

Is there an association between immunosuppressant therapy medication adherence and depression, quality of life, and personality traits in the kidney and liver transplant population?

Elizabeth Gorevski¹

Paul Succop¹

Jyoti Sachdeva¹

Teresa M Cavanaugh¹

Paul Volek¹

Pamela Heaton¹

Marie Chisholm-Burns²

Jill E Martin-Boone¹

¹University of Cincinnati, Cincinnati, OH, USA, ²University of Tennessee College of Pharmacy, Memphis, TN, USA

Objectives: To measure the association of transplant patients' personality, depression, and quality of life with medication adherence in kidney and liver transplant recipients.

Methods: A cross-sectional study of liver and kidney transplant recipients greater than 1 year post-transplant was conducted. Patients' adherence with medications was assessed using the Immunosuppressive Therapy Adherence Scale. Personality and depression were assessed using the NEO Five-Factor Inventory Scale and Patient Health Questionnaire 9, respectively. Quality of life was assessed using the Short Form-36, and functional status was determined using the Karnofsky Performance Status Scale.

Results: A total of 86 kidney and 50 liver transplant patients completed the surveys. Logistic regression analysis demonstrated an association between depression and adherence with immunosuppressive medications in kidney transplant recipients. Kidney transplant patients who exhibited "low openness" scores were 91% more likely to be nonadherent. Kidney transplant patients' physical functional status was strongly associated with nonadherence, and for each point increase in functionality the patients' adherence increased by 4%. In the liver sample, age was associated with adherence. For every year increase in age, adherence increased by 7%.

Conclusion: The presence of low openness as a personality trait, poor physical functional status, and depression were associated with adherence in the kidney transplant population. In the liver transplant population, younger age was associated with nonadherence.

Keywords: adherence, transplant, liver, kidney

Background

Traditionally, assessment of success in liver and kidney transplant recipients has been related to patient and graft survival. Currently, liver transplant patients' survival at 1 year and 5 years is approaching 90% and 70%, respectively.¹ Kidney transplant survival is approximately 89% at 1 year and 76% at 5 years.²

Patient survival over the years has improved with advances in surgery and more effective immunosuppressive therapy. Despite advances in immunosuppressive therapy, patients' medication-taking behavior remains a major weakness in the therapeutic chain.

Patient survival, organ rejection, and graft survival are largely impacted by patients' ability to be adherent to the prescribed medications. The available literature

Correspondence: Elizabeth Gorevski
University of Cincinnati, 3225 Eden
Ave, PO Box 67004, Cincinnati,
OH 45267-0004, USA
Tel +1 513 558 0526
Fax +1 513 558 0731
Email elizabeth.gorevski@uc.edu

emphasizing the negative impact of nonadherence on outcomes in transplant is focusing on the kidney transplant recipients. A literature review indicated that 22.6% of the kidney transplant patients were noncompliers and that 21.1% of these patients experienced a late acute rejection, compared with 8% in the group of compliers at 5-year postinclusion.³ Another literature review of transplant recipients showed that the odds of graft failure increased seven-fold in nonadherent patients compared with adherent patients.⁴ In this review, a total of ten cohort studies were included, indicating that nonadherence contributed substantially to graft loss, with 36% of graft losses due to poor adherence.⁵ Dew et al⁶ found a weak correlation between patient psychosocial factors and nonadherence, and suggested that focus should be directed toward provider-related and system-level factors. Further, nonadherence has been reported to be responsible for one in ten deaths in liver transplant recipients due to poor adherence to medications.⁷

Data on the economic impact of nonadherence are scarce but can be estimated based on the cost of additional diagnostic tests, the cost of augmentation of immunosuppression, and, ultimately, the cost of retransplantation. A report from the World Health Organization estimated that the economic impact of nonadherence in patients with chronic illnesses was \$100 billion to \$300 billion annually, and in solid-organ transplant recipients was \$15 million to \$100 million annually.⁸

Several factors have been observed with nonadherence in the transplant population. Poor social support, a history of alcohol abuse, being young, nonwhite, and male have been identified as strong predictors of nonadherence in lung, liver, and heart recipients.⁹ Poor quality of life has been reported as a risk factor for nonadherence in adolescents; however, no studies have been conducted in the adult transplant population.¹⁰ In the heart transplant population, one study indicates that psychiatric problems early after transplant are associated with nonadherence.¹¹ Two more recent studies in the kidney transplant population found that depression was associated with nonadherence.^{12,13}

