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Prevalence and correlates of medication non-adherence among kidney transplant recipients more than 6 months post-transplant: a cross-sectional study

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Abstract

Background: Among kidney transplant recipients, non-adherence with immunosuppressive medications frequently precedes allograft loss. We sought to determine the prevalence and correlates of medication non-adherence among kidney transplant recipients.

Methods: We performed a single-center, cross-sectional study of kidney transplant recipients who were at least 6 months post-transplant. We measured self-reported adherence using the Immunosuppressive Therapy Adherence Scale (ITAS, which is scored from 0 to 12, where higher scores indicate increased adherence) and barriers to adherence using the Immunosuppressive Therapy Barriers Scale (ITBS). We also used validated scales to measure perceived stress, health literacy, anxiety, depression, and interpersonal support.

Results: The 252 patients included in the study were 59.9% male, 27.0% Black, and at a median of 2.9 years post-transplant (interquartile range [IQR] 1.4-5.8). On the ITAS, 59.1% scored a perfect 12, 26.6% scored 10-11, and 14.3% scored 0-9. In univariate models, non-adherence (defined as ITAS score ≤ 9) was significantly associated with increased scores on scales for perceived stress (OR 1.12, 95% CI 1.01-1.25) and depression (OR 1.14, 95% CI 1.02-1.28), and with more self-reported barriers to adherence on the ITBS (OR 1.15, 95% CI 1.08-1.22). After adjusting for sociodemographic factors, stress and depression were not associated with non-adherence. Higher scores on the ITBS (corresponding to more self-described barriers to adherence) were associated with lower scores on the ITAS ($P < 0.001$). Several individual barriers were associated with non-adherence.

Conclusions: Among prevalent kidney transplant recipients, a minority is non-adherent. Practical barriers to adherence may serve as promising targets for future interventions.

Keywords: Kidney transplantation, Epidemiology, Compliance, Adherence

Background

Among recipients of kidney transplants, non-adherence with prescribed immunosuppressive medications commonly occurs and frequently precedes allograft loss [1-3]. A recent systematic review reported that in fifteen cross-sectional studies, a median of 22.3% of kidney

transplant recipients were non-adherent [1]. Furthermore, in ten cohort studies, a median of 36.4% of kidney allograft losses were associated with prior non-adherence [1]. Compared to recipients of other solid organ transplants, kidney transplant recipients may demonstrate higher rates of non-adherence [4].

Several factors are associated with post-transplant medication non-adherence [5]. Patient-related factors associated with non-adherence include younger age [2,6,7], increased time since the transplant [6], and possibly Black race [8]. Possible barriers to adherence include patients'

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personal schedules and routines [9], characteristics of the medicines and their dosage and schedules [8,9], practical issues related to access to medications and pharmacy refills [9], and medication costs [10]. Provider- and health systems-related factors also may contribute significantly to post-transplant medication adherence [4]. Unfortunately, few trials have tested interventions designed to increase adherence among transplant recipients [11]. Development of effective adherence interventions for transplant recipients requires a better understanding of factors potentially associated with non-adherence.

In this study, we sought to determine, among a population of stable, adult kidney transplant recipients who were more than 6 months post-transplant, (1) the prevalence of self-reported medication non-adherence, (2) psychosocial correlates of non-adherence, and (3) self-reported barriers to medication adherence.

Methods

Study design

A cross-sectional study was conducted in the outpatient transplant clinic of the Renal and Pancreas Transplant Division at Saint Barnabas Medical Center in Livingston, New Jersey, USA. To be eligible for this study, patients had to (1) have a functioning kidney-only transplant; (2) have received the transplant at Saint Barnabas Medical Center; (3) be at least 6 months post-transplant; (4) be 18 years of age or older at the time of the study; (5) be able to understand English; and (6) give informed consent. We excluded patients who had received a non-renal solid organ transplant, a simultaneous pancreas-kidney transplant, or more than one kidney transplant. The study was approved by the human subjects Institutional Review Boards at both Saint Barnabas Medical Center and the University of Medicine and Dentistry of New Jersey.

