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Depression, Quantified Medication Adherence, and Quality of Life in Renal Transplant Candidates and Recipients

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Abstract

Like patients with many chronic illnesses, ESRD patients experience psychological challenges with greater incidence of depression and reduced quality of life (QoL). A series of 139 transplant candidates' depression and QoL, and a subset of 82 candidates' medication adherence were monitored, revealing heterogenous patterns of depression and adherence and reduced QoL. Twenty-eight patients who received kidney transplants were re-evaluated 6 months post-transplant revealing mixed patterns. Mean depression and quantitated adherence decreased and QoL increased. Some patients improved whereas others declined in depression and adherence. Pre-transplant depression was negatively correlated with post-transplant adherence but positively correlated with post-transplant depression. Nevertheless, the ability to predict individuals' post-transplant adherence and depression, principal objectives of pre-transplant psychological evaluations, is limited. Consequently, it is important to provide periodic screening of ESRD patients for depression and adherence pre- and post-transplant as they reflect changing states, rather than static traits, with variable patterns across patients.

Keywords Transplantation · Depression · Adherence · Medication · ESRD

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The prevalence of end-stage renal disease (ESRD) has been increasing. By 2017, the U.S. prevalence of ESRD was estimated as 746,557. Treatments comprise hemodialysis (62.7%), peritoneal dialysis (7.1%), and transplantation (29.9%; United States Renal Data System [2019]). ESRD presents challenges to patients, families, and health professionals. Multiple factors may affect how well patients with ESRD function, and their experience if they proceed to kidney transplant. Whereas tremendous gains have been made in transplantation over time in driving improved clinical outcomes (Shrestha et al., 2015), the impact of mental health and behavioral phenomena, such as depression and adherence, have long been recognized and continue to be seriously limiting barriers to achieving optimal clinical results (Colón et al., 1991; Gokoel et al., 2020; Hucker et al., 2017). In this article, we review patterns of depression, adherence, and QOL in ESRD and transplant patients, including a University transplant center's series of transplant candidates and recipients.

Depression

Depression is a common comorbid psychiatric disorder in patients with chronic medical conditions, including ESRD (Cohen et al., 2007). Estimated rates of depression in ESRD have varied substantially in the literature over time (Smith et al., 1985), from as low as 8% (Craven et al., 1987) to 20–30% (Hedayati & Finkelstein, 2009) and as high as 50% (Montinaro et al., 2010). A systemic review and meta-analysis yielded an estimate of 39.3% based on rating scales

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(Palmer et al., 2013). Variability in these estimates reflects the interplay of multiple factors including differing methodological approaches, dissimilar recruitment and sampling, and heterogeneous criteria for diagnosing and characterizing depression. Various pathways have been considered that may contribute to depression in ESRD patients (Zalai et al., 2012) and kidney transplant recipients (Chilcot et al., 2014), including decreased function, symptom burden, dependence on life-sustaining treatments, loss of vocation/earnings, and disrupted social roles (Weissbord & McGill, 2007).

Better recognition of depression in ESRD patients is important as it is related not just to dysphoria and a diminished quality of life ([QoL]; Chilcot et al., 2014), but also is linked to missed or abbreviated dialysis sessions, interdialytic weight gain, weight, as well as increased pre-dialysis potassium and phosphorus levels (Afsar & Akman, 2009). Depression also is associated with increased risk of all-cause mortality in hemodialysis patients (Fan et al., 2014). In addition to potential impact on health outcomes, comorbid depression in ESRD patients yields heavy psychosocial and economic burdens (Wang et al., 2016). The seriousness of depression's consequences led to the standard for all adult U.S. dialysis patients to undergo periodic depression evaluations (Centers for Medicare & Medicaid Services, 2019).

In transplantation, psychiatric comorbidity has long been recognized as key to treatment planning pre-operatively and post-operatively (Olbrisch et al., 2002). At initial presentation to one transplant center, Kuntz and Bonfiglio (2011) found 15.1% of renal patients manifested depression symptoms based on the Patient Health Questionnaire-9 (PHQ-9). Varying rates of depression have been estimated for renal transplant recipients from 22.2% (Akman et al., 2004) to as high as 31% (Zelle et al., 2012). Palmer et al.'s (2013) systematic review estimated 26.7% prevalence of depression in kidney transplant recipients. A study of nearly 50,000 Medicare claims estimated increasing rates of depression of 5%, 7.3% and 9.1%, respectively in the first, second, and third year following renal transplant (Dobbels et al., 2008). By contrast, declining depression over time in kidney transplant patients based on CES-D ratings has been reported (Szeifert et al., 2010). Overall, depression rates in renal transplant patients are higher than in the general population (Veater & East, 2016). Among renal transplant recipients, depression is associated with increased risk for all-cause mortality, death-censored graft loss, acute graft rejection, infection, rehospitalization (Dew et al., 2015) and return to dialysis (Dobbels et al., 2008).

Medication Adherence

ESRD patients follow complex regimens (e.g., time-consuming dialysis schedules, dietary limitations, fluid restrictions, polypharmacy). A systematic review of medication nonadherence in hemodialysis patients yielded estimates ranging from 12.4 to 98.6% across multiple methodologies, with higher estimates of nonadherence recognized by electronic monitoring vis a vis self-report or biological assays (Ghimire et al., 2015).

Dobbels et al. (2009) confirmed the general observation that pre-transplant adherence is a predictor of post-transplant adherence and clinical outcomes based on self-report of Belgian liver, heart, and lung transplant recipients. In renal transplant recipients, adherence to immunosuppression regimens is necessary to optimize outcomes (Gaston et al., 1999; Nevins et al., 2001, 2014; Nevins & Thomas, 2009; Sellares et al., 2012). Potential consequences of nonadherence include graft dysfunction, antibody-mediated rejection, death-censored graft loss, and mortality. Early estimates of relatively limited medication nonadherence (5–18%) in renal transplant recipients (Douglas et al., 1996) are suspect in light of the higher estimates emerging across studies, i.e., 36% per year (Dew et al., 2007). Variability in estimates reflects heterogenous methodology, sampling, and criteria for defining adherence. Immunosuppressant nonadherence is estimated to be associated with about 50% of death-censored graft loss (Sellares et al., 2012) as well as return to dialysis and increased costs related to medical and other expenses (Pinsky et al., 2009).

