INTRODUCTION

Patients with end-stage kidney disease (ESKD) who are on dialysis have to make significant adaptions to their life, accepting dietary and fluid restrictions, rigorous medication regimens, and complex renal replacement therapy routines. Patients also have to cope with the multiple self-management challenges related to complications and comorbidities associated with ESKD, diminished independence, loss of time spent on dialysis, travel limitations, and financial burden.

Adherence to the demanding physical and behavioral adaptions are central to the effective delivery of ESKD care, yet low adherence to all domains of ESKD therapy (diet, fluid, medication, and dialysis) is common. Nonadherence to treatment is associated with increased risk of mortality, hospitalizations, complications, and poor quality of life in dialysis patients. Given the high baseline risk of adverse outcomes experienced by ESKD patients, it is instinctive to examine whether strategies to promote treatment adherence could improve clinical outcomes. In the context of long-term therapies of chronic diseases, it has been suggested that a more significant impact on the population health outcomes could result from the introduction of effective adherence interventions than any improvement in specific medical treatments.

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Several randomized and nonrandomized trials have examined the effectiveness of diverse adherence intervention strategies on the direct or indirect markers of adherence in dialysis patients. In this review, we plan to explore the nature of these interventions, examine their efficacy, and consider their limitations. We will also explore the potential of technology-based innovative interventions before envisioning the future directions in this field. However, a clear understanding of the nature of adherence behavior in dialysis patients, the barriers to optimal adherence, theoretical models underpinning adherence interventions, and the problems associated with efficacy estimation of adherence interventions, is essential if one is to interpret the results of these trials.

2 | TREATMENT ADHERENCE IN DIALYSIS PATIENTS

The World Health Organization (WHO) adherence project has adopted the definition of adherence to long-term therapy as “the extent to which a person’s behavior—taking medication, following a diet, and/or executing lifestyle changes, corresponds with agreed recommendations from a health care provider.” In patients undergoing dialysis, such behaviors include the habit of adhering to dietary recommendations, observing prescribed fluid restrictions, taking medications regularly in the recommended doses, and attending hemodialysis or peritoneal dialysis without missing or shortening treatment sessions. It should be recognized that treatment adherence is not the exclusive responsibility of the patient, and a collaborative approach in a “blame-free” environment is essential to address non-adherence. Identifying the actual barriers to adherence is essential for developing and implementing adherence improvement strategies.

3 | BARRIERS TO OPTIMAL ADHERENCE

Adherence is a multi-dimensional behavior influenced by five sets of factors, and patient-related factors make up just one of the dimensions, the others being: social and economic factors, health care system-related factors, condition or disease-related factors, and therapy-related factors. Examples of these factors as applicable to ESKD patients, are given in Table 1.

4 | THEORETICAL MODELS OF ADHERENCE

Health professionals make treatment recommendations using their scientific expertise, after due consideration of diverse patient variables. They typically rely on professional status and the provision of health information supporting their recommendation to persuade the patients to adopt the necessary changes. According to the Health Belief Model (HBM), patients’ adoption of the recommended treatment depends on perceived susceptibility (understanding that the health condition is sufficiently significant to motivate), perceived threat (recognition of vulnerability to a severe health problem or its sequelae), perceived benefits (acceptance that the treatment is likely to reduce the perceived threat), and perceived barriers (the cost of adherence to recommendations is acceptable). The Social cognitive theory, which significantly overlaps with the HBM, holds that behavior is regulated by expectancies (which include expectations about the consequences of one’s action—“outcome expectation” and expectations about one’s competence to execute behavior change to achieve those outcomes—“efficacy expectation”) and incentives (value of the health outcome in the setting of adherence) which serve as reinforcements. Outcome expectation is very similar to the perceived benefits in the HBM, whereas efficacy expectation, which is unique to the social cognitive theory, advances the concept of “self-efficacy.” The Self-affirmation theory suggests that self- affirming actions like reflecting on personally important values can reduce the defensive response to threatening health information and promote health behavior change.