Study procedures

We enrolled kidney transplant recipients who came for an appointment in our outpatient transplant clinic between May and September 2011. Prior to each clinic session, we identified the scheduled patients who met the study eligibility criteria. During the clinic visit, the nephrologist described the study to patients and invited them to participate. Interested patients then met with study personnel to confirm study eligibility, provide informed consent, and complete the study's self-administered questionnaires. Study instruments were all completed in-person at the time of the clinic and study visit. After completing the questionnaires, study participants were given a \$15 gift card in appreciation of their participation.

Self-report instruments

Adherence was measured using the self-administered Immunosuppressive Therapy Adherence Scale (ITAS).

The ITAS is a 4-item, 12-point scale that has been validated in kidney transplant recipients [12] and used in other studies of medication adherence [13,14]. A higher score corresponds with increased adherence.

Barriers to adherence were measured using the Immunosuppressive Therapy Barriers Scale (ITBS), a reliable and validated scale (Cronbach's alpha 0.91) [15]. The ITBS is a 13-item scale consisting of 5-point Likert responses that rate self-reported agreement with eight "uncontrollable" factors and five "controllable" factors. Scores range from 13 to 65. A higher score corresponds with more barriers to adherence.

Participants also completed self-report symptom rating scale, including Hospital Anxiety and Depression Scale (HADS) [16], Interpersonal Support and Evaluation List-12 (ISEL-12) [17,18], and Perceived Stress Scale-4 (PSS-4) [19,20]. On the HADS, anxiety and depression are each measured on a 22-point scale from 0 to 21, with a higher score denoting more anxiety or depression. Scale subscores for anxiety and depression of 0–7, 8–10, and 11–21 corresponded with no, doubtful, or definite anxiety or depression, respectively [16]. On the ISEL-12, social support is scored from 12 to 48, with a higher score corresponding to higher social support. On the PSS-4, perceived stress is rated from 0 to 16, with a higher score correlating to increased perceived stress. There are no scores cut-offs for the ISEL-12 or PSS-4.

Participants also completed the Short Test of Functional Health Literacy in Adults (sTOFHLA) [21]. On the sTOFHLA, health literacy is measured from 0 to 36, with a score of 0–16 deemed as "inadequate", 17–22 as "marginal", and 23–36 as "adequate" literacy.

Statistical analysis

Categorical variables were summarized as proportions, and their estimates across groups (e.g. adherence categories) were compared using chi-square testing or Fisher's exact test as appropriate. Continuous variables that were not normally distributed were summarized as medians with 25%-75% interquartile ranges (IQRs) and compared using Wilcoxon rank-sum tests. We used binary logistic regression [22] to model the unadjusted associations between independent variables (psychosocial and demographic covariates) and self-reported non-adherence, with non-adherence defined as an ITAS score of 9 or less. The Likert responses on the ITBS were modeled as ordinal variables. Candidate variables with $P < 0.20$ in the univariate analysis were eligible for inclusion in the multivariate models [22]. For the multivariate models, we adjusted each candidate psychosocial variable for the demographic variables that were significant. We also examined the unadjusted associations of the individual ITBS items with non-adherence (defined by the ITAS). We did not include the ITBS scores or individual ITBS items in adjusted,

multivariate models, given that these barriers to adherence are part of the causal pathway leading to non-adherence and do not function as confounders.

For continuous variables, linearity in the logit was confirmed. Goodness of fit of the multivariate logistic regression models was assessed using the Hosmer-Lemeshow test [22]. Two-sided P-values <0.05 were considered statistically significant.

Results

Study sample characteristics

From May through September 2011, we enrolled 252 kidney transplant recipients out of 603 screened (41.7%). At least 136 patients (22.6%) explicitly declined to participate, because of lack of interest or inability to complete the study instruments during their clinic visit. The remaining screened patients were not approached, due to clinical concerns (e.g. acute illness) at the time of the office visit. The characteristics of the study subjects are shown in Table 1. Participants had a median age of 54.7 years (IQR 44.6-62.9) and were a median of 2.9 years post-transplant (IQR 1.4-5.8). Over one-quarter (27.0%) were Black, 28.2% had an annual household income < \$35,000 (for comparison, median household income in the United States was \$50,054 in 2011 [23]), and 43.7% had private medical insurance. A high percentage of patients had a diagnosis of glomerular disease (40.5%) or received a kidney transplant from a live donor (62.7%). Median serum creatinine was 1.4 mg/dL (IQR 1.1-1.8).