The earliest longitudinal study our literature review identified revealing a connection between pre-transplant and post-transplant adherence in a cohort of patients was a retrospective chart audit of 126 transplant recipients over a 3-year period (Douglas et al., 1996). It found significant correlations ($rho = .33$, $p < .01$) between pre- and post-transplant adherence fairly broadly defined as noted by transplant team personnel, with 23 (18%) identified as non-adherent pre-transplant. Most (19; 83%) non-adherent pre-transplant patients continued to be non-adherent post-transplant. Most (61%) non-adherent pre-transplant patients lost grafts or died during the study period, a rate nearly three times that of pre-transplant adherent patients. Some (39.7%) who were adherent pre-transplant exhibited post-transplant nonadherence. This was less than half the incidence of post-transplant nonadherence in patients who had been non-adherent pre-transplant.

A more recent review of the experience of kidney transplant patients over time at six Swiss centers by De Geest et al. (2014) revealed a pattern of initially decreasing nonadherence from pre-transplant (29%, out of $n = 924$) to 6-month post-transplant (8.5%, out of $n = 688$) followed by a pattern of steadily increasing longitudinal nonadherence at 12 months (12.5%, out of $n = 600$), 24 months (12.8% out of $n = 434$), and 36 months (17.3% out of $n = 259$) based on two self-report items from the BAASIS instrument.

Whereas investigators have examined connections between adherence and diverse psychosocial factors, they

have generally used self-report measures of adherence (e.g., Scheel et al., 2018) which are less valid than behavioral measures. Further appreciation of the variation and complex associations among pre-transplant mental health challenges, nonadherence, and post-transplant outcomes is needed. The contributions to our understanding of adherence are arguably most precise when studies incorporate behaviorally based medication metrics, such as provided via electronic monitoring (Cramer, 1995; Riekert & Rand, 2002), which has been considered the "reference standard" allowing valid information, superior to other approaches for gauging individuals' medication use (Schäfer-Keller et al., 2008).

Pre-transplant mental health concerns and adherence are not necessarily predictive of post-renal-transplant outcomes (Gumabay et al., 2018). Nevertheless, psychosocial evaluations are routine components of workups for solid organ transplant intended to enhance judgement of suitability and identify the needs of candidates (Kuntz et al., 2015; Skillings & Lewandowski, 2015). Along with follow-up mental health services, pre-operative mental health services are required for transplant programs as encoded in the bylaws of the Organ Procurement and Transplantation Network (OPTN, 2020, p. 75). Such services include pre-operative psychosocial evaluations, substance use assessment, psychotherapy, treatment referral, monitoring of adherence to medications and to other health behaviors (e.g., smoking, diet, weight, substance use). Early identification of depression and nonadherence can provide opportunities for early or ongoing intervention to minimize or prevent adverse transplant outcomes related to those factors, and to enhance QoL. Assessments of depression and adherence are both integrated in the Stanford Integrated Psychosocial Assessment for Transplant (SIPAT; Maldonado et al., 2015).

Whereas psychological and behavioral factors have long been recognized as affecting renal transplantation outcomes (Olbrisch & Levenson, 1995), the relationship is complex and there is considerable variation. Self-ratings on measures of depression and adherence to medications and follow-up with other aspects of care have been negatively correlated in transplant recipients (Frazier et al., 1994). Prospective studies using standardized measures are needed to enhance psychologically informed approaches for assessing transplant candidates (Mori et al., 1999). Greater understanding of the association between depression and rigorous measures of adherence to medication regimens pre- and post-renal transplant has the potential to inform determinations of suitability for transplant, enhance care and perhaps most importantly to target supportive interventions that target behavioral (i.e., adherence) as well as mental health (i.e., depression) barriers to optimal outcomes, at least in identified at-risk patients.

Quality of Life

QoL is a multifaceted dimension of human functioning commonly assessed as part of appraising health and clinical outcomes. ESRD affects physical functioning, capacity to undertake diverse activities, and individuals' sense of well-being which are aspects of QoL. It may affect the initiating or conclusion of dialysis, decisions of whether to seek transplant, and participation in activities (Unruh & Hess, 2007). Jofre et al.'s (2000) review revealed QoL in ESRD populations is affected by diverse factors including disease severity, age, comorbidities, and other factors, including the treatment regimens. Its importance is evident in its association with clinical outcomes including morbidity and mortality, as well as its linkage to mental health, including depression.

QoL is generally higher in ESRD patients following transplant than prior to it, yet lower than QoL in healthy populations (Dobbels et al., 2007). After transplant, QoL is affected by comorbidities and side effects of immunosuppressant regimens (Unruh & Hess, 2007). Transplant recipients have reported lower post-transplant QoL than they had anticipated prior to surgery (Cleemput et al., 2003).

Aims

This prospective study had several aims. The first was to examine the patterns of depression, quantitated medication adherence, and QoL in ESRD transplant candidates and the associations among these variables. In addition, in a subset of transplant recipients, we investigated the association between depression and medication adherence and compared pre-transplant and post-transplant characteristics. We also evaluated physical and emotional QoL dimensions before and after transplant. The associations of depression and QoL with pre-transplant medication adherence and 6-month post-transplant medication adherence were also explored.

Methods

Procedure and Participants

This study is based on a series of 139 participants from a group of 170 patients approached by research staff for an investigation examining medication adherence in ESRD patients undergoing evaluation for kidney transplant at a midwestern academic medical center. The investigation is an outgrowth of earlier work exploring adherence patterns in renal transplant recipients (Nevins & Thomas, 2009). Thirty-one who did not return baseline forms were excluded. Participants volunteered for electronic monitoring of medication-taking prior to and post-transplant and to complete baseline psychological measures at the time of transplant

evaluation and follow-up at 6 months post-transplant. Of these, 28 received transplants during the study period and post-transplant completed psychological measures and were monitored for medication adherence. One recipient lost the post-transplant MEMS, but their other data were included in the post-transplant analyses. Table 1 presents demographic data about three groups: all transplant candidates completing baseline psychological measures, 81 candidates who also provided 3-month pre-transplant adherence data, and 28 transplant recipients who provided pre- and post-transplant adherence data and repeat psychological measures. Mean age was in the fifties. A majority were male and > 80% were White.

