platforms, both in the dialysis unit and at home, may be one way to overcome these challenges. Potential limitations to this strategy, such as low patient computer literacy and limited internet access and mobile device availability, should be considered when developing CBT programs.

Medication management may be needed in some patients. However, there are critical knowledge gaps about insomnia drug safety and efficacy that stem from a dearth of pharmacokinetic/pharmacodynamic (PK/PD) modeling studies among patients on dialysis. Such knowledge gaps may also have implications for drug costs. For example, existing observational data associate benzodiazepine- and nonbenzodiazepine-receptor agonist use with higher risk of death among patients on hemodialysis (23,24). Without PK/PD modeling studies to guide safety assessment, payers may label such drugs as high risk, creating barriers to access. Unfortunately, clinical trials of drugs with lower-risk side effect profiles, such as melatonin, demonstrate that sleep improvement is not sustained (25). More dialysis-specific studies of insomnia agents, particularly drugs that promote restorative sleep, not just sleep induction, should be conducted. Moreover, research aimed at understanding patient preferences and approaches to risk–benefit decision-making for drugs that may improve insomnia and quality of life but potentially increase death risk or other adverse outcomes is needed.

Research Goals. Participants prioritized three actionable, near-term insomnia research recommendations. First, participants identified CBT as the most important strategy to investigate. Specifically, they recommended performing an RCT to test CBT efficacy (with and without exercise) in treating insomnia among individuals on hemodialysis. Given the challenges associated with adapting CBT and sustainable exercise programs to the dialysis setting, engagement with expert, interdisciplinary teams with complementary dialysis and psychology expertise will be needed to develop such interventions. Second, the group recommended testing the effectiveness of site-specific insomnia protocols for telehealth, online and in-person CBT, in the dialysis setting. Such research is an essential foundational step for dissemination of CBT to the broader dialysis community. Provider outreach and development of clinic and organization infrastructure to support pilot tests of online CBT will be needed. Third, the group recommended testing the safety and efficacy of at least one insomnia drug in patients on dialysis *via* an RCT. Potential challenges to this goal include business risk to pharmaceutical companies, safety issues, and patient preferences for nonpharmacologic approaches. Industry and patient outreach, and safety studies will be important to overcoming these challenges.

Recently, there has been tangible progress toward achieving these research goals. A phase 3, randomized, open-label trial comparing the efficacy of telehealth CBT versus trazodone versus medication placebo for the treatment of chronic insomnia among patients on hemodialysis is underway (Clinicaltrial.gov identifier NCT03534284).

Muscle Cramps

The estimated prevalence of hemodialysis-related muscle cramps is 33%–78% (26). Muscle cramps can be excruciatingly painful and are a source of significant distress, interfering with sleep, activities of daily living, and quality of life (4). Moreover, muscle cramps associate with early dialysis termination and consequent underdialysis and adverse health outcomes (26).

Pathophysiology. Critical knowledge gaps about muscle cramp pathophysiology inhibit the development of targeted interventions. Hemodialysis-related fluid and electrolyte shifts are often cited as the primary causes of cramps. However, data suggest roles for other factors including muscle fatigue, neurologic dysfunction, impaired oxygen delivery, and electrolyte, vitamin, and other dietary deficiencies, among others (26,27). In the exercise physiology literature, the muscle fatigue hypothesis suggests that muscle fatigue induces muscle contraction by inhibiting the neural mechanisms that typically block contraction (27). Predisposing factors to such fatigue-induced cramping include older age, poor conditioning, and metabolic disturbances—common conditions among patients on dialysis (27).

Therapeutic Strategies. Although overly rapid fluid removal during dialysis can lead to cramps, oversimplification and attribution of all cramps to fluid shifts may lead to missed therapeutic opportunities. Research exploring alternative physiologic explanations is needed. Given the tendency of patients on dialysis to fatigue faster than those not on dialysis (28), emphasis on the muscle fatigue hypothesis is warranted (27). Exercise-based interventions may be effective for muscle fatigue-induced cramping. Home remedies for cramping, such as pickle juice and yellow mustard, also offer insight into the physiologic underpinnings of cramping in the setting of exercise. Exercise physiology data suggest that pungent tastes, like vinegar and ginger, can stimulate an oropharyngeal neural reflex that inhibits hyperactive α-motor neurons, leading to muscle relaxation and cramp relief (29,30). Such low-cost and seemingly low-risk interventions that are already in use by some patients, are ripe for safety testing and pragmatic trials.

In addition to significant gaps in knowledge about cramp pathophysiology, there is no accepted definition of, or PROM for, muscle cramps. Without standardized data capture, we lack the capacity to accurately (*1*) assess and compare muscle cramp prevalence, severity, and frequency; (*2*) study the effect of cramps on patient-reported and clinical outcomes; and (*3*) measure cramp response to intervention. Cramps can take many forms and simply asking patients a single question annually about cramps as part of a health-related quality of life survey is inadequate. There are also potential reporting barriers specific to muscle cramps. In a prior qualitative study, patients noted that personal pride and societal pressure sometimes affected their decisions to withhold the reporting of symptoms from their care teams (4); this was reinforced by patient comments during the stakeholder meeting.

Research Goals. Such knowledge gaps and reporting barriers led participants to recommend developing a muscle cramp PROM to facilitate characterization of population burden as its first actionable, near-term research goal. Given the potential challenges in capturing cramps across culturally divergent populations, inclusion of individuals from diverse backgrounds in measure development is essential. Second, participants recommended testing patient acceptability of available, low-risk interventions such as pickle juice and mustard to inform intervention selection for a future trial. Actionable steps in this regard include patient and dialysis organization engagement and exploration of potential funding opportunities. Third, the group recommended conducting a pragmatic clinical trial to test the effectiveness of the most promising treatment identified in acceptability testing. Additionally, given the gaps in pathophysiology knowledge, smaller trials incorporating physiologic measures to advance mechanistic knowledge will be important in efforts to uncover new therapeutic approaches.