Self-reported adherence

The majority of study participants reported excellent adherence (Figure 1). 59.1% scored 12 out of 12, while 26.6% scored either a 10 or 11. The remaining 14.3% scored between 2 and 9 on the 12-point ITAS.

Psychosocial measurements

The health literacy of our study population was high, with 97.6% having adequate health literacy on the sTOFHLA. The median sTOFHLA score was 35 (IQR 34-36). Only 6 patients (2.4%) had sTOFHLA scores of 22 or less, which suggest marginal or inadequate health literacy.

Most subjects reported lower anxiety and depression levels on the HADS. On the anxiety component of the HADS, 206 (81.8%) scored 0 to 7, 30 (11.9%) scored 8 to 10, and 15 (6.0%) scored 11 to 21, with 1 (0.4%) incomplete. The median anxiety score was 4 (IQR 2-7). On the depression component, 232 (92.1%) scored 0 to 7, 12 (4.8%) scored 8 to 10, and 5 (2.0%) scored 11 to 21, with 3 (1.2%) of responses incomplete and not scorable. The median depression score was 1 (IQR 1-3).

Interpersonal support was high, with a median ISEL-12 score of 45 (IQR 39-47). Perceived stress was variable, with a median PSS-4 score of 4 (IQR 1-7).

Univariate and multivariate analysis of psychosocial factors associated with adherence

We performed unadjusted binary logistic regression models to examine the associations of candidate variables with non-adherence, defined as an ITAS score of 9 or less (Table 2). In the univariate logistic regression, non-adherence was associated with increased depression (on the HADS) and increased perceived stress (on the PSS-4) as well as lower household income and lack of employment. Younger age and increased anxiety appeared were not significantly associated with non-adherence but were considered candidate variables for the multivariate models (given their $P < 0.20$). Interpersonal support, health literacy, and clinical factors were not associated with non-adherence.

In separate multivariate models, we adjusted each candidate psychosocial variable (anxiety, depression, and perceived stress) for candidate demographic variables with $P < 0.20$ in the unadjusted model (age, income, employment status). Therefore, we constructed three multivariable models. In these adjusted models, anxiety, depression, and perceived stress were no longer significantly associated with non-adherence (Table 2).

Barriers to adherence

The median ITBS score was 16 (IQR 13-20). Higher scores on the ITBS (corresponding to more self-described barriers to adherence) were significantly associated with lower scores on the ITAS ($P < 0.001$).

Seven of the thirteen individual items in the ITBS were significantly associated with adherence on the ITAS (Tables 3 and 4). Patients with lower adherence on the ITAS were more likely to rate increased agreement with statements that they skip doses when they go out of town or when they feel depressed. Patients with lower adherence were more likely to rate increased agreement that they run out of medications, find it hard to remember to take their medications, miss doses due to perceived side effects, miss doses when out of their daily routine, and skip doses when short of money.

The remaining six items in the ITBS were not associated with adherence (Table 4). In particular, lack of knowledge about the benefits of transplant immunosuppression was not associated with adherence [as measured by the ITBS items "I get confused about how to take my immunosuppressant medication"; "I do not understand when to take my immunosuppressant medication(s)"; and "I sometimes skip doses of my immunosuppressant medication(s) when I feel good (or better)"].