Research nurses and a social worker obtained informed consent, administered psychological measures, and trained volunteers to use electronic Medication Event Monitoring Systems™ (MEMS) caps with their medication vials. They collected baseline and 6-month post-transplant psychological measures, downloaded data from MEMS caps, and entered psychological and adherence data into an Excel spreadsheet. Participants were instructed to use the MEMS prior to transplant to monitor a medication or vitamin of their choosing for at least 3 months and to monitor immunosuppression medication following transplant. Data were not shared with the clinical team so did not affect clinical care. Because this was not an intervention trial, participants were not informed of their data other than on rare occasions when high baseline depression scores (i.e., BDI ≥ 20) indicated a need to inform patients of their depression status. For those cases, a psychologist on the research team contacted participants to share mental health resources if they were not already obtaining care. The study was approved by the University of Minnesota Institutional Review Board.

Measures

Beck Depression Inventory-II (BDI-II)

The BDI-II (Beck et al., 1996) is a 21-item self-report questionnaire that assesses the presence and severity of depressive symptoms in the last 2 weeks, which has been used in medical populations (Arnau et al., 2001). The BDI-II has been used to measure depression levels before and after renal transplant (e.g., Akman et al., 2004; Frazier et al., 1994; Mori et al., 1999). Items are rated on a 4-point scale [range = 0 (not at all) to 3 (extreme); total range = 0–63]. Higher scores indicate more severe symptoms. Due to overlapping symptoms between medical illness and depression, it has been recommended that a higher cutoff score (e.g., scores > 14–16) be used to identify depression in patients with ESRD (Cohen et al., 2007).

Millon Clinical Multiaxial Inventory III- Major Depression Scale (MCMI-MD)

A second index of depression, the MCMI-MD, was used to provide convergent validity. It is a 17-item scale with an alpha coefficient of .90 (Millon, 1997).

Table 1 Demographics of kidney transplant candidates, adherence-monitored candidates, and recipients

	Candidates with baseline psychological data ($n = 139$)	Candidates with baseline psychological data and 3-month MEMS data ($n = 81$)	Transplant recipients ($n = 28$)
Mean age (SD)	54.33 (12.69)	53.94 (13.31)	50.91 (14.00)
Gender, *n* (%)			
Female	59 (42.2)	35 (43.2)	11 (39.3)
Male	80 (57.6)	46 (56.8)	17 (60.7)
Race, *n* (%)			
African American	13 (9.4)	8 (9.9)	1 (3.6)
Asian	1 (0.7)	1 (1.2)	1 (3.6)
Caucasian	117 (84.2)	67 (82.7)	25 (89.3)
Hispanic	4 (2.9)	3 (3.7)	0 (.0)
Native American	3 (2.2)	2 (2.5)	1 (3.6)
Other	1 (0.7)	0 (.0)	0 (.0)
Transplant type, *n* (%)			
DDKPT			2 (7.1)
DDKT			6 (21.4)
LNRKT			8 (28.6)
LRKT			12 (42.9)

The three groups all began with baseline data. The middle group had 62 fewer candidates than the original group because they did not complete 3 months baseline MEMs data. The third group is only of those individuals who underwent kidney transplant and for whom baseline and follow-up data are available

Medication Event Monitoring System™ (MEMS)

The MEMS has been used in over 800 studies to quantitate medication adherence (AARDEX, 2021). MEMS caps record date and time of vial openings. Pre- and post-transplant data were downloaded to spreadsheets. Adherence was quantified as a percentage of medication doses taken relative to the number prescribed to be taken during the investigative period. Pre-transplant MEMS data are based on the use of a Nephrocap vitamin or concomitant medication. Post-transplant MEMS records were based on the immunosuppressant Mycophenolate mofetil (MMF) as prescribed by the transplant team. MEMS provides a more precise and conservative estimate of medication adherence than other approaches (e.g., self-report, pill count; El Alili et al., 2016).

Short Form-36

The SF-36 is a widely used 36-item self-report measure assessing QoL across eight domains of health with well-established psychometric properties (Hays & Morales, 2001). Items were derived for the Medical Outcomes Survey (Ware & Sherbourne, 1992), and scored according to RAND 36-Item Health Survey 1.0 instructions (Hays et al., 1993). Domain scores range from 0 to 100. Higher scores indicate more optimal state of health. Scores represent the percentage of total possible score achieved.

Statistical Analyses

Participants' demographic characteristics and baseline depression, adherence, and QoL measures were summarized with mean (SD), median, and mode for continuous and count (%) for categorical variables. Pearson correlation coefficients were calculated between measures of depression, adherence, and QoL. Paired *t*-test compared pre- and post-depression scores among those who had a transplant. The unadjusted relationships between post-transplant adherence, pre-transplant depression, and pre-transplant adherence were explored with correlations and scatterplots. A linear regression model was constructed to evaluate the effect of pre-transplant adherence and depression together on post-transplant adherence. All *p*-values are two sided and considered at the .05 level for statistical significance. As an exploratory study, corrections for multiple comparisons were not made. Analyses were principally conducted using Microsoft Excel and R (R Core Team, 2020), Version 4.0.3.

Results

Renal Transplant Candidates' Baseline Depression, Medication Adherence, and Quality of Life

I. Analyses were conducted on the 139 renal transplant candidates. Of these, 81 (58%) completed 3-month medication adherence monitoring; many provided 6-month pre-transplant monitoring.

Depression

As presented in Table 2, at baseline, transplant candidates' depression symptom levels on the BDI-II and MCMI-MD scales were heterogenous, ranging from 0 on both scales to 28 on the BDI-II and 100 on the MCMI-MD. Mean, median, and mode BDI scores were respectively 9.2, 8 and 4, all in the normal/minimal range. A fifth (21.6%) scored in the mildly to moderately depressed range in terms of general clinical norms (Beck et al., 1996). Most (77.7%) endorsed no to minimal depression (≤ 13). The rest were evenly divided between mildly depressed (11.5% scored 14–19) and moderately depressed (10.1% scored 20–28) ranges. None were severely depressed (i.e., ≥ 29). Using screening scores other than the Beck ranges, yielded positive depressive detection estimates of 37.2% for scores > 10 and 15.8% for scores > 15.

A similar pattern was seen on the MCMI-MD, with mean, median, and mode scores respectively 38.3, 40, and 70 (S.D. = 28.3). Few (12; 8.8%) met the base rate (BR) criteria of ≥ 75 for major depression, which is a more stringent benchmark (Choca et al., 1992). BDI-II and MCMC-MD scores were moderately correlated ($r = .58$; $p < .00001$).