### TABLE 1 Major barriers to treatment adherence in ESKD patients on dialysis

| Major adherence domain | Factors                                                                 |
|------------------------|-------------------------------------------------------------------------|
| Social and Economic factors | Cost of dialysis and medications, Poor socio-economic status, Low levels of education, Poor social support, Long distance from treatment centers, Cost of transport for dialysis |
| Health care system-related factors | Poorly developed or less accessible dialysis services, Inadequate health insurance plans, Overburdened health systems, Inadequate drug distribution networks (eg, cold chain for erythropoietin), Inadequate training of treatment providers, Inadequate engagement by treatment providers, Treatment providers’ lack of awareness about adherence |
| Condition/ Disease-related factors | Disability (eg, visual impairment in diabetic patients), Depression, Cognitive impairment, Multi-morbidity, Drug and alcohol use |
| Therapy-related factors | Complexity of dialysis regimen, Length of dialysis treatment, Intensity of the medication regimen, Frequent dose changes in medications, Side effects of treatment |
| Patient-related factors | Knowledge gaps relevant to disease and treatment, Attitude, Beliefs, Perceptions & Expectations, Anxiety and forgetfulness |
and contextual factors with individual cognition and affect, postulating that "self-regulation is a function of the representation of health threats and the targets for ongoing coping set by the representation, the procedures to regulate these targets and the appraisal of coping outcomes". While the above theories apply to diverse behaviors beyond adherence, Transtheoretical model, also known as the "Stages of change" model, was developed to explain the process of change in the context of substance abuse and proposes that behavioral change progresses through the stages of "precontemplation," "contemplation," "preparation," "action," and "maintenance," and at any given time people are in different stages of changing their behavior. During the journey through the various stages, individuals commonly relapse to the old behavior or a lower level and several cycles of change may be required before the patient stabilizes on the new behavior. A majority of the theory-based adherence interventions discussed in this review have invoked one of the above models, but since the models are overtly broad, interventions based on the same theoretical model may show significant diversity.

5 | OUTCOME MEASURES OF ADHERENCE INTERVENTIONS AND THE CHALLENGES

Choosing reliable and valid patient-important outcomes in interventional trials minimizes the risk of measurement bias and provides greater confidence that the true effect lies closer to the efficacy estimate observed in the trial. In a successful adherence intervention trial, one would expect to see improvement in a reliable and valid measure of adherence in response to the implemented intervention. The choice of outcome measurement in this setting depends on the domain of ESKD adherence under evaluation, whether it is dietary, fluid, medication, or dialysis adherence. Extrapolating from adherence to long-term therapies, adherence outcomes in ESKD can be broadly classified as direct and indirect measures of adherence. Each method has its advantages and disadvantages, and no single method can be considered as the gold standard.

Direct measures of adherence are superior to indirect measures but are practical only for some domains of ESKD adherence. Even when direct measures are used, the outcomes can be impacted by factors unrelated to adherence. For instance, missed or shortened dialysis sessions denoting dialysis nonadherence can be directly recorded by nurses; but vascular access problems and technical issues could result in the same outcome (missed or shortened treatments) and should be recognized to avoid misclassification. Even with objectively collected direct or indirect measures of adherence, studies have dichotomized patients to "adherent" and "nonadherent" categories based on nonstandardized clinical cut-off scores, which can be contentious. For example, an educational intervention study classified "dialysis nonadherence" as missing one or more HD treatments over 12 weeks whereas another study evaluating health-system/patient education interventions classified it as missing more than 5% of their prescribed total dialysis time.

Directly observed therapy (DOT) is the most accurate method to measure medication adherence. It is also an adherence intervention by itself that removes multiple barriers in the delivery of therapy. It is more effective than psycho-educational interventions in addressing nonadherence in the treatment of tuberculosis and human immunodeficiency virus (HIV) infections, especially in low resource settings. In-center hemodialysis patients have to attend the dialysis facility three times a week, and DOT may be feasible if it is medically appropriate. Though ESKD patients have one of the highest pill burdens among chronic diseases, few categories of medications other than erythropoietin and paricalcitol are ideally suitable for three times a week therapy.