Discussion

In this cross-sectional study of prevalent adult recipients of kidney transplants, most patients were very adherent with their medications, at least by self-report. A minority

Table 1 Socio-demographic and clinical characteristics of study population, based upon score on the Immunosuppressive Therapy Adherence Scale (ITAS)

Characteristic	Overall (N = 252)	ITAS score ≤ 9 (N = 36)	ITAS score = 10-11 (N = 67)	ITAS score = 12 (N = 149)	P
Median age in years (IQR)	54.7 (44.6-62.9)	48.1 (38.1-61.1)	54.6 (37.7-64.3)	55.0 (46.3-62.6)	0.17
Median years since transplant (IQR)	2.9 (1.4-5.8)	3.3 (2.2-5.1)	2.7 (1.4-5.7)	2.6 (1.3-5.9)	0.47
Male, n (%)	151 (59.9%)	22 (61.1%)	36 (53.7%)	93 (62.4%)	0.48
Female, n (%)	101 (40.1%)	14 (38.9%)	31 (46.3%)	56 (37.6%)	
Race/ethnicity, n (%)					0.79
White	145 (57.5%)	20 (55.6%)	39 (58.2%)	86 (57.7%)	
Black	68 (27.0%)	12 (33.3%)	16 (23.9%)	40 (26.9%)	
Asian	14 (5.6%)	1 (2.8%)	6 (9.0%)	7 (4.7%)	
Hispanic	25 (9.9%)	3 (8.3%)	6 (9.0%)	16 (10.7%)	
Etiology of kidney disease, n (%)					0.57
Diabetes mellitus	42 (16.7%)	8 (22.2%)	11 (16.4%)	23 (15.4%)	
Hypertension	65 (25.8%)	13 (36.1%)	16 (23.9%)	36 (24.2%)	
Glomerulonephritis	102 (40.5%)	10 (27.8%)	27 (40.3%)	65 (43.6%)	
Other	43 (17.1%)	5 (13.9%)	13 (19.4%)	25 (16.8%)	
Highest education level, n (%)					0.65
11 th grade or below	16 (6.4%)	3 (8.3%)	4 (6.0%)	9 (6.0%)	
High school graduate or GED	50 (19.8%)	8 (22.2%)	9 (13.4%)	33 (22.2%)	
Some college	95 (37.7%)	14 (38.9%)	25 (37.3%)	56 (37.6%)	
College graduate or above	90 (35.7%)	11 (30.6%)	28 (41.8%)	51 (34.2%)	
Unknown	1 (0.4%)	0	1 (1.5%)	0	
Marital status, n (%)					0.72
Married	167 (66.3%)	22 (61.1%)	42 (62.7%)	103 (69.1%)	
Widowed, divorced, separated, or never married	78 (31.0%)	13 (36.1%)	22 (32.8%)	43 (28.9%)	
No response	7 (2.8%)	1 (2.8%)	3 (4.5%)	3 (2.0%)	
Annual household income, n (%)					0.51
0-\$34,999	71 (28.2%)	15 (41.7%)	17 (25.4%)	39 (26.2%)	
\$35,000-\$74,999	57 (22.6%)	8 (22.2%)	17 (25.4%)	32 (21.5%)	
\$75,000 and above	97 (38.5%)	9 (25.0%)	27 (40.3%)	61 (40.9%)	
Unknown	27 (10.7%)	4 (11.1%)	6 (9.0%)	17 (11.4%)	
Employment status, n (%)					0.05
Working full-time	92 (36.5%)	8 (22.2%)	27 (40.3%)	57 (38.3%)	
Working part-time	36 (14.3%)	4 (11.1%)	12 (17.9%)	20 (13.4%)	
Not working	124 (49.2%)	24 (66.7%)	28 (41.8%)	72 (48.3%)	
Primary health insurance, n (%)					0.62
Private insurance	110 (43.7%)	12 (33.3%)	34 (50.8%)	64 (43.0%)	
Medicare	106 (42.1%)	16 (44.4%)	24 (35.8%)	66 (44.3%)	
Medicaid	27 (10.7%)	7 (19.4%)	6 (9.0%)	14 (9.4%)	
Medicaid and medicare	7 (2.8%)	1 (2.8%)	2 (3.0%)	4 (2.7%)	
Charity or self-pay	2 (0.8%)	0	1 (1.5%)	1 (0.7%)	
Type of kidney transplant, n (%)					0.35
Deceased donor transplant	94 (37.3%)	11 (30.6%)	22 (32.8%)	61 (40.9%)	
Live donor transplant	158 (62.7%)	25 (69.4%)	45 (67.2%)	88 (59.1%)	

Table 1 Socio-demographic and clinical characteristics of study population, based upon score on the Immunosuppressive Therapy Adherence Scale (ITAS) (Continued)