Pre-transplant Medication Adherence

Proportional adherence for 81 candidates providing 3-month pre-transplant MEMS data varied, ranging from 7.8 to 100%, with mean, median, and mode, respectively 82.1%, 90.1%, and 100% (S.D. = 20.9%). During the pre-transplant period, few (12.2%) demonstrated perfect (i.e., 100%) adherence. Many had good to excellent adherence: 40% exhibited adherence in the 90–99% range; 18.3% achieved 95–99% adherence; 24.4% were 90–94% adherent. Others demonstrated marginal adherence: 14.6% were in the 80–89% range; 11% were in the 70–79% range. Poor adherence was evident in nearly a fifth: 9.8% were 50–69% adherent and 9.8% were below 50%. Pre-transplant adherence was not significantly correlated with age $r(79) = .13$, $p = .226$. There were not differences between males and females in pre-transplant adherence $t(79) = -.31$, $p = .76$.

Table 2 Renal transplant candidates' baseline depression, medication adherence, and quality of life

	Mean	S.D	Mode	Median	*n*	Reference
Depression						
BDI-II	9.2	6.6	4	8	139	
MCMI-MD	38.3	28.3	70	40	139	
Proportional medication adherence (1st 3 months)						
MEMS	82.1%	20.9	100%	90.1%	81	
Quality of life (SF-36)						Rand mean[a]
Physical functioning	56.6	27.4	25	60	139	70.6
Role limitations—physical	43.6	41.7	0	25	136	53.0
Role limitations—emotional	73.0	38.0	100	100	136	65.8
Energy-fatigue	45.0	20.0	50	45	139	52.2
Emotional well-being	72.9	16.5	90	75	139	70.4
Social functioning	66.7	24.9	75	75	136	78.8
Pain	68.0	24.8	100	67.5	139	70.8
General health	40.5	19.0	30	40	136	57.0

[a]For reference, our sample's SF 36 scores can be compared with those or the larger Medical Outcomes Study ($N = 2471$; Rand Health Services Program, 1992)

Quality of Life

Candidates' QoL varied across the SF-36 scales. It was generally greater on the emotional scales (i.e., emotional well-being), interfering less with emotional functioning than physical functioning. On six of eight scales, mean scores were lower than for the Medical Outcomes Study reference sample, which were also presented in Table 2, reflecting more physical challenges than the general population. On two scales, Role Limitations-Emotional and Emotional Well-Being, candidates' scores exceeded the Rand study mean. All but one of the 28 QoL scale pairs were positively correlated with each other revealing general correspondence among the scales.

Correlations Among Candidates' Depression, Adherence, and Quality of Life

Table 3 presents Pearson correlations among the three variables. Both depression measures were significantly negatively correlated with pre-transplant adherence and with all eight QoL scales. Figure 1 reveals the scatterplot of adherence by depression for transplant candidates including the trend line of lessening adherence with increasing depression. Adherence was positively correlated with six of the eight QoL scales, all but Physical Functioning and Energy-Fatigue. Three-month pre-transplant adherence was highly correlated with 6-month pre-transplant adherence ($r = .89$); our focus throughout this study is on the 3-month pre-transplant adherence as it is more pragmatic to collect data for a shorter period.

II. Renal Transplant Recipients' Depression, Adherence, and Quality of Life

Depression

As presented in Table 4, on both the BDI-II ($M_{pre} = 9.3$; $M_{post} = 7.9$) and the MCMI-MD (M_{pre} 41.3; $M_{post} = 29.7$), mean pre-transplant depression scores were higher than post-transplant scores, with changes of − 1.41 and − 10.68, respectively. Paired *t*-tests on the MCMI-MD revealed significant change ($p < .04$), but not on the Beck. Participants' changes in self-rated depression from pre- to post-transplant, the absolute values of which were correspondingly 5.93 for the Beck and 18.5 for the MCMI-MD.. Median scores showed a similar pattern on the BDI-II (pre = 8; post = 7) and MCMI-MD (pre = 42.5; post = 19) of relatively greater depressive symptomatology prior to transplant. On the BDI-II, more individuals endorsed levels of mild (score > 10; 46% cf. 29%) or moderate (score > 15; 14% cf. 14%) depressive symptomatology prior to transplant than post-transplant. Chi-square did not reveal this to be statistically significant. Sixteen had lower scores post-transplant than at baseline; eleven had higher BDI-II scores post-transplant. On the MCMI-MD, the percentages of individuals meeting criteria for depression was identical pre- and post-transplant, despite higher mean pre-transplant ratings. Fifteen had higher baseline scores; eight had higher post-transplant scores. Others showed no change.

Table 3 Correlations among renal transplant candidates' baseline depression, adherence, and quality of life

	BDI-II	MCMI MD	Adherence	Physical functioning	Role limitations—physical	Role limitations—emotional	Energy-Fatigue	Emotional well-being	Social functioning	Pain	General health	*n*
BDI-II		.58***	− .31*	− .18*	.31**	− .48***	− .45***	− .59***	− .46***	− .34***	− .45***	139
MCMI-MD			− .27**	− .34**	− .42***	− .34***	− .49***	− .49***	− .44***	− .29***	− .38***	139
Adherence pre-3 mo				.05	.24*	.19	.12	.26*	.30**	.26*	.25*	82
Physical functioning					.56***	.33***	.41***	.15	.41***	.36***	.30***	139
Role limitations—physical						.45***	.43***	.24**	.56***	.45***	.29***	136
Role limitations—Emotional							.24*	.37***	.51***	.30***	.23**	136
Energy-fatigue								.47***	.48***	.44***	.44***	139
Emotional well-being									.36***	.22*	.31***	139
Social functioning										.64***	.35***	136
Pain											.33***	139
General health												136

*$p < .05$, **$p < .01$, ***$p < .001$

Adherence

Pre-transplant 3-month ($M = 80.8\%$; median = 90%; S.D. = 20.96) medication adherence levels were relatively, but not significantly, greater than post-transplant adherence ($M = 70.6\%$; median = 79.1%; S.D. = 79.10). A majority (59%) achieved higher levels of adherence for non-immunosuppressant drugs prior to transplant than when taking immunosuppressant medications post-transplant.

Ten (36%) demonstrated adherence rates < 80% before transplant; 14 (52%) exhibited problematic post-transplant adherence (i.e., < 80%) when using immunosuppressants. Of the 10 whose pre-transplant adherence was < 80%, only 6 (i.e., 60%) were problematic after transplant; the other 4 (40%) improved. Eight transplant recipients with adherence < 80% at 6 months post-transplant had pre-transplant adherence > 80% for the first 3 months of baseline monitoring, including four who had been above 90% and one who had demonstrated perfect 3-month pre-transplant adherence. One outlier exhibited < 10% adherence both pre- and post-transplant.