Nevertheless, researchers have trialed directly supervised posthemodialysis administration of atenolol or ACE inhibitors for uncontrolled hypertension, cholecalciferol for nutritional Vitamin D deficiency, and cinacalcet for secondary hyperparathyroidism. Postdialysis DOT with antihypertensive agents in small-scale studies improved BP control, but large-scale trials supporting this strategy have not been reported. Although DOT may have improved adherence in the cinacalcet trial, the study found that PTH control was worse in the intervention arm due to the physiological inferiority of intermittent cinacalcet administration, which highlights DOT’s limitation in dialysis patients. DOT is impractical for ESKD patients undergoing home-based dialysis.

Indirect measures of adherence are widely used to measure medication, dietary, fluid, or dialysis adherence in ESKD patients. Medication adherence is frequently assessed in clinical research using measures of medication possession or dispensing, though this does not guarantee medication consumption. Pill counts and pharmacy refill reports are easy, inexpensive, objective, and quantifiable, but much less precise than the electronic medication dispensing systems, which are expensive and unsuitable for routine use, especially with multiple medications.

Dietary adherence is frequently measured in clinical trials by diet diaries or adherence questionnaires. Diaries have the benefit of minimizing recall bias but have the limitation of being a patient-reported item and therefore vulnerable to manipulation. Numerous questionnaires and self-reported measures have been used to assess various aspects of adherence and are listed in Table 2.

Adherence intervention trials in dialysis patients frequently report on clinical response to specific medications or dietary/fluid restrictions by measuring physiological or biochemical markers as surrogate adherence outcomes. While the use of a surrogate marker is justified when the measurement of the underlying primary outcome is expensive or difficult, the potential for confounding, which could invalidate the conclusions about the efficacy or lack of efficacy of an intervention based on that surrogate marker, should always be considered. For example, changes in blood pressure control, attributed to interventions promoting antihypertensive adherence, might be confounded by variations in the salt intake or fluid volume changes. Inter-dialysis weight gain (IDWG), measured as a surrogate of adherence to prescribed fluid restriction, can be confounded by urine output and extra-renal...
fluid losses. Phosphate level, measured as a surrogate marker of adherence to dietary restriction or phosphate binder intake or both, may be confounded by the variations in dietary phosphate absorption as well as up to two-fold variations in the efficacy of phosphate binders and variance in dialytic phosphate clearance among individuals. Similarly, measurements of other biochemical parameters like calcium, parathyroid hormone (PTH), sodium, potassium, albumin, and solute clearance measures such as $Kt/V$, while essential in the patient’s clinical care, are susceptible to confounding if used as measures of adherence, due to similar biological variability. The lack of standardized measures to quantify adherence is responsible for the range of estimates of nonadherence that exists, and makes it difficult to judge and compare the efficacy of the very interventions aimed to improve it.

6 | INTERVENTIONS TO IMPROVE ADHERENCE

For the sake of simplicity and consistency, the adherence interventions evaluated in clinical trials can be classified using the WHO dimensions of adherence framework.

| Test/measure of adherence | Advantages | Disadvantages |
|---------------------------|------------|---------------|
| Direct measures           |            |               |
| Directly observed therapy | Most accurate | Practical only for few medications (eg, Erythropoietin, Paricalcitol) |
| Missed dialysis sessions  | Objective | Nonadherence-related factors (like access dysfunction) can also lead to missed or shortened dialysis sessions |
| Shortened dialysis sessions |            |               |
| Remote monitoring of automated peritoneal dialysis |            |               |
| Indirect measures of adherence (subjective) | Simple, Inexpensive | Self-reported measures can overestimate adherence |
| Dialysis Diet and Fluid Questionnaire (DDFQ) | Practical in routine clinical setting | Instruments should be validated for the patient population |
| Diet diary/checklist       |            |               |
| End Stage Renal Disease Adherence Questionnaire (ESRD-AQ) |            |               |
| Medication Adherence Report Scale (MARS) |            |               |
| Morisky-Green 4-item medication scale |            |               |
| Morisky Medication Adherence Scale (MMAS) |            |               |
| Patient interviews         |            |               |
| Renal Adherence Behavior Questionnaire (RABQ) |            |               |
| Researcher designed/modified questionnaires |            |               |
| Indirect measures of adherence (objective) | Highly reliable | Expensive, Less practical for multiple medications |
| Electronic medication event monitoring system (MEMS) | Simple, Inexpensive | Medication possession or dispensing does not guarantee medication consumption |
| Pill count (of unused medicine) | Objective | Practical only for limited medications (eg Vitamin D) |
| Prescription refill data   |            |               |
| Measurement of the level of drug or metabolite |            |               |
| Indirect measures of adherence (surrogate) | Objective | Can be affected by factors other than adherence like biological variability or medications used to control these measures |
| Calcium                    | Easily available, Often tested as part of routine care | Adjusting for confounding variables may be difficult |
| Phosphate                  |            |               |
| Calcium x phosphate product |            |               |
| PTH                        |            |               |
| Albumin                    |            |               |
| Potassium                  |            |               |
| $Kt/V$                      |            |               |
| Inter-dialysis weight gain |            |               |
| Blood pressure             |            |               |
7 | SOCIAL-ECONOMIC INTERVENTIONS