Among other objectives at the Transplant Non-Adherence Conference in 2009, the predictors of nonadherence were also a major topic of discussion. The proceedings from this conference, published in the *American Journal of Transplantation*, strongly advocated that further studies are urgently needed to determine which objective and subjective measures are the most accurate in predicting nonadherence in transplant recipients.¹⁵ In response to this need, the association of transplant patients' personality, depression, and quality of

life with medication adherence in kidney and liver transplant recipients was assessed in this study.

Methods

Design

This is a cross-sectional study of liver and kidney recipients conducted at the University Hospital in Cincinnati, OH, USA, to determine the association of patients' quality of life, personality, and depression with nonadherence to medications. The research study was conducted at the University of Cincinnati Medical Center Outpatient Liver and Kidney Transplant Clinics. This study has University of Cincinnati Institutional Review Board approval.

Patient enrolment

Patients included in the study had only one transplant, were aged over 18 years, were English speaking, and had been transplanted for more than 6 months. Patients treated and not treated for depression were included in the study, and these data were collected from the patients' medical records.

Patients who had received a pancreatic transplant in addition to kidney or liver were excluded from the study. If Prograf® (Astellas Pharma US, Inc, Northbrook, IL, USA) or cyclosporine levels were unavailable; patients were not included in the study.

Determination of the patients' personalities, level of depression, and quality of life necessitated their completion of several surveys. It was very important to ensure that patients would be able to complete the four surveys in a reasonable amount of time without impacting the clinic schedule. Therefore, a pilot study of five patients was conducted to determine the ease and time consumption of the survey administration. Survey administration and completion took approximately 20 minutes, and the five pilot patients successfully completed the surveys.

In addition to the survey data, demographics, laboratory, medication, and transplant-related information were collected for each study participant.

Surveys administered

Patients were approached in the liver and kidney clinics prior to their appointment by the primary investigator, and were given the option to either accept or decline participation in the study. Patients completed the surveys while they were waiting, before their appointment started.

Adherence to immunosuppressive therapy was assessed with the help of the Immunosuppressive Therapy Adherence Scale® (ITAS®). The ITAS is a four-item measure in

which transplant recipients indicate the frequencies of the following immunosuppressive therapy adherence-related behaviors in the previous 3 months: forgetfulness to take medications, carelessness regarding medication taking, cessation of medication taking due to feeling worse, and neglect of medication taking for many reasons. Response options on a four-point Likert scale were as follows: 3 = 0% (none of the time), 2 = 1%–20%, 1 = 21%–50%, and 0 = >51% of the time. Item responses were summed with possible total scores ranging from 0 to 12.¹⁶

Personality traits (neuroticism, extraversion, openness to experience, agreeableness, and conscientiousness) were assessed with the 60-item NEO Five-Factor Inventory (NEO-FFI) Scale. NEO-FFI is a self-reported scale with proven validity that is used in assessing personality in multiple patient populations.¹⁷ Each question is rated on a five-point scale, ranging from “strongly disagree” to “strongly agree.” Completed questionnaires with more than 40 items missing were not evaluated based upon validity data from Costa and McCrae.¹⁸

Patients' depression was assessed with the Patient Health Questionnaire 9 (PHQ-9), which is a nine-item depression scale. The nine items of the PHQ-9 are based directly on the nine diagnostic criteria for major depressive disorder in the *Diagnostic and Statistical Manual Fourth Edition*. This helps track a patient's overall depression severity as well as the specific symptoms that are improving or not with treatment. PHQ-9 has specificity and sensitivity of 88% for scores > 10.¹⁹

Short Form (SF)-36 determined the quality of life of the transplant patients. The SF-36 is scored so that a higher score indicates higher mental and physical functioning. The Physical Composite Score and Mental Composite Score have a range of 0 to 100 and were designed to have a mean score of 50 and a standard deviation of 10 in a representative sample of the US population. The SF-36 has sensitivity and specificity of 74% and 81%, respectively.²⁰

Statistical analysis

A power calculation based on the expected partial correlation was performed to determine how many patients would be required for this study. In order to reach 80% power with an α value of 0.05 and a partial correlation of 0.31, we needed a total of 80 patients, and to demonstrate a significant partial correlation of 0.2 with 80% power we needed to enroll 195 patients.

