Current Transplantation Reports (2018) 5:174–188
https://doi.org/10.1007/s40472-018-0195-8

KIDNEY TRANSPLANTATION (M HENRY AND R PELLETIER, SECTION EDITORS)

Posttransplant Medical Adherence: What Have We Learned and Can We Do Better?

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Published online: 17 April 2018

Abstract

Purpose of review Non-adherence to the medical regimen after kidney transplantation can contribute to poor clinical outcomes, and strategies to maximize adherence are sought by care providers and patients alike. We assessed recent evidence on prevalence, risk factors, and clinical outcomes associated with non-adherence to the medical regimen after kidney transplantation. We summarized recent clinical trials testing interventions to improve adherence and generated recommendations for future research and clinical practice.

Recent findings A large evidence base documents rates of non-adherence to each of the multiple components of the regimen, including medication-taking, lifestyle activities, clinical care requirements, and substance use restrictions. Some risk factors for non-adherence are well known but the full range of risk factors remains unclear. Non-adherence to immunosuppressants and to other components of the regimen increases morbidity and mortality risks. Recent interventions, including education and counseling; electronic health strategies; and medication dose modifications, show promise for reducing immunosuppressant non-adherence. However, most of these interventions would be difficult to deploy in everyday clinical practice. Systematic dissemination of efficacious interventions into clinical practice has not been undertaken.

Summary Rates and risk factors for non-adherence to the medical regimen have been examined and there is evidence that non-adherence may be ameliorated by a range of interventions. Although gaps in the evidence base remain, it would be timely to devote greater efforts to dissemination of findings. Thus, efforts are needed to assist transplant programs in using existing evidence to better identify patients who are non-adherent and to design and implement strategies to reduce or prevent non-adherence.

Keywords Kidney transplantation · Medical non-adherence · Immunosuppressant non-adherence · Substance use · Risk factors · Non-adherence interventions

This article is part of the Topical Collection on *Kidney Transplantation*

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Introduction

Despite several decades of clinical and research attention, non-adherence to the medical regimen after kidney transplantation remains an area of ongoing concern for patients, healthcare providers, and researchers. From the patients' perspective, the medical regimen is complex and patients struggle with managing its various components, as well as balancing these requirements with problematic side effects and other health-related concerns. From the healthcare providers' perspective, it can be challenging to monitor patient adherence, identify strategies to effectively address patient non-adherence, and incorporate those strategies into routine patient care. From the researchers' perspective, the development of novel protocols to better identify key risk factors for non-adherence and to test innovative, scalable interventions remain priorities in order to support and address patients' and providers' concerns about posttransplant adherence. Given sustained clinical and research attention to the issue of posttransplant non-adherence, what are the key gaps remaining in this field and where are efforts most needed in order to make new inroads in reducing non-adherence after kidney transplantation?

In this review, we summarize recent evidence concerning the prevalence and risk factors for non-adherence to the posttransplant medical regimen and the role of non-adherence in increasing risk for poor health outcomes after kidney transplantation. We also consider findings from recent clinical trials testing novel strategies to reduce non-adherence. We then discuss translation of research findings into routine clinical care provided by kidney transplant programs. Our review focuses on adult kidney transplantation. Adherence issues are different for pediatric recipients, given the necessary involvement of family caregivers, and these issues have been the subject of several recent reviews [1–4].

Prevalence of Non-Adherence

What Have We Learned?

Over the past 40 years, numerous studies have examined the prevalence of non-adherence to elements of the multifaceted medical regimen after kidney transplantation, as documented in systematic reviews and meta-analyses [5•, 6–8]. Although immunosuppressant non-adherence has received the greatest attention, non-adherence to other components of the regimen has also been considered. In the only analysis to date to consider all components of the regimen, we found average non-adherence rates across studies of kidney recipients to be 36% of patients annually for immunosuppressant medications, 22 to 31% annually for lifestyle activities (diet, exercise) and 5 to 15% annually for completion of medical care requirements (e.g., clinic appointment attendance, laboratory testing) [8]. Not only was immunosuppressant non-adherence more prevalent than non-adherence to other components of the regimen, but it was more common in kidney recipients than in other types of organ recipients [8]. More recent systematic reviews, focused primarily on immunosuppressant non-adherence, show no indication that average rates of medication-taking have improved [5•].

Nevertheless, some new evidence suggests that moving from twice-daily to once-daily dosing of the mainstay of the immunosuppressive regimen, the calcineurin inhibitor, may ultimately shift non-adherence prevalence rates downward. Thus, following on a randomized clinical trial (RCT) demonstrating better adherence with once-daily tacrolimus dosing [9••], Lehner et al. [10•] reported on a multisite longitudinal observational study of patients receiving once-daily dosing of tacrolimus. They found self-reported non-adherence rates of between 9 and 13% during the month before each study assessment time point (through a maximum of 18 months of follow-up). Although self-reported non-adherence has been criticized as likely underestimating non-adherence, the non-adherence rates observed by Lehner et al. were similar to those reported in the Kuypers et al. RCT [9••], which relied on electronic medication monitoring. Lehner et al. additionally reported that the rate of "drug holidays" was very low (0–2% across assessment time points), although non-adherence to the required timing to take doses was common (~ 42% across assessment time points). A weakness acknowledged by Lehner and colleagues was absence of a comparison group. Nevertheless, convergence of observed non-adherence rates for medication-taking with those found in the earlier RCT [9••] strengthens the conclusions that can be drawn.