Treatment of ESKD is costly. The number of patients per million population on dialysis therapy in upper-middle-income and high-income countries is 13-16 times higher than in low and low to middle-income countries, suggesting that access to dialysis is highly limited in resource-poor settings. Even in high-income countries, the cost of therapy can impact adherence. In a study of dialysis patients from 12 counties, out-of-pocket expenses predicted medication nonadherence, with monthly expenses ranging from $8 in the United Kingdom to $114 in the United States.

Large-scale interventions to improve adherence in the social and economic domain are typically initiated by health administrators, health payers, and policymakers. Government-sponsored subsidization of treatment costs or establishment of insurance schemes for poor people in resource-limited countries is the standard social/economic interventions that would lead to improved access to and adherence to dialysis therapy. At a community level, a nonrandomized Canadian study in peritoneal dialysis patients reported that the provision of phosphate binders free of charge led to significant improvement in phosphate levels, a surrogate measure of adherence. Cost-focused interventions would be expected to have a more significant impact on adherence in resource-limited settings.

8 | HEALTHCARE SYSTEM-RELATED INTERVENTIONS

Bridging the gaps in the provision of care as well as improving the communication between providers and patients are key principles underlying health system-related interventions that can improve patient adherence.

A nurse-led chronic disease management program based on the principle of 4 Cs model (Comprehensiveness, Collaboration, Coordination, and Continuity) resulted in significant improvement in some domains of self-reported adherence in an RCT in peritoneal dialysis patients. The effect of the implementation of primary nursing care models, where the same nurse cares for the patient providing greater accountability and continuity of care, was evaluated in a non-RCT and found no significant benefits in markers of adherence (IDWG, phosphate, potassium). Proactive engagement of a researcher with nephrologists and patients with a focus on sub-optimal dialysis access, dialysis prescription, and treatment time in an RCT resulted in significant improvement in adherence as indicated by an increase in measured Kt/V and prescribed dialysis dose. Management protocol implementation by dedicated specialist dietitians and pharmacists resulted in significant improvement in adherence measured by phosphate levels and drug regimen compliance. Health system- or provider-centered interventions described above also have elements of patient education.

Developing clinical tools to assist in evaluating and addressing nonadherence are important health system-related adherence improvement strategies. Active monitoring for adherent behavior can be thought of as a clinical tool that could improve adherence, based on the “Hawthorne effect” which denotes behavior change in response to the awareness of being observed. Remote telemetric monitoring of body weight in the inter-dialysis period with follow-up phone calls for weight gain above threshold daily goals has been shown to improve IDWG in an RCT. Remote monitoring of patients on automated peritoneal dialysis, which has been shown to improve hospitalizations in observational studies, has the potential to improve adherence by a similar mechanism.

9 | DISEASE-RELATED INTERVENTIONS

Multi-morbidity is common in ESKD patients. With regards to treatment adherence, cognitive impairment, and depression, which are highly prevalent in this population, are particularly relevant.