Quality of Life

On the SF-36, higher levels of QoL were seen 6 months post-transplant on seven of the eight dimensions (all but Pain) relative to pre-transplant. Of these, statistically significant differences emerged on paired *t*-tests for three Energy/Fatigue ($M\Delta = 10.93$; $p < .01$), Emotional Well-Being ($M\Delta = 8.64$; $p < .005$), and General Health ($M\Delta = 22.55$ $p < .005$).

III. Associations Among Renal Transplant Recipients' Baseline and 6-Month Post-transplant Psychological Characteristics and Adherence

Table 5 presents Pearson correlations between pre- and post-transplant depression and adherence and with post-transplant QoL.

Depression Pre- with Post-transplant

Pre-transplant depression scores for the BDI-II ($r = 52$; $p < .01$) and MCMI-MD ($r = .63$; $p < .01$) were significantly correlated with post-transplant MCMI-MD depression. The MCMI-MD pre-transplant score was significantly correlated with the post-transplant BDI-II ($r = 39$; $p < .05$), whereas the pre-BDI was positively, but not significantly, correlated with the post-transplant BDI-II.

Adherence Pre- with Post-transplant

Pearson correlation of pre-transplant and post-transplant adherence did not reach significance ($r = .33$; $p < .10$),

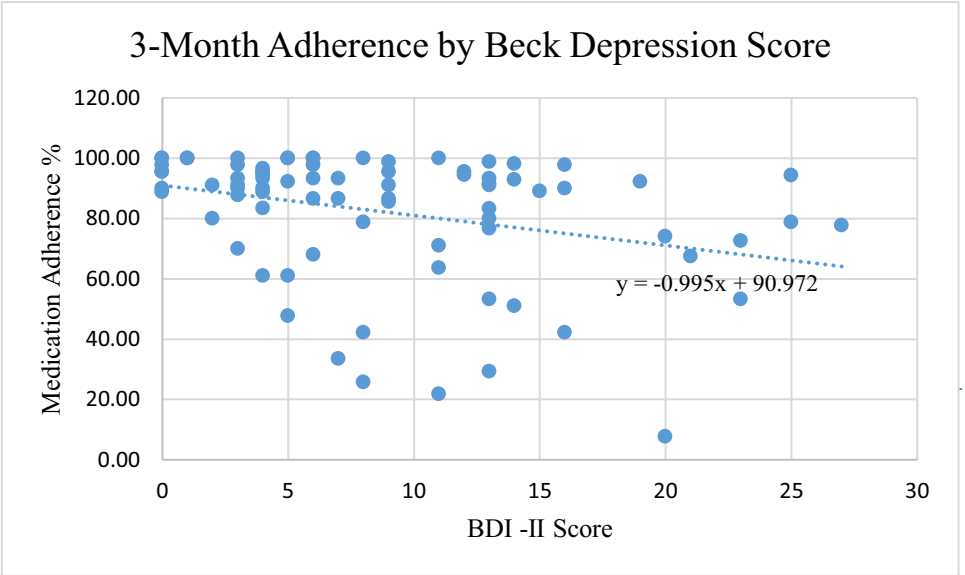

Fig. 1 Unadjusted 3-month pre-transplant adherence by Beck Depression Score with trend line. $n = 81$

accounting for 10.9% of the variance. The scatterplot in Fig. 2, yielded a positive trend line.

Pre-transplant Depression with Pre-transplant Adherence

Pre-transplant depression measures correlated negatively with pre-transplant adherence, significantly for the BDI-II ($r = -.38$; $p < .05$), but not the MCMI-MD.

Pre-transplant Depression with Post-transplant Adherence

Pre-transplant depression was negatively correlated with post-transplant adherence, but significantly so only for the BDI-II ($r = -.46$; $p < .05$). The scatterplot in Fig. 3 reveals the negative trend line.

Post-transplant Depression with Pre-transplant Adherence

Post-transplant depression measures were not significantly correlated with pre-transplant adherence.

Post-transplant Depression with Post-transplant Adherence

Post-transplant depression measures were not significantly correlated with post-transplant adherence.

Post-transplant Quality of Life

SF-36 scores were often correlated with other SF-36 variables, reaching significance in 19 of 28 correlations (68%).

Pre- and Post-transplant Depression with Post-transplant Quality of Life

In general, depression and QoL were negatively correlated, reaching significance in 11 of 16 pairings for post-transplant depression with both post-transplant depression measures. Only two of 16 correlations between pre-transplant depression and post-transplant QoL were statistically significant.

Pre- and Post-transplant Adherence with Post-transplant Quality of Life

Pre-transplant adherence was significantly negatively correlated only with Energy-Fatigue ($r = -41$; $p < .05$). Post-transplant adherence was significantly negatively correlated with two post-transplant QoL scales, Physical Functioning ($r = -40$; $p < .05$) and Energy-fatigue ($r = -42$; $p < .05$).

Regression Analysis

Of all of the variables examined, one of the most important questions is whether or not post-transplant adherence is associated with pre-transplant variables. Linear regression showed that with a one unit increase in pre-transplant adherence, post-transplant adherence increases by .19 units, 95% CI (.31, .70) on average, holding pre-transplant depression constant. This effect was not statistically significant.

Discussion

This study provides quantitative indices of medication adherence at two points in the transplant process, making it more valid and precise than earlier adherence studies that

Table 4 Mean depression, adherence, and quality of life for renal transplant recipients pre- and 6-month post-transplant[a]

	Mean pre	Pre S.D	Mean post	Post S.D	Mean Δ	Mean absolute Δ	Median pre	Median post	Pre % CS[b]	Post % CS[b]	Pre % CS[b]	Post % CS[b]	*P*-value based on paired *t*-test (pre–post)
Depression													
BDI-II	9.33	6.07	7.93	7.04	− 1.41	5.93	8	7	46.4%	29.6%	14.4%	14.8%	n.s
MCMI-MD	41.25	26.89	29.70	28.68	− 10.68	18.50	42.5	19	7%	7%			.04
Proportional medication adherence													
MEMS	80.8[c]	20.58	70.6[d]	27.03	− 10.2		90	79.1					.09
Quality of life (SF-36)[e]													
Physical functioning	53.73	26.42	62.92	28.12	9.61		47.5	70					n.s
Role limitations—physical	35.43	38.95	42.59	44.00	6.78		25	25					n.s
Role limitations—emotional	76.19	34.34	79.01	31.62	3.70		100	100					n.s
Energy-fatigue	37.58	21.65	48.33	20.73	10.93		35	50					.01
Emotional well-being	70.89	17.98	79.63	15.24	8.64		74.2	83.3					.005
Social Functioning	59.26	24.20	65.28	31.97	9.26		62.5	75					n.s
Pain	66.52	24.43	59.72	25.12	7.13		67.5	57.5					n.s
General health	37.04	18.52	58.47	21.15	22.55		35	65					.005