With respect to other components of the medical regimen after kidney transplantation, substance use is an important concern. Our meta-analysis found that, on average, from 1 to 3% of kidney recipients annually were non-adherent to transplant program recommendations regarding substance use (e.g., abstinence from tobacco use, drug use, and excessive alcohol consumption) [8]. The greatest focus of research has been on tobacco use, and a recent review reported that, averaged across studies, 24% of kidney recipients smoked tobacco at some point posttransplant [11••]. Because few studies have examined use of any other substances by kidney recipients [12], recent work examining marijuana use is significant. Marijuana has been legalized for medicinal and/or recreational use in a number of states in the USA. In a single-center cross-sectional cohort study, Greenan et al. [13•] estimated that 3% of kidney recipients were marijuana users, based on medical record information (either self-report or urine toxicology screens). However, these patients varied in time since transplant, and thus it is difficult to estimate either the annual or posttransplant lifetime marijuana use in the kidney transplant population.

Finally, it is noteworthy that patients' level of adherence to any single component of the posttransplant medical regimen is unlikely to remain static over time. Non-adherence to immunosuppressant medications has repeatedly been found to begin within months of the kidney transplant and grow more common with time [14–17]. Similar patterns would be expected for other components of the regimen, in keeping with evidence from the general chronic disease literature indicating that non-adherence rates increase over time after treatment initiation [18, 19].

Can We Do Better?

In heavily studied components of the medical regimen (e.g., immunosuppression medication-taking), the added value of new studies documenting prevalence rates is likely to be small. Exceptions would be longitudinal observational studies, like the work of Lehner et al. [10•], which focus on examining non-adherence rates among programs that adopted empirically supported adherence promotion strategies. However, for any new studies, it would be important to reconsider the cut points traditionally used to identify non-adherent patients. For example, a commonly used cut point for non-adherence is taking 80% or less adherence of required doses [20]. However, this definition—adopted because it has been used with medication-taking for other chronic diseases [21]—may not be clinically meaningful: even kidney recipients who are less than 95% adherent to immunosuppressants appear to be at increased risk for acute graft rejection and graft loss [22]. This suggests that future descriptive studies should employ definitions of non-adherence that are more closely aligned with clinical evidence regarding the impact of deviations from prescribed immunosuppressant medication dosing on clinical outcomes.

Beyond immunosuppressant medication-taking, additional work is needed to understand the nature and patterns of onset of non-adherence to other components of the medical regimen, including lifestyle and medical follow-up requirements, and substance use restrictions. Such work could help to identify areas requiring greater attention to intervention development and deployment posttransplant.

Risk Factors for Non-Adherence

What Have We Learned?

There are two sources of information on risk factors: quantitative studies of risk factor-outcome associations and qualitative reports of kidney recipients' views about what factors affect their medical adherence. Within the quantitative literature, the major risk factors for non-adherence in chronic disease populations have been conceptualized as falling into five classes [23]. These five classes, which we view as reflecting three broad domains, are shown in Table 1. The table also provides examples of specific risk factors found to be important for kidney recipients. Among these, past non-adherence is the strongest, most consistently identified risk factor for future non-adherence in kidney recipients [7, 8, 15, 24, 25••]. In the case of posttransplant substance use, not only does past use predict future use [8, 11••], but use of any one substance after transplantation is highly correlated with use of other substances [11••, 13•, 26, 27].

Risk factors for posttransplant medication non-adherence have received the greatest attention. As for other chronic disease groups [28], the more complex the posttransplant medication regimen (in terms of both dosing frequency and total number of medications), the greater the risk for non-adherence among kidney recipients [5•]. The impact of the remaining factors in Table 1 appears to be modest [8, 20]. Furthermore, for some of the listed risk factors, evidence regarding their impact on non-adherence is inconsistent. For example, some studies find that minority race/ethnicity increases medication non-adherence risk in kidney recipients [17, 29–31] while other studies do not [32–34]. Inconsistent findings may arise because race/ethnicity is best considered to be a proxy for factors such as insurance status and access to care that more directly contribute to non-adherence. Once such factors are taken into account, any association of race/ethnicity with non-adherence may be reduced or disappear [34].