Depression is linked to dietary, fluid, and medication nonadherence as well as to missed hemodialysis sessions and peritoneal dialysis exchanges. Some improvement in adherence markers may be expected with the successful treatment of depression. Cognitive behavioral therapy (CBT), an effective treatment for depression, has improved fluid adherence in hemodialysis patients in RCTs. However, CBT has obvious behavioral components, and the improvement in adherence may not be solely due to improvement in depression. In depressed hemodialysis patients, sertraline therapy was associated with greater reductions in depression scores than was CBT. A systematic review of antidepressant medications in dialysis patients reported variable benefits with depression scores but did not report on measures of adherence. Published protocols of two RCTs evaluating sertraline in depressed dialysis patients have listed treatment adherence as a prespecified outcomes, and may provide valuable insights.

Cognitive impairment may hinder adherence to the complex treatment regimens in ESKD patients. Forgetfulness leading to random un-intentional nonadherence is common in clinical practice but could worsen with cognitive impairment. Reminders with human communication as well as telephone and tele-video reminders have been shown to improve adherence in older adults with cognitive impairment, but such strategies have not been reported in dialysis patients. Nevertheless, reminders are likely to be beneficial in improving adherence in this population.

10 | THERAPY-RELATED INTERVENTIONS

Intensity and complexity of therapy, as well as the patient’s inability to deal with treatment-attributed adverse events, constitute major therapy-related barriers to adherence. The pill-burden in dialysis patients is the highest among chronic diseases, with up to one-quarter of patients taking more than 25 pills every day. A cross-sectional study of 556 elderly patients with severe renal failure...
found that 77% had at least one renally inappropriate medication, and 58% had at least one old-age inappropriate medication. Targeted de-prescribing, which is routinely practiced in geriatric patients, has been successfully trialed as a therapeutic strategy in outpatient hemodialysis patients. Although de-prescribing cannot be considered an adherence intervention, avoidable medications should be promptly discontinued to reduce the risk of adverse events, which can precipitate nonadherence. Polypills, which contains multiple active pharmaceutical ingredients in a single pill, improve treatment adherence in cardiovascular diseases and could be one of the most scalable strategies to reduce cardiovascular mortality. A similar approach might face enormous challenges in the dialysis setting due to the unique pharmacotherapeutic needs of ESKD patients.

11 | PATIENT-RELATED INTERVENTIONS

Since treatment adherence is a heterogeneous behavior, and the selection bias associated with nonrandomized intervention trials can compromise the reliability of the efficacy estimates, we have not examined non-RCTs for patient-related interventions in this review. More than 90% of the 40 RCTs evaluating strategies to improve adherence in dialysis patients have used patient-related intervention. This may be partly because health providers often consider adherence as a patient-centered problem or because this is the most easily implemented strategy in routine clinical practice. It is tempting to organize these interventions into well-defined categories to understand their scope and compare different interventions, but this task is difficult.

De Bleser et al, in their systematic review of interventions to improve treatment adherence after transplantation have classified patient-level interventions as:

1. Educational/cognitive interventions which provide information or knowledge about disease or treatment to the patient
2. Counselling/behavioral interventions which address patient’s thoughts and behavior, enhance their skill relevant to self-care or empower them to participate in their care
3. Psychologic/affective interventions that appeal to the patient’s feelings and emotions or social support and
4. Mixed interventions which are a combination of the interventions mentioned earlier.

In this review, we have tried to group the patient-related interventions on similar lines, but several interventions showed significant overlap between categories. We will discuss the efficacy of these interventions as a group, rather than individual studies, to give a broader perspective.

Educational/cognitive strategies were the dominant components in the majority of RCTs evaluating patient-related interventions. Information deficits concerning disease or treatment-specific knowledge are common in dialysis patients, and their correction by educational strategies may modify the patient’s perspectives about the need to adhere to treatment. Educational/cognitive interventions were trialed either as the sole strategy (Aghakhani et al, Ashurst Ide et al, Baraz et al, Chen et al, de Araujo et al, Ford et al, Karavetian et al, Lou et al, Sehgal et al, Shi et al, Skoutakis et al, Vrdoljak et al, Wong et al, Yookum et al) or in combination with counselling/behavioral strategies (Brantley et al, Cukor et al, Griva et al, Hare et al, Hou et al, Karavetian et al, Kauric-Klein et al, Molaison et al, Morey et al, Reese et al, Sevick et al, Sharp et al, Sullivan et al, Tsay et al, Welch et al, Zhianfar et al). The primary interventions were delivered mostly through individual format, but some studies which used a combination of cognitive and behavioral strategies used a group format.