On dialysis prior to transplant, n (%)	190 (75.4%)	28 (77.8%)	51 (76.1%)	111 (74.5%)	0.84
Required dialysis during first post-transplant week, n (%)	30 (11.9%)	5 (13.9%)	4 (6.0%)	21 (14.1%)	0.22
Acute rejection episodes since transplant, n (%)	25 (9.9%)	8 (22.2%)	7 (10.5%)	10 (6.7%)	0.02
Calcineurin immunosuppressant, n (%)					
Cyclosporine	34 (13.5%)	6 (16.7%)	9 (13.4%)	19 (12.8%)	0.83
Tacrolimus	217 (86.1%)	30 (83.3%)	58 (86.6%)	129 (86.6%)	0.87
Median serum creatinine, in mg/dL (IQR)	1.4 (1.1-1.8)	1.59 (1.3-2.1)	1.35 (1.03-1.69)	1.38 (1.11-1.79)	0.06

Abbreviation: IQR Interquartile range.

P-values were obtained from chi-square test for proportions and Kruskal-Wallis test for medians.

of patients reported non-adherent medication-taking behaviors. Non-adherence was associated with higher perceived stress, anxiety, and depression. In adjusted, multivariate models, however, we could no longer detect any associations between non-adherence and stress, anxiety, and depression. The presence of self-described barriers to adherence was associated with non-adherence. These barriers to adherence may serve as potential targets for future interventions designed to increase medication adherence.

Our results confirm that a notable minority of kidney transplant recipients are non-adherent with their prescribed medications. Clearly, our study patients had been adherent enough to maintain a functioning allograft for a median of three years. Nevertheless, over 40% of patients were non-adherent in some form, as measured by the ITAS, and 14.3% were especially non-adherent, with an ITAS score of 9 or below. Other studies of prevalent kidney transplant recipients have reported similar rates of non-adherence [13]. Such long-term non-adherence may be associated with antibody-mediated rejection and allograft loss [3]. At least two ongoing clinical trials are

testing interventions designed to increase adherence among prevalent kidney transplant recipients [24,25].

Our results also suggest possible targets for future interventions intended to increase medication adherence. Several specific barriers were significantly associated with non-adherence and may be amenable to modification. For example, changes in the patient's routine, including travel, were associated with non-adherence; contingency plans may help patients remain adherent despite changes in daily routines [13]. Patients admitted to running out of their medications or simply forgetting to take them; reminder cues, systems, and alarms can prompt patients to take their medications and to refill their medication prescriptions. At least one ongoing trial is attempting to determine whether reminders can increase adherence among incident kidney transplant recipients [26]. Interventions that address these "practical" barriers to adherence may be effective in increasing adherence.

This study has several important limitations. First, we assessed medication adherence by self-report, using a single instrument (the ITAS). Other methods of measuring adherence include electronic monitoring [27-29],

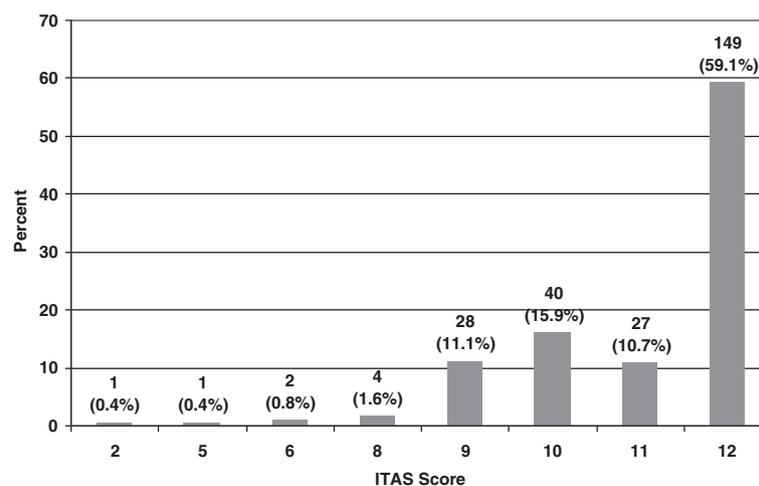


Figure 1 Distribution of scores on the Immunosuppressive Therapy Adherence Scale (ITAS).