Risk factors for posttransplant non-adherence in areas beyond medication-taking have received limited consideration. An exception is posttransplant tobacco smoking, for which evidence on risk factors has been steadily growing. Although a recent meta-analysis [11••] does not single out studies of kidney recipients from those of other types of organ recipients, studies of kidney recipients comprised the bulk of available reports. The authors found that, across studies, male sex, younger age, and higher body mass index (BMI) increased smoking risk. Common comorbidities (hypertension, diabetes, cardiovascular disease) were not reliable risk factors for smoking. Other factors (e.g., psychological distress, coping styles) were included in too few studies to evaluate their impact [11••]. For use of other substances by kidney recipients, the few available studies indicate that male sex is an important risk factor for heavier alcohol use [27, 35]. In contrast, Greenan et al. [13•] found that sex was not related to recreational marijuana use. Instead, less education, being unmarried, current alcohol and tobacco use, and a history of treated substance addiction were associated with marijuana use.

A large qualitative literature has focused on posttransplant medication adherence, as well as general self-management of the regimen. Systematic reviews and in a recent meeting report [36•, 37••, 38] summarize this evidence and capture kidney recipients' and other organ recipients' own perceptions about factors that affect their adherence. For example, at a recent public meeting of the US Food and Drug Administration

Table 1 World Health Organization conceptualization of factors that increase risk for non-adherence to medical regimen requirements in chronic disease [23]

Classes of risk factors for non-adherence	Subtypes of risk factors within each class, with examples of factors important for kidney transplant recipients
Clinical factors	Condition-related
	Longer time since transplant
	Transplant from a living donor
	Better perceived health
	Physical limitations
	Treatment-related
	More medications
	More frequent medication dosing
	Lack of use of reminder/alerting systems to prompt adherence-related activities
	Bothersome side effects of medications or other treatments
Patient personal factors	Psychosocial
	Past non-adherence
	Low health literacy
	Low knowledge about one's illness
	Low self-efficacy
	Poor social supports
	Forgetfulness/cognitive impairment
	Psychological distress
	Daily routine changes
	Sociodemographic
	Younger age
	Minority race/ethnicity
	Low socioeconomic status
	2Male gender (for non-adherence to substance use restrictions)
Healthcare system factors	Health system/healthcare provider
	Insurance status
	Access to care
	Provider-patient communication
	Transitioned from pediatric to adult transplant program

designed to obtain feedback from organ transplant recipients on current pharmacotherapies after transplantation, key challenges and difficulties patients noted with regard to maintaining adherence to immunosuppressants included (a) frequent dosing; (b) difficulties coordinating medications with dietary requirements; (c) burdens associated with frequent clinic visits and with self- and clinical team monitoring of health indicators; (d) medication side effects, including their long-term consequences; and (e) difficulties remembering to take medications on time [36•]. These comments both echo and build on findings from systematic reviews, which note that managing the medical regimen is considered by patients to be a complex task that can lead to feelings of anxiety and burn-out [37••, 38]. At the same time, patients strongly endorse a desire to protect their new chance at life [37••, 38]. Overall, a balance between adequate self-management of the regimen vs. a satisfactory quality of life with tolerable side effects is an important goal but can be difficult to achieve.

Can We Do Better?

Despite a multitude of studies, we continue to have an incomplete picture of the full spectrum of key risk factors for non-adherence to the medical regimen after kidney transplantation. Few quantitative reports have simultaneously considered risk factors across all of the classes shown in Table 1 in order to determine which factors are most important for any given component of the medical regimen. Many reports focus on demographic and clinical factors assessed through medical records, and do not assess patient psychosocial or healthcare system-level factors. Recent studies have attempted to include a more complete array of factors [32, 33, 39, 40]. However, many such studies focus on bivariate risk factor-non-adherence associations and have samples too small to undertake complete consideration of all factors' unique associations with non-adherence in multivariable analyses.

Furthermore, cross-sectional research predominates, and—for many putative risk factors—this can preclude any determination that any given factor is a predictor rather than a consequence of non-adherence. For example, instead of increasing risks for non-adherence, psychosocial factors such as psychological distress or feelings of low self-efficacy may result from patients' experience of difficulties in managing the posttransplant regimen.

In the qualitative literature, excellent systematic reviews summarize evidence across many individual report. Thus, new research must more clearly define what gaps remain that have not received sufficient attention in the many qualitative studies conducted to date. In addition, the quantitative and qualitative literatures seem to continue to evolve largely in parallel, with little integration. For example, although qualitative research provides rich descriptions of factors and circumstances that patients feel matter most for their medical adherence, these elements are not necessarily assessed in quantitative research to determine the consistency and magnitude of their impact [41].

Finally, although immunosuppressant medication-taking is a critical component of the posttransplant medical regimen, risk factors for other components of the regimen (e.g., other medications, lifestyle activities, follow-up care, substance use restrictions) deserve greater attention. For example, whether the risk factors that are most important for immunosuppressant medication-taking are equally important for adherence in these other areas remains largely unknown. In addition, it would be important to examine whether non-adherence to any one component of the regimen is associated with or increases the risk for non-adherence to other components. Although it appears that non-adherence behaviors are not highly linked to each other (i.e., patients who have difficulty taking medications are not necessarily the ones who have difficulty with lifestyle or substance use issues), there has been relatively limited consideration of patterns of associations [8].