[a] $n = 28$ for all data except post-transplant adherence for which $n = 27$

[b] Clinically significant (CS) operationalized as BDI score > 10; MCMI score > 75. Higher the scores indicate greater depression. Chi-squares for percentage of BDI scores ≥ 10 between pre- and post-measurements were n.s

[c]Proportional Adherence quantified with MEMS for 3 months after enrollment ($n = 28$)

[d]Proportional Adherence quantified with MEMS for 6 months post-transplant ($n = 27$) because 1 participant lost their MEMS cap post-transplant

[e]On the SF-36 higher scores indicate less disability

Table 5 Correlations among transplant recipients' pre-transplant depression and adherence and their 6-month post-transplant depression, adherence, and quality of life

	BDI-II pre	MCMI MD-pre	BDI-II post	MCMI MD-post	Adherence pre	Adherence post	Physical functioning post	Role limitations—physical post	Role limitations—emotional post	Energy-fatigue post	Emotional well-being post	Social functioning post	Pain post	General health Post
BDI-II pre	–	.62**	.28	.52**	− .38*	− .46*	.00	.05	− .25	− .11	− .45*	− .14	− .15	− .32
MCMI-MD Pre		–	.39*	.63**	− .06	− .28	− .04	− .06	− .44*	− .26	− .35	-.12	-.01	− .29
BDI-II post			–	.63**	.31	.18	− .42*	− .37*	− .73**	− .57**	− .67**	-.58**	-.25	-.57**
MCMI-MD post				–	.09	.10	− .32	− .08	− .40*	− .55**	− .55**	-.30	-.15	-.55**
Adherence MEMS pre					–	.33	− .32	− .26	− .34	− .41*	− .13	-.23	-.02	-.24
Adherence MEMS post						–	− .40*	− .33	.10	− .42*	.05	-.20	-.24	-.32
Physical functioning							–	.54**	.43*	.57**	.28	.33	.60**	.54**
Role limitations—physical								–	.38*	.59**	.40*	.67**	.39	.45*
role Limitations—Emotional									–	.30	.62**	.33	.13	.43*
Energy-fatigue										–	.47**	.65**	.41*	.73**
Emotional well-being											–	.67**	.02	.54**
Social functioning												-	.34	.54**
Pain													-	.36
General health														-

$n = 28$ for all pre-measures. One did not complete the post-transplant psychological measures but did complete the MEMS, and another did not have post-MEMS, so the correlations for post BDI, MCMI-MD, and SF36 have n of 26 or 27

*$p < .05$, **$p < .01$

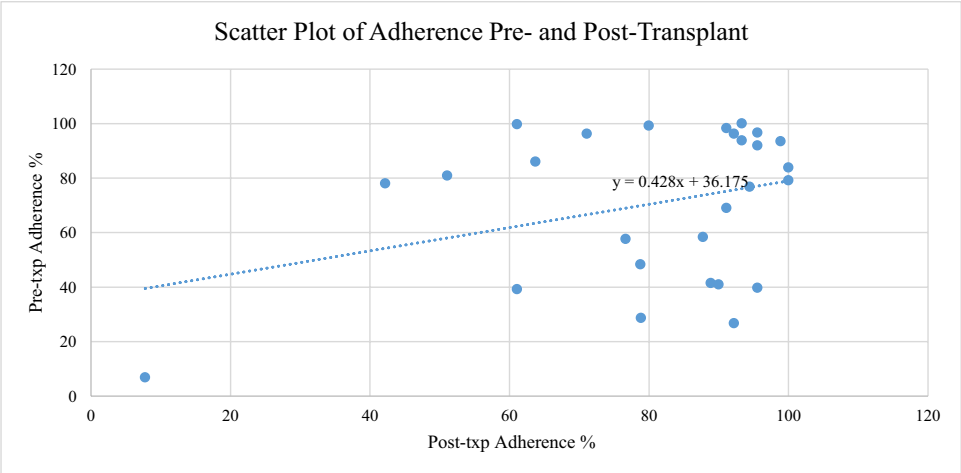

Fig. 2 Unadjusted relationship between pre- and post-transplant medication adherence with trend line. $n = 27$

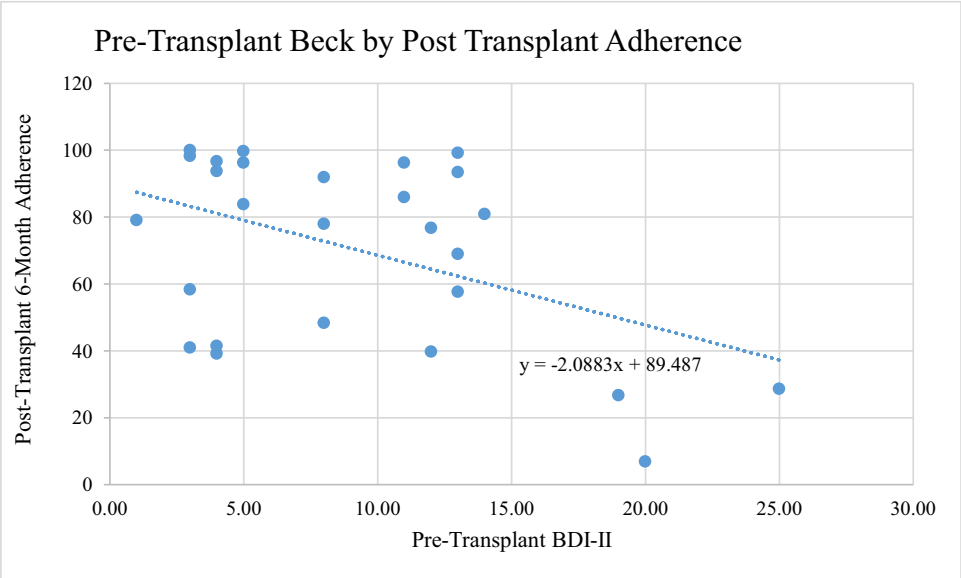

Fig. 3 Unadjusted relationship between pre-transplant BDI-II by post-transplant adherence with trend line. $n = 27$

relied on patient self-report. It is prospective, having longitudinal pre-and post-transplant assessments of a cohort of transplant recipients, in contrast to studies that are cross-sectional, comparing two different groups of patients rather than comparing individuals' status (i.e., vis a vis depression and adherence) at two points in time. This approach reveals variability in depression levels, adherence, and QoL in kidney transplant candidates and recipients. ESRD patients report heterogeneous levels of depressive symptoms and QoL presumably associated with their disease, personal treatment course, comorbidities, and potentially other circumstances, and they exhibit variable medication adherence patterns.