Table 2 Univariate and multivariate associations between Non-adherence (ITAS score of 9 or below) and psychosocial, socio-demographic, and clinical factors

Predictor	Univariate models			Adjusted, multivariate models*		
	Odds ratio	95% confidence interval	P	Odds ratio	95% confidence interval	P
Psychosocial instruments						
sTOFHLA Score	1.10	0.93-1.30	0.26			
HADS Anxiety Score	1.10	1.00-1.22	0.06	1.08	0.96-1.20	0.21
HADS Depression Score	1.14	1.02-1.28	0.02	1.13	1.00-1.28	0.06
ISEL-12 Score	0.99	0.94-1.05	0.71			
PSS-4 Score	1.12	1.01-1.25	0.04	1.10	0.97-1.24	0.12
ITBS Score	1.15	1.08-1.22	<.001			
Socio-demographic factors						
Age (years)	0.98	0.95-1.00	0.09			
Female (vs. male)	0.94	1.46-1.95	0.87			
Non-white race (vs. white)	1.10	0.54-2.24	0.79			
High school graduate and below (vs. some college and above)	1.28	0.59-2.77	0.53			
Not married or partnered (vs. married or partnered)	1.32	0.63-2.78	0.47			
Annual household income < \$35,000 (vs. ≥ \$35,000)	2.16	1.01-4.62	0.047			
Public health insurance (vs. private insurance)	1.66	0.79-3.49	0.18			
Unemployed (vs. employed)	2.32	1.10-4.88	0.03			
Clinical factors						
Living donor (vs. deceased donor)	1.42	0.66-3.03	0.37			
Primary diagnosis (vs. glomerulonephritis)						
Diabetes	2.17	0.79-5.94	0.13			
Hypertension	2.30	0.94-5.61	0.07			
Other	1.21	0.39-3.78	0.74			
Serum creatinine (mg/dL)	1.83	1.18-2.83	0.007			
Albumin (g/dL)	0.83	0.33-2.05	0.68			
6 months to 2 years since transplant (vs. >2 years since transplant)	0.53	0.26-1.09	0.08			

*Adjusted for socio-demographic factors that had P < 0.20 (age, income, employment).

clinicians' collateral reports [30,31], serum assays for immunosuppressive medication concentrations [32-34], pill counts, and prescription refill and claims records [35]. Use of multiple methods, rather than a single method such as self-report, may be the most valid way to detect and measure non-adherence [36].

Second, we categorized adherence using cut-off scores for the ITAS. Although the ITAS itself has been validated, these cut-offs and categories of ITAS scores have not been validated for their association with outcomes. The clinical significance of different ITAS scores and categories is uncertain. To our knowledge, the correlation between specific amounts of adherence (whether measured on the ITAS or other instruments) and post-transplant outcomes remains unknown.

Second, we measured adherence among transplant recipients at a single transplant center in the northeastern United States. Our results are not necessarily generalizable to other transplant centers. Transplant centers differ in their staffing levels, the frequency with which they follow-up transplant recipients, the cultural competency of their providers, and the instructions they give transplant recipients regarding medications. Provider-level and health systems-level factors that vary between transplant centers may affect patients' adherence and contribute to inter-center variability in adherence [8].

Third, our convenience sample of prevalent transplant recipients who appeared for outpatient transplant follow-up was probably an especially adherent subset of kidney transplant recipients. Our study sample excluded

Table 3 Significant barriers to immunosuppressant adherence, based upon responses to the ITBS (Immunosuppressive Therapy Barriers Scale)