The educational interventions in RCTs were delivered through different methods. The face to face session could be as short as one hour or less, but more often comprised of multiple interactions, each lasting 20-60 minutes, spread over several sessions, with the longest total education time up to 12-36 hours over six months. Videos, booklets, information boards or posters were also used to supplement patient education.

The educational content in the adherence interventions included pathophysiology of ESKD, complications of ESKD and principles of dialysis, practical aspects of nutritional management including menu suggestions, food exchanges, dietary phosphate restriction, and understanding nutrition facts labels, principles of phosphate binder use, self-monitoring of blood pressure and principles of antihypertensive use, and restriction of salt and fluid intake. Most educational contents highlighted the consequences of noncompliance and the benefits of adherent behavior.

Change in knowledge in response to the intervention was objectively assessed by pre and postintervention knowledge questionnaires in some studies. Information about the complications of disease and details of the treatment is essential to build awareness which may drive behavior change, but the acquisition of knowledge alone may not be sufficient to maintain behavior change.

Twenty-four of 31 RCTs, which trialed interventions that utilized some educational components, noted an improvement in one or more markers of adherence after the intervention or during the follow-up period. The adherence outcomes that showed a beneficial change in these studies included IDWG, edema, changes in blood pressure, serum phosphate, calcium x phosphate product, potassium, Kt/V, missed dialysis sessions, self-reported adherence, disease/treatment-specific knowledge by questionnaire, stage of behavior change, and vascular access self-care. However, 11 of 24 trials reporting an improvement in one or more adherence outcomes also reported a lack of improvement or worsening in some other adherence measure. For instance, a study evaluating cognitive behavioral strategies to improve fluid adherence in peritoneal dialysis patients reported improvement in edema as a beneficial outcome, but the trial failed to achieve the prespecified
weight-change goal or BP control. Another study evaluating an intervention based on the Transtheoretical model reported that a greater proportion of patients in the intervention arm were in the maintenance phase of behavioral change as a beneficial outcome. However, the IDWG worsened in the intervention arm compared to controls. Conflicting results on measures of the same adherence domain raise questions about the validity of the reported outcome measurement and how to determine which outcome is more reliable.

Behavioral/ counseling strategies were important components of numerous adherence intervention trials. In many studies, they were combined with educational/cognitive strategies as listed above, but in others, they constituted the dominant intervention (Cho et al, Cummings et al, Forni Ogna et al, Howren et al, Moattari et al, Neuman et al, Tanner et al). Facilitating the identification of adherence barriers by the patient and setting achievable and meaningful adherence goals by negotiation were frequently used behavior strategies in these trials. While the behavior change is being implemented, positive reinforcement either directly or by phone calls, through praise, encouragement, or support is beneficial in achieving and sustaining adherence behavior. Regular feedback about suboptimal adherence during the intervention, such as abnormal laboratory results, excessive IDWG, or objective measures of adherence like MEMS, may provide negative reinforcement and promote uptake of adherence behavior. Periodic re-evaluation of the adherence training in partnership with the patient to identify which strategies work and which do not work and adopting a flexible approach to consider alternate strategies when necessary could make the intervention more effective.

Contingency health contracts between patients and healthcare providers to improve patient adherence have been studied since the 1970s and can yield some benefits. RCTs have examined the effect of health contracting to improve adherence measures in dialysis patients. Health contracts are formal agreements between patients and healthcare providers outlining mutually agreed goals, a timeline for achieving those goals, maintaining a record of patient’s progress, reviewing such records, and re-contracting periodically as necessary. Contingency contracts also specify rewards of some value to the patients upon achieving agreed goals, which may be financial rewards like lottery tickets or simply smiley stickers. Ethical concerns arise when the access to therapy becomes dependent upon the patient’s behavior as stipulated in the contract or when financial rewards are offered. Financial incentives without a health contract may overload, whereas the controls were given the same health information related to poor phosphate control or fluid overload, whereas the controls were given the same health information following non-self-affirming questions. Self-affirmation was purported to modify the patient’s perception of health risks, and improve their intentions, self-efficacy, and treatment adherence. While the studies showed improvement in phosphate control and IDWG as surrogate adherence measures, the intervention and control arms did not differ in their evaluation of health risk, intention for behavior change, or self-efficacy. The lack of biological plausibility for the improvement in adherence markers based on the study hypothesis raises concerns about the reliability of the conclusions.