Non-Adherence as a Risk Factor for Transplant-Related Morbidity and Mortality

What Have We Learned?

As illustrated in numerous recent reports, immunosuppressant medication non-adherence has a central role in increasing risks for adverse clinical outcomes after kidney transplantation, including (a) acute graft rejection [16, 42, 43]), (b) chronic rejection and long-term graft-related abnormalities [44], (c) graft failure [16, 42, 45–49], and (d) patient mortality [46]. Immunosuppressant non-adherence is also associated with higher rehospitalization rates [50] and healthcare costs [51].

Important recent findings help to explain linkages between immunosuppressant non-adherence, acute graft rejection, and graft failure [52–55, 56••]. The formation of donor-specific antibodies (DSAs) is a major cause of late (> 1 year posttransplant) graft loss [54]. Donor-recipient human leukocyte antigen (HLA) mismatching, namely class 2 or higher mismatching, provides the context for de novo DSA formation (and, consequently, antibody-mediated rejection) and/or T cell-mediated graft rejection [55, 56••]. Immunosuppressant non-adherence also increases the likelihood of DSA formation [53, 54, 56••]. Late graft loss due to antibody-mediated and T cell-mediated rejection is accelerated in the presence of immunosuppressant non-adherence. In contrast, recipients of kidneys from HLA-mismatched donors below class 2 do not show these outcomes, even if they are non-adherent to immunosuppressants. These findings underscore the importance of identifying transplant recipients with the greatest need for interventions to maximize adherence.

Aside from immunosuppressant non-adherence, failure to abstain from tobacco smoking after kidney transplant has received considerable attention in relation to clinical outcomes. The Duerinckx et al. [11••] systematic review indicates that smoking has been linked to both cardiovascular disease and patient mortality after kidney transplantation, and it is also associated with graft failure [57]. Concerning other substances, a small (and likely underpowered) study did not find any association between marijuana use and patient or graft survival, or graft function [13•]. Finally, kidney recipients with poorer rates of attendance at posttransplant clinic follow-up appointments are at greater risk for graft rejection and graft loss [31, 42], and those who are non-adherent to medications prescribed to treat cardiovascular comorbidities have poorer survival [58].

Can We Do Better?

Although the ability of immunosuppressant medication non-adherence to increase risk for poor outcomes after kidney transplantation is well-documented, there are major gaps in our understanding of the clinical impacts of other components of the posttransplant medical regimen. For example, concerning substance use, a greater examination of marijuana use would be timely, given recent controversy regarding its role in transplant program selection of patients to list for transplant [59••]. Inhaled marijuana use has been linked to increased lung infection risks in case reports in organ recipients, including kidney recipients [59••]. Marijuana may alter immunosuppressive medications' metabolism [60]. However, large-scale studies of these issues in kidney recipients have not yet been undertaken.

Table 2 Randomized controlled trials of interventions to improve immunosuppressant medication adherence after kidney transplantation

First author, year(s)	Sample size	Intervention	Exposure time	Follow-up time	Impact on adherence[a]
Education and counseling					
Chisholm-Burns, 2013 [61]	150	Pharmacist-led behavioral contracting; education, counseling on adherence goals and problem-solving	Five 20–30 min clinic or phone sessions over 12 months	3 months post-intervention	Intervention group had higher adherence (pharmacy refills) than usual care group at each assessment after baseline.
Garcia, 2015 [62]	111	Nurse-led medication-taking education; counseling on adherence goals and problem-solving	Ten weekly 30 min clinic sessions	3 months post-intervention	Intervention group had higher adherence (self-report) than usual care control group.
Bessa, 2016 [63]	126	Pharmacist-led medication-taking education	Nine sessions (session duration not noted) in first 90 days posttransplant	End of intervention	No differences in adherence (blood level data, self-report) between intervention and usual care groups.
Breu-Dejean, 2016 [64•]	110	Multidisciplinary team-led medication-taking education	Eight weekly 2-h small group sessions	3 months post-intervention	Intervention group had higher adherence (self-report) than usual care group at intervention end and end of follow-up.
Cukor, 2017 [65]	33	Psychologist-led cognitive-behavioral therapy, motivational interviewing focused on adherence	Two 2-h small group sessions over 1–2-week period	~4 weeks post-intervention	Intervention group had higher adherence (self-report) at follow-up and more improvement in adherence pre- to post-intervention than usual care control. No group difference in blood level data from baseline but improvement in intervention group after intervention compared to control group.
Electronic reminder, alerting, and monitoring systems					
McGillicuddy,[b] 2013 [66]	19	EM box for all meds, with alerts; text message reminders; treating physician given feedback on patient data	3 months of use of strategies	End of intervention	Intervention group had higher adherence (based on EM) than usual care controls at each time point until end of intervention. No data provided on immunosuppressants separately from other medications.
Reese, 2017 [67•]	117	EM monitor with alerts, used alone or with provider notification. Text and e-mail reminders. In one study arm, patients were called if adherence declined; clinical team was informed	6 months of use	Last 90 days of intervention (EM); end of intervention (self-report); 6 months post-intervention (blood levels)	Reminders + provider notification group and reminder alone group had higher adherence (based on EM) than usual care control group. No group differences in blood levels or self-report.
Schmid, 2017 [68•]	46	Nurse case manager-led telemonitoring and coaching (video consultation)	Daily monitoring, coaching on demand for 12 months posttransplant	End of intervention	Intervention group had higher adherence (composite adherence measure of clinician ratings, self-report, blood levels) at all assessments than usual care control group.
Dosing/medication formulation changes					
Kuypers, 2013 [9••]	219	Switch from twice- to once-daily tacrolimus	6 months	6 months post-randomization	Intervention group had higher adherence (based on EM) compared to usual dosing group.