Logistic regression analyses were performed to determine which variables were significantly associated

with nonadherence. The logistical regression model included sociodemographic variables, personality traits, quality of life, and depression categories. A *P*-value of 0.05 was used to judge statistical significance.

Results

Liver and kidney cohort descriptions

A total of 134 surveys were administered and a total of 86 kidney transplant recipients fully completed the surveys, with a nonresponse rate of 36%. The mean age for these patients was 50.3 ± 12.4 years, and 58 (67%) of them were males (Table 1). The most common indications for transplant in the kidney transplant recipients were diabetes mellitus type 1 ($n = 14$ [16.3%]), diabetes mellitus type 2 ($n = 12$ [14%]), malignant hypertension ($n = 15$ [17.4%]), and polycystic kidney ($n = 7$ [8.1%]). A total of 86 surveys were administered and a total of 50 liver transplant recipients fully completed the surveys, with a nonresponse rate of 42%. The mean age for these patients was 57.0 ± 9.7 years, and 33 (66%) of them were males with an overall average time since transplant of 57.9 ± 56.8 months (Table 1). The most common indications for transplant in the liver transplant recipients were hepatitis C virus ($n = 11$ [22%]), idiopathic cirrhosis ($n = 7$ [14%]), and Laennec's cirrhosis ($n = 5$ [10%]). More liver transplant patients had pretransplant depression ($n = 8$ [20%]) compared with the kidney transplant patients ($n = 8$ [9.3%]).

Table 1 Demographics of the liver and kidney transplant recipients

Demographic data	Kidney mean (standard deviation)	Liver mean (standard deviation)
Time since transplant (months)	80.8 (86.3)	57.9 (56.8)
Age (years)	50.3 (12.4)	57 (9.7)
Gender		
Male	58 (67%)	33 (66%)
Female	28 (33%)	17 (34%)
Race		
Caucasian	69 (80.2%)	44 (88%)
African-American	15 (17.4%)	5 (10%)
Hispanic	1 (1.2%)	1 (2%)
Asian	1 (1.2%)	0 (0%)
Education		
High school	36 (41.9%)	8 (16%)
Attended college/tech school	10 (11.6%)	3 (6%)
Associate's/bachelor's degree	12 (14%)	7 (14%)
Postcollege (graduate school)	3 (3.5%)	0 (0%)
Unknown	25 (29.1%)	32 (64%)
Comorbidities	4.7 (2.3%)	4.8 (1.8%)
Pretransplant depression		
Yes	8 (9.3%)	10 (20%)
No	78 (90.7%)	40 (80%)

The most common primary immunosuppressant in kidney and liver transplant recipients was tacrolimus (Prograf) ($n = 73$ [84.8%] and $n = 40$ [80%], respectively). A total of 68 (79.1%) kidney transplant recipients were taking mycophenolate mofetil (CellCept[®], Genentech USA, Inc, South San Francisco, CA, USA), and 33 (66%) of the liver transplant recipients were taking mycophenolate mofetil (CellCept). None of the liver transplant recipients was taking prednisone; however, 33 (38.4%) of the kidney transplant recipients were taking prednisone (Table 2).

Adherence to medications

Overall, 49 (57%) and 28 (56%) of the kidney and liver transplant recipients, respectively, were adherent with medications.

None of the kidney transplant recipients reported that they forgot to take their immunosuppressant medication in the last 3 months due to feeling worse, based on questions asked by the ITAS. From the kidney transplant recipients, $n = 23$ (26.7%), $n = 29$ (33.7%), and $n = 31$ (36%) did not take their immunosuppressant medications in general, were careless about taking their immunosuppressant medications, or missed taking their immunosuppressant medication between 0% and 20% of the time, respectively. None of the kidney transplant recipients did not take their immunosuppressant medications more than 50% of the time for any reason. A very small number, $n = 2$ (2.4%), either forgot to take or missed taking their immunosuppressant medications between 21% and 50% of the time in the last 3 months (Table 3).