Depression

Depression is the most common psychiatric disorder in ESRD (Cohen et al., 2007). Estimates of depressive phenomena vary based on measurement methodology (i.e., what objective measures and criteria are used) and when it is measured during the course of individuals' experience, such as where they might be along a transplant trajectory. In these renal transplant candidates, most (77.4%) were not depressed according to BDI and Millon scores. None were severely depressed. More than 10% generated BDI-II scores in each of the mild and moderate ranges of depressive symptomatology. By contrast, transplant candidates generated slightly lower BDI-II scores than previously reported for dialysis patients when on ($M = 11.9$–12.9; Chilcot et al., 2011; Chilcot et al., 2008) and off dialysis ($M = 11.1$) patients (Chilcot et al., 2008).

The significant correlations between the BDI-II and the MCMI-MD scales were generally consistent with earlier estimates (Goldberg et al., 1987; Millon, 1997; Saulsman, 2011) and provide convergent validity about using these

measures with ESRD patients, though their correlations with other variables are not identical. This reflects, in part, the enhancement of this MCMI-MD scale in the 3rd edition over earlier editions, in that it contains vegetative symptoms, which increase its convergence with the BDI-II and considers overlapping symptoms of depression and renal disease. The observation of fewer meeting clinical criteria for depression on the MCMI-MD than the BDI II suggests the BDI may be a more stringent measure of depression, or at least one that may be more sensitive to some health issues, and demonstrates that detection and classification of depression vary based on measurement approach, which speaks to the potential benefit of using multiple measures when assessing transplant candidates and recipients.

Depression rates in ESRD patients when considering transplant exceeds the 7.1% of the US adult population (Substance Abuse and Mental Health Services Administration [SAMHSA], 2018). Even after transplant, characterized by a decrement in depressions scores, depression incidence exceeds general population rates. The pattern is generally in line with reported depression in ESRD and transplant patients (Veater & East, 2016). The trend for decreased incidence and severity in depression following transplant is consistent with reported lower depression levels in kidney transplant recipients than in ESRD patients including wait list candidates (Akman et al., 2004; Alavi et al., 2009; Lin et al., 2011; Palmer et al., 2013; Pawar et al., 2006; Szeifert et al., 2010; Veater & East, 2016). Decreased prevalence of depression in transplant recipients has also been inferred from the lower rates of antidepressant use in the first year post-transplant in comparison to the year prior to transplant; nevertheless, about half of transplant recipients on anti-depressants pre-transplant still take them post-transplant (Lentine et al., 2018).

Not all investigators have found differences in depression between dialysis patients and transplant recipients (Karaminia et al., 2007) underscoring the reality that our data demonstrate variation in how individuals respond emotionally to transplant. Various factors have been associated with depression in renal transplant recipients, such as being unable to work, proteinuria, lower physical activity level, and longer dialysis duration (Zelle et al., 2012). In light of the heterogeneity of emotional responses, periodic monitoring of patients pre- and post- transplant is prudent to screen for depression so that clinical teams can facilitate appropriate care. Just as patients are more routinely monitored for depression pre-transplant, e.g., in dialysis units, transplant teams should consider individuals' patterns of pre-transplant depression for which there is documentation prior to transplant work-up when formulating plans for supporting patients throughout the transplant process and post-transplant. Depression tends to be negatively correlated with adherence and with QoL albeit with considerable variation. People can change both in terms of their levels of adherence and their depression status pre- and post-transplant: these are neither static nor uniform patterns.

Adherence

For both pre- and post-transplant timeframes, ESRD patients demonstrated varying adherence levels. Whereas many individuals achieve relatively sufficient medication adherence, few persist in taking their medications wholly in accord with prescribed regimens. Whereas for many behaviors, past behavior is a reasonable predictor of future behavior, the marginal correlation between pre- and post-transplant medication-taking reveals variability warranting more systematic and frequent assessment of pre- and post-transplant adherence.

We had anticipated that post-transplant medication adherence would be higher than pre-transplant adherence due to the graft-sustaining imperative of immunosuppression. It is not known why the data were discordant with that expectation. Attempts to minimize side effects may have resulted in some patients' deliberate under-medication. Another possibility is that post-transplant, participants may lead less structured lives in other ways (e.g., not needing to complete three hemodialysis runs/week, resulting in less attention to time, and therefore less precise and more inconsistent medication-taking patterns). It can also be postulated that it reflected the natural history of eroding medication adherence over time (Nevins et al., 2001).

This limitation cautions that pre-transplant adherence and even behavioral run-in trials for taking medication ultimately may have limited power in predicting post-transplant medication-taking. Although ideally it would be helpful to be able to predict individuals who will manifest post-transplant adherence problems, pre-transplant medication-taking is an imperfect indicator. It is informative for some patients in identifying post-transplant adherence problems, but pre-transplant adherence has limited sensitivity and specificity in predicting post-transplant adherence as individual medication-taking patterns vary and may change dynamically over time. Pre-transplant nonadherence identifies some, but not all, individuals whose nonadherence only manifests later, and may inappropriately categorize some as nonadherence whose post-transplant adherence improves. Because nonadherence is multifaceted, and because individual circumstances and treatment response vary, forecasts of post-transplant adherence based on pre-transplant adherence patterns are inexact.

The connection between adherence and depression is also complex. We found variability across time for both variables and between the two measures of depression. The finding of the association between post-transplant nonadherence and depression has been noted by other authors in

both a single site correlational study with self-rated depression and self-rated adherence ($r = .36$, $p < .01$; Cukor et al., 2008) and through analysis of Medicare Claims (Jindal et al., 2009), which reveals a connection between nonadherence with both pre- and post-transplant depression. Variability we observed in the association of depression and adherence reveals depression can be, but is not necessarily, a potent factor contributing to medication nonadherence. These findings about depression and adherence are similar to those of Dew et al. (2007) who noted that other variables, i.e., demographics, social support and perceived health show limited correlation with adherence.