BP blood pressure, *EM* electronic monitoring, *ES* effect size, *HRQOL* health-related quality of life, *N/A* not applicable

[a] Group differences reported are statistically significant; lack of differences indicates that effects were not statistically significant. Studies did not consistently report effect sizes.

[b] Intervention also included a blood pressure monitoring component, not described.

Interventions Focused on Non-Adherence to the Medical Regimen

What Have We Learned?

Similar to work on prevalence and risk factors for non-adherence, posttransplant adherence intervention research in kidney recipients is dominated by a focus on immunosuppressant medication-taking. Table 2 provides details on nine RCTs for immunosuppressant non-adherence conducted in the past 5 years [9••, 61–63, 64•, 65, 66, 67•, 68•]. As shown, the interventions fall into three major categories: educational and counseling interventions, interventions relying on electronic health (e-health) approaches, and a dosing/medication formulation change intervention.

Eight of the nine trials found evidence of intervention efficacy. Such effects were found despite heterogeneity in sample size and methods used to assess adherence (e.g., electronic medication monitoring, patient self-report, immunosuppressant blood levels). There was also considerable variability in the duration of exposure to the interventions (ranging from 2 weeks to 12 months) and variability in whether and how long patients were followed after interventions ended. A recent systematic review of kidney recipient adherence intervention studies completed in the last three decades, including both RCTs and non-randomized studies, concluded that the most efficacious interventions were multimodal, i.e., they combined different strategies, such as education plus counseling [69•]. Indeed, six of the nine trials in Table 2 were multimodal. However, even single-component interventions such as the Kuypers et al. [9••] examination of once-daily tacrolimus dosing have been found to be efficacious. In general, education alone is not likely to be effective in most circumstances [25••, 70•]; this is evident when considering adherence-promoting interventions across all types of organ recipients [70•] and, in fact, the "usual care" control arms in the RCTs in Table 2 usually relied on education-only approaches.

Several of the trials in Table 2 also examined clinical outcomes, including infections [63], graft function [62, 68•], graft rejection and loss [63, 68•], and death [62, 63, 64•]. Some considered indirect measures of health outcome, including rehospitalizations [61, 63, 68•], and emergency and outpatient visits [61, 68•]. The adherence interventions reduced rehospitalization risk in two studies [61, 68•]. However, it is striking that there were no other effects on clinical outcomes.

Some recent attention has been directed to testing interventions to promote adherence to other components of the posttansplant medical regimen. For example, McGillicuddy et al. [66] incorporated blood pressure monitoring into their RCT (see Table 2) and found that remote monitoring, along with alerting the transplant team when blood pressure readings were outside of the safe range, led to lowered systolic (but not diastolic) blood pressure by the end of the trial. This effect was maintained at a 12-month follow-up [71]. In addition, interventions to facilitate weight control, exercise, and diet have been found capable of changing kidney recipients' behaviors and improving health parameters [72, 73]. However, high drop-out in these studies suggests that either the intervention activities or the trial designs were not acceptable to patients and thus conclusions from these studies are limited. We have been unable to identify any studies evaluating interventions to reduce risk of tobacco, alcohol, or other substance use in kidney recipients. A published protocol described a trial testing a non-pharmacologic intervention (brief counseling plus feedback on patients' carbon monoxide oximetry) in order to promote smoking cessation in kidney recipients [74]. However, no results have yet been reported.

Can We Do Better?

Studies have either not examined or been unable to demonstrate that immunosuppressant adherence-promoting interventions improve clinical outcomes. Such results may largely reflect the inclusion of follow-up periods that are too brief in most studies to accrue enough clinical events for meaningful analysis. A focus on determining clinical impact, with sufficient statistical power, would be a critical area to pursue in the future. Moreover, the long-term durability of intervention effects on adherence behaviors also has not been adequately examined. Indeed, it has been noted that short-term, time-limited interventions themselves are unlikely to lead to sustained adherence after intervention completion [21, 70•, 75]. Clearly, labor-intensive, complex interventions (e.g., some of the counseling interventions in Table 2) are unlikely to be realistically offered over many years in either RCTs or clinical practice. Hence, there is a great need to focus on developing and testing strategies that could be deployed for sustained use. As suggested by some of the RCTs in Table 2, as well as others in other types of organ recipients, electronic health (e-health) interventions, including smartphone apps, text messaging, and remote monitoring, may have particular promise [70•, 76••]. Indeed, text messaging is a prime example of a low-cost, low technology approach that has been found to be surprisingly effective in chronic disease populations and does not even require a smartphone, a home computer, or other monitoring tools [77•].