ITBS questions	Overall (N = 252) N (%)	ITAS Score ≤ 9 (N = 36) N (%)	ITAS Score =10-11 (N = 67) N (%)	ITAS Score =12 (N = 149) N (%)	P-value
I skip doses of my immunosuppressant medication(s) when I go out of town					0.04
Strongly disagree	214 (84.9)	24 (66.7)	61 (91.0)	129 (86.6)	
Disagree	26 (10.3)	7 (19.4)	5 (7.5)	14 (9.4)	
Neutral	5 (2.0)	2 (5.6)	0	3 (2.0)	
Agree	4 (1.6)	2 (5.6)	1 (1.5)	1 (0.7)	
Strongly agree	3 (1.2)	1 (2.8)	0	2 (1.3)	
I miss doses of my immunosuppressant medication(s) when I feel depressed					0.009
Strongly disagree	216 (85.7)	24 (66.7)	60(89.6)	132 (88.6)	
Disagree	27 (10.7)	7 (19.4)	7 (10.5)	13 (8.7)	
Neutral	4 (1.6)	2 (5.6)	0	2 (1.3)	
Agree	4 (1.6)	3 (8.3)	0	1 (0.7)	
Strongly agree	1 (0.4)	0	0	1 (0.7)	
I often run out (or do not have enough) of immunosuppressant medication(s)					<0.0001
Strongly disagree	202 (80.2)	21 (58.3)	48 (71.6)	133 (89.3)	
Disagree	30 (11.9)	5 (13.9)	12 (17.9)	13 (8.7)	
Neutral	11 (4.4)	6 (16.7)	3 (4.5)	2 (1.3)	
Agree	7 (2.8)	4 (11.1)	2 (3.0)	1 (0.7)	
Strongly agree	1 (0.4)	0	1 (1.5)	0	
Missing	1 (0.4)	0	1 (1.5)	0	
It is hard for me to remember to take my immunosuppressant medication(s)					<0.0001
Strongly disagree	209 (82.9)	24 (66.7)	50 (74.6)	135 (90.6)	
Disagree	35 (13.9)	8 (22.2)	16 (23.9)	11 (7.4)	
Neutral	5 (2.0)	2 (5.6)	0	3 (2.0)	
Agree	2 (0.8)	2 (5.6)	0	0	
Strongly agree	0	0	0	0	
Missing	1 (0.4)	0	1 (1.5)	0	
I miss a dose of my immunosuppressant medication(s) when I think there may be side effects					0.02
Strongly disagree	215 (85.3)	26 (72.2)	56 (83.6)	133 (89.3)	
Disagree	24 (9.5)	4 (11.1)	7 (10.5)	13 (8.7)	
Neutral	5 (2.0)	2 (5.6)	1 (1.5)	2 (1.3)	
Agree	7 (2.8)	4 (11.1)	2 (3.0)	1 (0.7)	
Strongly agree	0	0	0	0	
Missing	1 (0.4)	0	1 (1.5)	0	
I miss doses of my immunosuppressant medication(s) when I get out of my daily routine					<0.0001
Strongly disagree	173 (68.7)	113 (36.1)	31 (46.3)	129 (86.6)	
Disagree	39 (15.5)	9 (25.0)	13 (19.4)	17 (11.4)	
Neutral	8 (3.2)	3 (8.3)	4 (6.0)	1 (0.7)	

Table 3 Significant barriers to immunosuppressant adherence, based upon responses to the ITBS (Immunosuppressive Therapy Barriers Scale) (Continued)

Agree	28 (11.1)	9 (25.0)	17 (25.4)	2 (1.3)
Strongly agree	3 (1.2)	1 (2.8)	2 (3.0)	0
Missing	1 (0.4)	1 (2.8)	0	0
I skip doses of my immunosuppressant medication(s) when I am short of money				0.001
Strongly disagree	214 (84.9)	23 (63.9)	57 (85.1)	134 (89.9)
Disagree	29 (11.5)	7 (19.4)	9 (13.4)	13 (8.7)
Neutral	4 (1.6)	2 (5.6)	1 (1.5)	1 (0.7)
Agree	3 (1.2)	2 (5.6)	0	1 (0.7)
Strongly agree	2 (0.8)	2 (5.6)	0	0

patients who no longer have a functioning allograft or follow-up with our transplant center. To qualify for the study, patients had to appear for a scheduled clinic appointment, which is itself a marker for adherence. Only 41.7% of screened patients agreed to participate and complete our study questionnaires; we suspect that these study participants were more adherent than the overall population of screened patients. Our final study sample included large proportions of patients with favorable characteristics associated with increased allograft survival (e.g. recipients of live donor kidneys, patients with glomerular disease). Overall, this selection bias likely led us to overestimate the self-reported adherence of kidney transplant recipients in general.