Some aspects of depression are cognitive and may be factors in nonadherence. Positive expectations about the efficacy of treatment contribute to patient adherence. Depression may diminish hopefulness about efforts to manage health undermining adherence. Our findings are partially consistent with those of Cukor et al. (2009), who found an inverse relationship between self-rated adherence on the Immunosuppressive Therapy Adherence Scale-Medication (ITAS-M) and depression in both ESRD patients and kidney transplant recipients. Using more sophisticated MEMS methodology, our findings build on the results of Cukor et al. (2008) also finding negative correlations between depression and adherence. Whereas there are negative correlations between depressive symptomatology and adherence, the variability cautions that depression does not necessarily lead to nonadherence.

Quality of Life

QoL tended to improve following renal transplant, significantly so for several of its dimensions. This is generally consistent with studies that reveal enhanced QoL following transplantation (e.g., Kostro et al., 2016; Simmons et al., 1981). It is also consistent with cross-sectional reports comparing dialysis patients with renal transplant recipients (Bremer et al., 1989; Cannavò et al., 2019; Evans et al., 1985). The associations we observed between QoL and depression are also consistent with earlier observations (Baguelin-Pinaud et al., 2009). Low QoL raises the index of suspicion for depression.

However, the association between QoL and medication adherence was variable and puzzling. Six of the eight QoL dimensions were significantly *positively* correlated with adherence pre-transplant. By contrast, two QoL dimensions Physical Functioning and Energy-Fatigue) were significantly *negative*ly correlated with adherence post-transplant. The linkage between QoL and adherence is more variable than between depression and medication adherence and warrants further exploration. QoL appears to provide a clearer signal about depression than adherence. Whereas we present numerous correlations among the eight SF-36 scales, we decline interpreting them recognizing that multiple comparisons increase the risk of Type I error.

Questions and Concerns Raised by the Data

These data reinforce the importance of having policies and procedures that screen for adherence and depression in ESRD and transplant populations. The benefits of screening are most meaningfully realized if once depression or nonadherence is detected, there are plans and resources for addressing them. Our data suggest that monitoring patients is important in that patients not initially identified as depressed or non-adherent may become depressed and or non-adherent, leading to increased risk for adverse clinical outcomes. Larger studies are needed to confirm these findings and potential links with clinical outcomes. Periodic screening for depression in primary care is now common and could be a model for ESRD and transplant patients.

Whereas most of the data confirm expectations based on previous literature and clinical experience, other data are more heterogeneous and not readily interpreted. For example, although, as expected, the pre-transplant depression data reveal significant negative associations with pre-transplant adherence and quality of life data, why does the post-transplant depression data *not* reveal a similar negative association with post-transplant adherence? A second finding raising questions is what accounts for the decreased adherence in some transplant recipients relative to their pre-transplant adherence levels and how common might it be? Future research into these trends is warranted to increase understanding of the diverse emotional and behavioral trajectories of transplant recipients so as to better address their needs and barriers to achieving positive clinical outcomes.

Limitations

Limitations of this investigation included accruing a smaller sample of transplant recipients than we had hoped, all of whom were treated at a single transplant center. Anecdotal conversations with the recruiters revealed the limited sample was due to slower recruitment reflecting various factors including patient resistance to the study at a time that they were stressed with comprehensive workups and medical concerns, and fielding requests to participate in other studies, as well as the lack of incentives for participation. The representativeness of the sample is partially known. Our sample was similar to a national sample of kidney transplant candidates in terms of age and percent female, but had a higher percentage of White candidates and lower percentages of Black, Hispanic and Asian patients (Purnell et al., 2018). However, it is not known how or whether this difference may have affected the results. It is possible that volunteers who were willing to participate may be biased in

the direction of greater adherence and lower depression than the general population of ESRD patients seeking transplant. The sample size reflected research staff discontinuities and variable funding during the project that hampered recruitment. This was particularly limiting in comparing pre-and post-transplant data, and may have hindered finding significant correlations among some variables, such as between pre-transplant and post-transplant adherence, that may reach conventional levels of significance with larger samples.

Methodological limitations included monitoring diverse compounds during the pre-transplant MEMS monitoring. Future studies specifying pre-transplant monitored agents would reduce variance. It is not known how the monitoring of different compounds (i.e., pre-transplant vitamins and other drugs vs. post-transplant immunosuppressants) may have affected the associations we found, though it is acknowledged that patients are likely to perceive post-transplant immunosuppressants as more essential than vitamins. Presentation of correlations among variables, such as between depression and adherence, provides insights into their association, but precludes inferences of causality and directionality of how variables influence each other.

A final limitation of this study is that it did not address the association between depression and clinical course. Other authors have explored this association (Dew et al., 2015; Novak et al., 2010), revealing depressed renal transplant recipients to be a vulnerable population for adverse clinical outcomes underscoring the need for evaluating depression in ESRD patients pre-transplant and monitoring depression following transplant. Other research has found pre-transplant nonadherence to be predictive of post-transplant outcomes for kidney and other solid organ recipients (Dobbels et al., 2009; Nevins et al., 2001).

Further investigations tracking depression and using electronic monitoring of adherence with larger samples, for longer periods, and incorporating clinical outcomes, are needed to further elucidate longitudinal trends in how depression and adherence individually and together affect transplant recipients' well-being, health, and survival. Additional research is needed to refine how sensitively and specifically pre-transplant psychological and behavioral assessment identifies at-risk ESRD patients, including transplant candidates, and predicts adaptation to transplant, and ultimately leads to improved transplant outcomes. Additional research could also investigate the association of demographic factors, such as age, age ESRD diagnosis, age at transplant, sex, and ethnicity, as well as personality, expectations about transplant experiences, quality of support structures and the impact of interventions on some of these clinical phenomena that are critical to successful transplantation. Our findings indicate the need for future studies to further our understanding of why some initially adherent patients' adherence declines over time and what might be done to prevent such behavioral decay that undoubtedly limits the benefits associated with transplant.

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Declarations

Conflict of interest William N. Robiner, Megan L. Petrik, Nancy Flaherty, Thyra A. Fossum, Rebecca L. Freese and Thomas E. Nevins declare that they have no relevant financial or non-financial interests to disclose.

Ethical Approval This research was approved by the University of Minnesota IRB. Data are available from the corresponding author.

Human and Animal Rights The procedures followed for this study were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national). All persons gave their informed consent prior to their inclusion in the study.

Consent to Participate Informed consent was obtained from all individual participants included in the study.

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