Future studies would also do well to consider findings from the qualitative literature in designing new interventions. For example, patients' concerns about how to establish workable daily routines and about the key barriers to those routines could facilitate the development of novel e-health or even more conventional interventions. Indeed, user-centered design—an approach frequently used in the development of e-health strategies—includes end-users in all phases of intervention development, and it may be a powerful tool for creating new strategies that patients find helpful and easy to adopt [78, 79]. End-users also likely include transplant program

personnel, who thus should also be involved in the design of new interventions.

These considerations for future work would also likely apply to intervention development beyond medication adherence. Clearly, there is a considerable void in terms of evidence-based interventions to promote adherence to other components of the posttransplant medical regimen. Applying principles of user-centered design, for example, may help to overcome past problems in mounting efficacious lifestyle modification interventions for kidney recipients.

Strategies Used in Clinical Practice to Improve Kidney Recipients' Adherence

The evidence on prevalence, risk factors, and empirically evaluated interventions leads us to make two major recommendations. We offer them first, then describe work relevant to their use, and conclude with suggestions for work needed in the future.

> Recommendation 1. Screening: consistent with clinical care guidelines [25••, 80••], kidney recipients should be routinely screened, using reliable screening tools, for difficulties related to adherence to the posttransplant medical regimen. Recipients with one or more known risk factors for non-adherence should be screened more frequently and/or extensively.
>
> Recommendation 2. Adherence interventions: when non-adherence problems are identified, kidney transplant programs should employ evidence-based interventions, drawing on either studies demonstrating efficacious interventions in kidney recipients or—absent such evidence—interventions tested in other transplant or chronic disease populations. Kidney transplant programs may also consider preventive tactics, i.e., implementing evidence-based interventions in all recipients (or at least in those at high risk for non-adherence) to avert or limit non-adherence.

What Have We Learned?

Berben and colleagues [81] conducted a survey of nursing professionals' screening and intervention practices to promote medication adherence in organ recipients. The sample consisted of 86 nurses almost exclusively from European programs that included but were not limited to kidney transplantation. From a list of possible screening practices, 61% of respondents reported that they "frequently" (as opposed to "seldom" or "never") used questioning during follow-up visits to identify non-adherence, and 2% used blood levels for this purpose. In addition, 43% reported that they frequently screened for non-adherence risk factors (although their methods for this screening were not reported), and 5% frequently used an electronic monitoring device to track medication adherence levels. Regarding adherence-enhancing interventions, although respondents were queried about a variety of possible approaches encompassing education, counseling, support groups, and behavioral contracts, by far the most common strategies (each used by 79% of respondents) were providing reading materials and providing inpatient education on how to take medications before patients were discharged after transplant. It was not clear whether any of the strategies endorsed were modeled after or replicated evidence-based interventions (e.g., those listed in Table 2).

Given the relatively small intervention literature in either kidney or other types of organ transplantation, Oberlin and colleagues [82•] conducted a "scoping review" to consider literature well beyond transplantation, and even beyond healthcare settings, in order to identify potentially useful medication adherence promotion approaches for dissemination and uptake by kidney transplant programs. Scoping reviews seek to map broad literatures on a particular topic or research area; they are exploratory and aim to provide an overview of sources and types of available evidence that could inform practice, policymaking, and research [83]. Oberlin et al. [82•] concluded that kidney transplant programs should adopt five strategies in order to incorporate evidence-based interventions into their clinical care activities. These strategies, shown in Fig. 1, are equally applicable to components of the posttransplant medical regimen beyond medication-taking. As detailed in the figure, screening and active intervention, particularly with high-risk subgroups, are critical activities but likely must occur in combination with building a foundation of trust with the patient and collaboration with other healthcare providers (e.g., patients' primary care physicians).

Can We Do Better?

To date, there is little evidence that kidney recipients are routinely screened for non-adherence problems during clinical follow-up, and no evidence that evidence-based interventions have been systematically adopted by transplant programs to either remediate or prevent non-adherence. We are unaware of any published trials that focused on dissemination and uptake of interventions by transplant programs, despite the importance of such activities [84].