Eighteen out 24 RCTs which trailed interventions that had some behavioral/counseling components noted an improvement in one or more markers of adherence after the intervention or during the follow-up period. Efficacy data of the 17 RCTs that had both cognitive/educational and behavioral/counseling strategies are already described above. Of the remaining seven RCTs, the adherence outcomes that showed a beneficial change included IDWG, changes in PTH, potassium, self-reported adherence, medication compliance by electronic medication event monitoring system (MEMS), and disease/treatment-specific knowledge by questionnaire. However, four out of the above seven trials, which reported an improvement in one or more adherence outcomes, also reported a lack of improvement in some other adherence measure. For instance, a study evaluating health contract intervention reported significant improvement in IDWG, but the phosphate levels showed no improvement. Another study reported improvement in potassium levels, but IDWG was not better for patients who entered in the contingency contract with their health provider.

Psychological/affective adherence interventions evaluated in RCTs in ESKD patients have used Benson’s relaxation techniques or interventions based on self-affirmation theory. In the latter two trials patients were required to recall their past acts of kindness based on a self-affirmation questionnaire before they were given health risk information related to poor phosphate control or fluid overload, whereas the controls were given the same health information following non-self-affirming questions. Self-affirmation was purported to modify the patient’s perception of health risks, and improve their intentions, self-efficacy, and treatment adherence.

Though the majority of evaluated strategies resulted in improvement of some measure of adherence, the overall quality of evidence from
RCTs of adherence interventions was graded as "very low certainty" in a recent systematic review, for the commonest reported outcomes, namely IDWG and change in serum phosphate levels, both of which showed significant improvements in meta-analyses. The "very low certainty" grading was due to the following reasons: most comparisons were unblinded; most were not analyzed as intention-to-treat; studies trialed highly diverse interventions; and studies frequently used surrogate adherence outcomes without accounting for relevant confounders leading to indirectness of evidence. Matteson et al suggested that cognitive behavioral interventions are the most promising category of interventions to improve adherence in dialysis patients. Murali et al noted that efficacy was not significantly associated with the type of interventionist (dietitian or nurses or others), the category of intervention (educational/cognitive or others), or the use of a theoretical model of behavior in planning the intervention. Tao et al have more recently observed that individually administered interventions are more likely to yield beneficial outcomes.

Educational tools are essential to ensure that knowledge gaps limiting adherence are addressed, and a variety of behavioral tools are useful in modifying adherence at least in the short term. Changes in health beliefs and changes in the way an individual think may be more effective in achieving long-term behavior modification, as patients internalize the cognitive rationale for reshaping their behavior. It is therefore likely that a combination approach incorporating aspects of educational/cognitive, counseling/behavioral, and psychologic domains will be more effective.

Cognitive behavior therapy (CBT) is a short-term and focused psychotherapy commonly used to treat less severe depression and many other mental health conditions. It aims to help patients identify their cognitive distortions and challenge those distortions, enabling patients to improve their coping behavior. CBT has been trialed to improve fluid adherence in peritoneal dialysis and hemodialysis patients. Rational emotive behavior therapy (REBT), another form of cognitive-based psychotherapy, has been evaluated to improve fluid adherence. BP control, and ultrafiltration volume in hemodialysis patients. REBT framework proposes that psychological disturbances are created and sustained by irrational and self-defeating thoughts, and the therapy strives to achieve behavioral change through disputation of the underlying irrational philosophies. These cognitive-based psychotherapies significantly reduced IDWG in hemodialysis patients, but did not achieve the prespecified weight reduction goals in PD patients though there was an improvement in edema. One should appreciate that the construct of IDWG as a fluid adherence marker in hemodialysis patients may not be directly transferable to prespecified weight loss in PD patients.