Fourth, we were likely underpowered to detect associations between multiple factors and non-adherence. Although we examined over 250 transplant recipients, a study to examine the multiple factors plausibly associated with non-adherence may require a much larger study

sample. Multi-center studies [6] may be necessary to accrue the larger numbers needed to properly study medication adherence.

Finally, we performed a cross-sectional study. This cross-sectional study design precluded meaningful analysis of the associations between adherence and acute rejection. For example, study participants with lower ITAS scores were more likely to have had prior rejection episodes. However, we lacked information on these patients' adherence and ITAS scores prior to the rejection episodes. An alternative study design would be a prospective cohort study, in which transplant recipients are followed over time. A cohort study would permit correlation of medication adherence with subsequent transplant outcomes, such as rejection or renal function.

Conclusions

In this single-center, cross-sectional study, a minority of recipients of kidney transplants was non-adherent with

Table 4 Unadjusted, univariate model of ITBS items associated with non-adherence (ITAS score of 9 or below)

Immunosuppressant Therapy Barrier Scale (ITBS) items	Odds ratio	95% confidence interval	P
I have to take the immunosuppressant medication(s) too many times per day.	1.34	0.96-1.86	0.09
I have to take too many capsules (or tablets) of my immunosuppressant medication(s) at one time.	1.16	0.86-1.56	0.34
I cannot tell if my immunosuppressant medication(s) is (are) helping me.	1.18	0.86-1.62	0.30
I skip doses of my immunosuppressant medication(s) when I go out of town.	1.83	1.22-2.73	0.003
I miss doses of my immunosuppressant medication(s) when I feel depressed.	2.30	1.42-3.74	<0.001
I get confused about how to take my immunosuppressant medication(s).	1.14	0.39-3.36	0.81
I do not understand when to take my immunosuppressant medication(s).	0.73	0.26-2.08	0.55
I often run out (or do not have enough) of my immunosuppressant medication(s).	2.22	1.50-3.30	<0.001
It is hard for me to remember to take my immunosuppressant medication(s).	2.72	1.53-4.84	<0.001
I miss a dose of my immunosuppressant medication(s) when I think there may be side effects.	2.05	1.32-3.19	0.001
I sometimes skip doses of my immunosuppressant medication(s) when I feel good (or better).	1.68	0.71-3.97	0.24
I miss doses of my immunosuppressant medication(s) when I get out of my daily routine.	1.78	1.35-2.37	<0.001
I skip doses of my immunosuppressant medication(s) when I am short of money.	2.86	1.70-4.80	<0.001

Odds ratios reflects odds of higher degree of agreement with each statement, based upon responses on a 5-point ordinal Likert scale (Strongly agree to strongly disagree).

their medications. Non-adherence to medications was associated with increased anxiety, depression, and stress, but these associations did not persist in multivariate models. Practical barriers to adherence, such as forgetfulness and missing medications when one's routine is different, were significantly associated with non-adherence. These practical barriers may serve as promising targets for future interventions to increase adherence among recipients of kidney transplants.

Competing interests

This study was funded in part by Novartis Pharmaceuticals Corporation (East Hanover, New Jersey), as a research project with Drs. Weng and Demissie. Drs. Zacker is an employee of Novartis Pharmaceuticals. Dr. Chisholm-Burns receives licensing royalties from use of the ITAS and ITBS instruments from Pharmacotherapy Solutions.

Authors' contributions

FLW led the study conception and design; contributed to data acquisition, analysis, and interpretation; and drafted the manuscript. SC contributed to the study design and data acquisition, led the data analysis and interpretation, and contributed to revision of the manuscript. KMK contributed to the data analysis and interpretation and revision of the manuscript. CZ contributed to the study conception and design, data analysis and interpretation, and revision of the manuscript. MC-B contributed to the study design, data analysis and interpretation, and revision of the manuscript. KD contributed to the study conception and design, data analysis and interpretation, and revision of the manuscript. All authors read and approved the final manuscript.

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