Screening for Adherence Problems

Recommendations for screening strategies for kidney recipients are listed in Table 3. Available screening approaches include patient-report measures, biologic assays, and review of patients' electronic health records for trends on key parameters. For medication-taking,

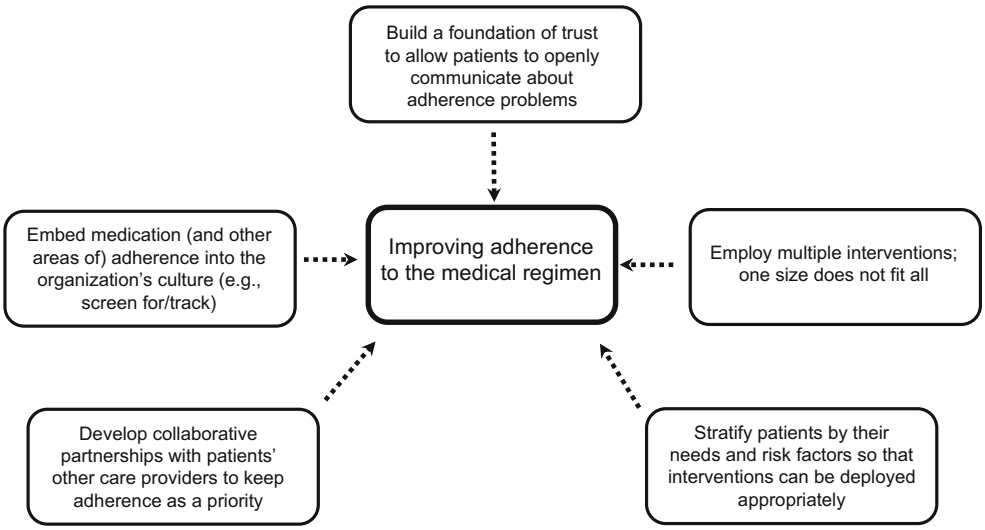

Fig. 1 Strategies for incorporating evidence-based approaches into daily practice in order to maximize kidney recipients' adherence to the posttransplant medical regimen (adapted from the work of Oberlin et al. [82•])

self-report is often considered inferior to methods such as electronic monitoring. However, electronic medication monitoring is rarely feasible in clinical settings [110]. Self-report measures can yield valid information [111••], and several brief measures are available for immunosuppressant non-adherence [112]. These measures evolved from assessments of medication-taking in other chronic disease populations, suggesting that the measures could be further modified to assess other medications required by kidney recipients. Rather than using self-report measures, a common clinical practice is to employ open-ended questioning. If such an approach is used, clinicians should follow experts' recommendations on appropriate questioning [28]. However, open-ended questioning may be inconsistently applied and thus should not be the sole source of information. No matter what assessment approach is used, face-to-face screening may not always be feasible because kidney recipients return to the transplant program with decreasing frequency as time goes by posttransplant. Especially for patients with strong risk factors for non-adherence, remote screening (e.g., via telephone or other telehealth communication strategies) or collaboration with recipients' local healthcare providers (e.g., primary care physicians) to perform screening may be options.

Concerning other strategies to identify medication non-adherence, transplant programs should avoid reliance on biopsy evidence of graft rejection or low blood levels of a given medication. Both sources of evidence may be heavily influenced by factors unrelated to non-adherence. Blood level data may be more useful if clinicians employ a measure that determines whether blood level variability over time exceeds that likely due to biological factors, interactions with other medications or foods, or measurement error. These measures are not unduly difficult to calculate and rely on data usually readily available in patients' medical records. Alternatively, transplant programs may be able to employ algorithms within their medical record systems that could monitor variability in blood levels automatically and provide alerts to clinicians.

Patient difficulties with some other components of the medical regimen may also be relatively easily determined by medical record review, including clinic appointment attendance, completion of laboratory testing, and BMI level (as an indicator of difficulty with diet and possibly exercise) (Table 3). Self-report screeners have been developed for physical activity, level of exercise, and dietary habits. Finally, for patients at risk for relapse to one or more types of substance use, a number of screening tools and approaches are available, as noted in Table 3. Among these, biological assessments are the most costly, require patients to be seen in person, and may not detect sporadic use. Thus, they should be reserved for situations in which substance use risk is high or frequent use is suspected [106]. Clinical interviewing, in conjunction with self-report measures, may uncover more substance use than biological measures [113].

Clinical Intervention for Adherence Problems

Kidney transplant programs should consider a number of options for intervention with their patients (Table 3). The interventions tested in kidney recipients to date are relevant possibilities. Among these, the reduction of tacrolimus dosing from twice to once daily is perhaps the most likely to be successfully mounted. The intervention tested by Reese and colleagues [67•], involving text messaging and e-mail reminders about medication-taking, was also efficacious and may be a realistic option for use in some transplant programs. However, electronic

Table 3 Recommendations and strategies for addressing adherence issues in kidney transplant program clinical practice