The composite adherence intervention called “HED-SMART” trialed by Griva et al also merits a focused examination. The program was designed to be delivered in a routine clinical setting and aimed to enhance patients’ confidence and capacity for self-management behavior, through goal setting, barrier identification, problem-solving, peer support, follow-up sessions, and phone calls to minimize relapse. The program also included disease/treatment specific educations as well as monthly audits and structured reviews to ensure implementation fidelity. While being comprehensive, this practical approach resulted in significant improvement in multiple markers of adherence but showed a tendency for relapse during follow-up, which is a common characteristic of nonadherent behavior. In a recent systematic review, among the RCTs that reported on the persistence of adherent behavior beyond the first outcome assessment, the beneficial effect waned or was not detectable by 12 months in the majority of trials, which underscores the need for a longer duration of adherence interventions and strategies to prevent relapse in intervention programs.

### 13 | TECHNOLOGY-DRIVEN INNOVATIVE ADHERENCE INTERVENTIONS

We are living in the cusp of the fourth industrial revolution fueled by artificial intelligence (AI) and machine learning, driven by big data, in an increasingly interconnected world with high-speed internet and portable computing. Technology-driven solutions hold tremendous potential to generate precise and personalized tools to monitor and manage adherence in dialysis patients. Targeted structured text messaging has been employed to improve dietary and lifestyle behaviors in hemodialysis patients. Remote monitoring of ESKD patients on automated peritoneal dialysis not only reduces the risk of hospitalizations, but has the potential to improve adherence by being able to identify missed exchanges promptly. Expansion of telehealth consultation options from home or stand-alone dialysis units not only increases patient satisfaction but could improve patient outcomes, including adherence. Artificial intelligence and machine learning have already been evaluated in several areas of dialysis including service delivery, dialysis procedure, treatment of infections, and cardiovascular event prediction, but have the potential to improve adherence to therapy.

### 14 | CONCLUSIONS AND FUTURE DIRECTION

Published trials to improve adherence in ESKD patients have mostly addressed patient-related factors and have tested educational/cognitive, counseling/behavioral, psychological interventions, or combination strategies. Surrogate adherence outcomes such as inter-dialysis weight gain or changes in phosphate level were frequently used without adequately accounting for confounding factors. Accepting this limitation, a majority of adherence intervention trials reported improvement in some adherence outcomes, though many of these trials showed no improvement in some other adherence outcomes, questioning the validity of outcome measurement. Nonadherence behavior also showed a tendency to relapse on follow-up. Cognitive behavioral strategies, combination strategies, and interventions delivered in an individual format demonstrated some advantages.
To better evaluate barriers to improved adherence in ESKD patients, future trials should employ standardized adherence outcomes to increase our confidence in the efficacy estimates of adherence intervention in dialysis patients. When surrogate adherence markers are used in trials, robust analysis models should account for relevant confounders to minimize the risk of biased outcome measurement. Dichotomizing adherence behavior based on clinical cut-offs should be done only with broad consensus. The prospect of evaluating adherence as a continuous variable, though challenging, could be explored. Nonadherence behavior is not an all-or-none attribute; the severity of suboptimal adherence can vary between patients and within the same patient between time points. Large-scale future trials should also employ streamlined multifaceted interventions that can be replicated in different clinical settings and include steps to prevent, identify, and manage relapse of nonadherence. Technology-based monitoring and intervention strategies targeting adherence offer tremendous promise in the coming decades.

Though effective adherence interventions could improve population health outcomes, this has not become a policy priority in chronic diseases, including ESKD, itself constituting a barrier to improved adherence. Finally, low adherence is unlikely to be "cured" easily, and practical tools to monitor and manage non-adherence should be integrated to routine clinical care while awaiting guidance from large-scale studies addressing this under-recognized problem with significant impacts on clinical outcomes in ESKD patients on dialysis.

CONFLICT OF INTEREST

The authors certify that they have no affiliations with or involvement in any organization or entity with any financial interest, or non-financial interest in the subject matter or materials discussed in this manuscript.

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