Offering optimism for future advances, efforts to develop a PROM for dialysis-related muscle cramps are underway, as evidenced by the endorsement of a related project proposal by the KHI (31).

Fatigue

Fatigue is perhaps the most common symptom experienced by patients on hemodialysis, with prevalence estimates ranging 60%–97% (7). A recent international consensus effort prioritized fatigue as one of the most important outcomes for hemodialysis clinical trials (7). Fatigue is associated with a higher risk of mortality and depression and lower quality of life among individuals on dialysis (32).

Pathophysiology and Therapeutic Strategies. The multifactorial nature of fatigue and dearth of targeted treatments for fatigue in any population present challenges to innovation in fatigue therapeutics for the dialysis population. Contributors to fatigue include comorbid medical conditions (mood disorders, thyroid and parathyroid dysfunction, sleep disorders, and others), muscle fatigue, inflammation, nutritional status, medication side effects, and dialysis-related factors such as toxin accumulation, volume status, and potentially, modality, schedule, treatment time, and fluid removal practices (33). Data supporting causal associations between these factors and fatigue are weak, but do point to therapeutic development opportunities. Inflammatory cytokines such as IL-6 and TNF-α are potential targets because they are elevated in ESKD and associate with lower functional status and higher mortality among patients on dialysis (34,35). Dialysis treatment modifications, and particularly fluid removal practices, offer actionable targets, but data supporting their effects are mixed (36,37), and patient acceptance of treatment time extension is not clear (38). Additional bench and translational research aimed at elucidating fatigue pathophysiology may point to opportunities for targeted drug development.

Challenges associated with determining the drivers of patient-specific fatigue affect development of targeted interventions. Most patients on dialysis have numerous potential fatigue contributors given their high burden of comorbid conditions and prescribed medications, and there is not an accepted approach to the medical work-up of fatigue. More standardized approaches to fatigue work-up may help identify candidate targets for intervention. However, work-up cost and unclear ownership of results could challenge implementing such an approach in the dialysis setting.

Research Goals. Participants prioritized three actionable, near-term fatigue research goals. First, participants recommended developing a standardized checklist for medical work-up of fatigue to help clinicians identify patient-specific fatigue contributors. To overcome challenges associated with the need to balance completeness, feasibility, cost, duplicative testing, and ownership of results, engagement of multidisciplinary partners (*e.g.*, geriatricians and oncologists), and review of fatigue algorithms in nondialysis populations will be necessary. Second, the group recommended performing a RCT to test the efficacy of standard of care versus exercise versus exercise and CBT in treating fatigue among patients on hemodialysis. The group recognized challenges with scaling exercise programs, noting barriers related to implementation, sustainability, and facility workflows. Aligning CBT and exercise interventions with existing social work programs and engaging expert, interdisciplinary teams throughout the research process will help overcome these challenges. Third, the group recommended exploring psychostimulants as a potential therapy and called for physiologically based PK/PD modeling studies and studies assessing patient risk–benefit, tolerance, and preferences. Early engagement with industry will be essential to realizing these pharmacologic, study-related goals.

As with insomnia and cramping, there is reason for optimism. An RCT testing the effectiveness of collaborative care (a multidisciplinary management plan with individualized pharmacologic and/or behavioral therapy interventions) on fatigue among patients on hemodialysis is underway (Clinicaltrials.gov identifier NCT03440853).

Charting a Path Forward to Improve the Hemodialysis Symptom Experience

Innovative research designed to improve symptom management among individuals receiving hemodialysis has the potential to meaningfully affect patients' lives. KidneyX, a public–private accelerator, is one exciting new path for such innovation (39). Tables 3 and 4 display overarching recommendations for fostering innovation in symptom management. Initial focus on patient-prioritized symptoms, such as insomnia, muscle cramps, and fatigue, will ensure that research is responsive to the most pressing patient needs. Investigation of CBT with and without exercise as management strategies and execution of drug PK/PD modeling studies are research areas that offer opportunity for meaningful developments across all three prioritized symptoms. Additionally, drawing upon known and yet-to-be-discovered symptom pathophysiology from non-nephrology disciplines will create opportunities to develop more targeted therapies. Once therapies are identified, partnerships with patients, dialysis provider organizations, medical providers, and industry will be essential for designing and implementing clinical trials testing the effect of interventions on symptom management.

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Table 4. Overarching recommendations for fostering innovation in symptom management

No.	Recommendation
1.	Develop definitions for individual symptoms accounting for culturally divergent patient experiences.
2.	Develop validated and standardized measures for individual symptoms to accurately assess burden.
3.	Conduct research to better understand the biologic basis for these symptoms in patients on dialysis.
4.	Conduct clinical trials of promising treatments including drugs, devices, and behavioral therapy.
5.	Test modifying dialysis care delivery to support and seamlessly integrate evidence-based treatments.
6.	Demonstrate the effect of symptoms on patient-reported and clinical outcomes.
7.	Advocate for payment reform that incentivizes improved treatment and management of symptoms.
8.	Perform focused prioritization and gap assessments among patients on peritoneal dialysis and patients on home-based hemodialysis.

Health Initiative (KHI), a public–private partnership between the American Society of Nephrology, the US Food and Drug Administration, and >75 member organizations and companies to enhance patient safety and foster innovation in kidney disease.

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See Supplemental Table 1 for meeting participants.

Disclosures

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