Recommendation	Strategies to consider
1. Screen for non-adherence to the medical regimen	• Use screening strategies with all kidney recipients • Implement screening at all clinic visits since non-adherence can begin even soon posttransplant • Plan for more intensive screening (more frequent or more extensive assessments) in recipients at high risk for non-adherence to a given component of the regimen • Choose screening tools that are accurate, valid, and easy to use, including the following examples: Medication-taking Patient self-report surveys: Immunosuppressant Therapy Adherence Scale [85]; Basel Assessment of Adherence Immunosuppression Scale [86] Blood level variability assessments: Medication Level Variability Index [87]; Coefficient of Variation [88] Clinic appointment and laboratory test attendance; lifestyle issues Review of patient medical records for repeated failure to keep appointments and for elevated or rising BMI levels Patient self-report surveys of physical activity: International Physical Activity Questionnaire, Short Form "Past 7 days" [89]; General Practice Physical Activity Questionnaire [90] Patient self-report survey of diet: Rapid Eating and Activity Assessment for Participants, Short Version [91] Substance use Patient self-report surveys of tobacco use: Fagerström Test for Nicotine Dependence, smoked [92] and smokeless [93] Patient self-report surveys of alcohol use: CAGE Questionnaire [94]; Michigan Alcoholism Screening Test (full, short, brief versions) [95–97]; Alcohol Use Disorder Identification Test [98, 99] Patient self-report surveys of drug use or polysubstance use: Single-Item Screen [100]; Drug Abuse Screening Test (and its derivatives) [101, 102]; Alcohol, Smoking and Substance Involvement Screening Test [103]; CAGE Questionnaire Adapted to Include Drugs [104]; RAFFT Questionnaire [105] Biologic measures of tobacco, alcohol, or other drug use: blood, urine, hair, saliva sampling [106, 107]
2. Implement evidence-based interventions to address or prevent non-adherence	• Implement interventions for kidney recipients found to have adherence problems; interventions offered may need to become permanent components of the care provided to those recipients • Consider implementing interventions to prevent non-adherence in all kidney recipients • Consider employing interventions found effective in kidney recipients (see Table 2) • Aim to identify simpler interventions (e.g., modifications in immunosuppressant dosing) to implement, as opposed to complex multicomponent interventions • Consider employing e-health interventions (text messaging, remote monitoring) • Consider referral to formal intervention programs to improve adherence to lifestyle requirements (e.g., diet, exercise) • When no interventions have been tested in kidney or other organ recipients, consider interventions known to be effective for similar problems in other populations. Interventions for substance use are prime examples [12, 108, 109]: Counseling-based strategies (e.g., cognitive-behavioral therapies, motivational interviewing) Self-help approaches (e.g., Alcoholics Anonymous and Narcotics Anonymous) Nicotine replacement therapies (gum, transdermal patch, nasal spray, inhaled nicotine, oral tablets/lozenges) Other pharmacotherapies for nicotine or other substance addictions

medication monitoring was an integral feature of the intervention, and as we noted above, such monitoring is difficult to use in clinical practice. Nevertheless, the Reese et al. study suggests that mobile or e-health intervention strategies could be useful for kidney recipients, as we discussed earlier [70•, 76••, 77•].

Many of the remaining interventions tested in kidney recipients (e.g., Table 2), although successful, involved multiple face-to-face sessions and multiple activities (e.g., education, counseling, and other components). These individual and group-based coaching/counseling interventions may thus require resources (time, staffing support, expertise) that transplant teams do not have. Furthermore, these interventions may be difficult to replicate. It is not clear that step-by-step instructions and full manuals of operation are available for the multicomponent interventions tested in Table 2; it seems doubtful that healthcare providers trying to replicate the interventions in clinical practice would be able to create the exact intervention that was tested in a research protocol. Nevertheless, it is possible that transplant programs' review of published reports on interventions found effective to date may suggest ways in which the programs might begin to modify their current practices in order to increase effectiveness in addressing and/or preventing non-adherence.

At least for some components of the regimen (e.g., lifestyle issues related to diet, exercise, obesity), an option may be to refer patients to services outside of the transplant program rather than for transplant programs to design in-house programs. Some patients may have health insurance coverage that would allow for such referrals. Similar considerations would arise for the treatment of substance use issues. Although no intervention strategies have been tested to address non-adherence to substance use restrictions specifically in kidney recipients, there are many examples of both non-medication-based and medication-based strategies that have been found effective in other patient populations (Table 3) [12, 108, 109].

Finally, as transplant programs consider ways to modify the care that they offer in order to promote adherence to the regimen, it would be wise for them to heed comments resulting from a systematic review of the general literature on non-adherence in chronic disease, which noted that there is no permanent "cure" for non-adherence [21]. Interventions are therefore likely to be required as part of the lifelong care of each transplant recipient [70•, 75].

Conclusions

The evidence base defining the scope of medical regimen non-adherence in kidney recipients is growing, and risk factors for non-adherence to specific components of the medical regimen are becoming better understood. This body of work, in turn, facilitates the design and testing of intervention strategies to reduce or prevent non-adherence to the posttransplant regimen. Nevertheless, greater headway is needed in identifying the full range of risk factors for this problem, as well as in developing and testing strategies that transplant programs can readily incorporate into their routine care of kidney recipients. Refinements in screening and identification of patients who have become non-adherent or are at greatest risk for this problem may lead to the more targeted deployment of transplant program efforts to assist patients to adhere to the medical regimen.

Acknowledgements Preparation of this report was supported in part by Grants R01 DK101715 and R01 DK110737 from the National Institute of Diabetes and Digestive and Kidney Diseases.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- • Of importance
- •• Of major importance

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