Of the liver transplant cohort, 35 (70%) did not forget, 36 (72%) were not careless, and 36 (72%) did not miss taking their immunosuppressant medications in the last 3 months. Approximately twelve to 13 (24%–26%) of the liver transplant patients forgot, were careless, or missed taking their immunosuppressant medications in the last 3 months between 0% and 20% of the time. In the liver transplant sample, four (6.4%) of the patients forgot, missed, or did not take their immunosuppressant medications more than 50% of the time (Table 4).

Table 2 Kidney and liver immunosuppressive drugs

Immunosuppressive drugs	Kidney	Liver
Tacrolimus	73 (84.8%)	40 (80%)
Cyclosporine	5 (5.8%)	7 (14%)
Sirolimus	7 (8.1%)	3 (6%)
Azathioprine	6 (7%)	1 (2%)
Mycophenolate mofetil	68 (79.1%)	33 (66%)
Prednisone	33 (38.4%)	0 (0%)

Personality, depression, and quality of life results

Many of the kidney transplant patients belonged to the “average” category for all personality traits (neuroticism, extraversion, openness, agreeableness, and conscientiousness) ($n = 32$ [37.2%], $n = 30$ [34.9%], $n = 38$ [44.2%], $n = 27$ [31.4%], and $n = 40$ [46.5%], respectively). However, 39 (45.6%) of the kidney transplant patients showed “low” and “very low” openness to actions and ideas, 34 (39.5%) had low compliance and straightforwardness, and 30 (34.9%) exhibited “low” self-discipline, dutifulness, and achievement striving. A similar pattern is observed with the liver transplant recipients. Most of the personality traits (neuroticism, extraversion, openness, agreeableness, and conscientiousness) were comparable with the average of the general population ($n = 21$ [42%], $n = 20$ [40%], $n = 23$ [46%], $n = 17$ [34%], and $n = 14$ [28%], respectively).²¹ About 52% of the liver transplant patients exhibited “low” or “very low” compliance, self-discipline, competence, and dutifulness.

The mental component of the SF-36 for nearly half of the kidney and liver transplant recipients was above average ($n = 36$ [41.9%] and $n = 24$ [48%], respectively). However, 29 (33.8%) and 18 (36%) of the kidney and liver transplant recipients were “well below average” and “below average,” respectively (SF-36 values are reported for age and gender norms). On the other hand, patients showed poorer quality of life based on the physical health component of the SF-36 compared with the mental health component. Half of the liver transplant patients had a “well below average” mental component quality of life, and another eight (16%) were “below average.”

The preponderance of kidney and liver patients had minimal to mild depression (52 [60%] and 36 [52%], respectively). Only approximately one-fifth of both patient populations did not have depression. Moderately severe to severe depression was observed in a few of both the liver and kidney transplant recipients (three [6%] and eight [9.8%], respectively).

Adherence correlates

Logistic regression analysis demonstrated an association between depression and adherence with immunosuppressive medications in kidney transplant recipients (odds ratio [OR] = 1.51, confidence interval [CI] = 0.98–2.32, $P < 0.05$). Kidney transplant patients with high scores on PHQ-9 were more likely to be nonadherent. In the assessment of the kidney patients’ personalities, one domain, openness, was significantly related to adherence. Kidney transplant patients

Table 3 Kidney transplant patient responses to the Immunosuppressive Therapy Adherence Scale® (ITAS®)

ITAS®	A (0%)	B (1%–20%)	C (21%–50%)	D (>51%)
In the last 3 months, how often did you forget to take your immunosuppressant medication(s)?	58 (67.4%)	23 (26.7%)	1 (1.2%)	0 (0%)
In the last 3 months, how often were you careless about taking your immunosuppressant medication(s)?	57 (66.3%)	29 (33.7%)	0 (0%)	0 (0%)
In the last 3 months, how often did you stop taking your immunosuppressant medication(s) because you felt worse?	86 (100%)	0 (0%)	0 (0%)	0 (0%)
In the last 3 months, how often did you miss taking your immunosuppressant medication(s)?	54 (62.8%)	31 (36%)	1 (1.2%)	0 (0%)

who exhibited low openness scores were 91% more likely to be nonadherent (OR = 0.09, CI = 0.01–0.51, $P < 0.02$) compared with patients with moderate to high openness scores. Kidney transplant patients' physical functional status according to the Karnofsky Performance Status Scale was strongly associated with nonadherence. For each point increase in functionality, patients' adherence increased by 4% (OR = 1.04, CI = 1.0–1.08, $P < 0.02$) (Table 5). In the liver sample, age was associated with adherence. For every year increase in age, the adherence increased by 7% (OR = 1.07, CI = 1.00–1.14, $P < 0.04$) (Table 6).

Discussion

In our study we found that 49 (57%) of the kidney patients were adherent to immunosuppressive medications, and in the liver sample 28 (56%) were adherent to immunosuppressive medications, according to the ITAS. Our adherence rates are similar to the currently reported adherence rates in the literature. Depending upon the method and the operational definition used, the incidence of medication nonadherence in the adult renal transplant recipients ranges from 4.7% to 53%.^{3,22,23} According to a recent study using self-report, the incidence of nonadherence in the liver transplant population is about 50%.²⁴ It is important to note that the ITAS is a self-report instrument that has its limitations, as are described in other publications, including a long recall period of 3 months and a broad range of nonadherence scoring options.

As previously stated, prior research found that poor social support, a history of alcohol abuse, and being young, non-white, and male are all strong predictors of nonadherence in lung, liver, or heart transplant recipients.⁹ The current study adds an association between patient nonadherence and the presence of depression, select personality traits (low openness), and poor physical function in the kidney transplant patients. In addition, we found that as liver transplant patients become older their adherence improves.

The factors associated with nonadherence are different for the liver and kidney transplant recipients, possibly due to the differences these two samples exhibit. In our kidney sample, 33 (38.4%) of the patients were taking prednisone, whereas none of the liver transplant patients was taking prednisone. Administration of prednisone is associated with depression in the transplant population.²⁵ It is likely that more kidney transplant patients became depressed pretransplant due to the exposure to prednisone. At baseline, eight (9.3%) and ten (20%) of the kidney and liver patients were depressed, respectively. Post-transplant, 52 (60%) and 36 (52%) of the kidney and liver transplant patients had minimal to mild depression, respectively. Severe depression was observed in eight (9.8%) and three (6%) of the kidney and liver patients, respectively. We cannot exclude the possibility that more kidney patients became depressed post-transplant, resulting in depression being associated with nonadherence in the kidney transplant population.

Table 4 Liver transplant patient responses to the Immunosuppressive Therapy Adherence Scale® (ITAS®)

ITAS®	A (0%)	B (1%–20%)	C (21%–50%)	D (>51%)
In the last 3 months, how often did you forget to take your immunosuppressant medication(s)?	35 (70%)	12 (24%)	0 (0%)	2 (4%)
In the last 3 months, how often were you careless about taking your immunosuppressant medication(s)?	36 (72%)	12 (24%)	2 (4%)	0 (0%)
In the last 3 months, how often did you stop taking your immunosuppressant medication(s) because you felt worse?	47 (94%)	2 (4%)	0 (0%)	1 (1.2%)
In the last 3 months, how often did you miss taking your immunosuppressant medication(s)?	36 (72%)	13 (26%)	0 (0%)	1 (1.2%)

Table 5 Adherence correlates for kidney transplant recipients

Correlate	Odds ratio and confidence interval	P-value
Depression	1.51 (0.98–2.32)	0.05
Openness	0.09 (0.01–0.51)	0.02
Functional status	1.04 (1.0–1.08)	0.02

Previous investigators have evaluated psychiatric factors and their association with adherence. A recent study from 2009 by Dobbels et al²⁶ evaluated some of the same psychosocial factors as our study and their association with patient adherence. Their study examined which pretransplant psychosocial factors (depression, anxiety, personality traits, social support, per-transplant medication adherence, and smoking status) predicted post-transplant nonadherence with immunosuppressant medications and clinical outcomes in heart, liver, and lung transplant recipients. They found that pretransplant self-reported medication nonadherence, receiving lower social support, a higher education, and lower “conscientiousness” were independent predictors of post-transplant nonadherence. It is important to note that this study was done in a Belgian pretransplant population on the waiting list for a transplant, and the surveys for measuring depression and personality were administered before they received their transplant. Also, their reported outcomes were for the combination of lung, liver, and heart transplant recipients with up to 1-year post-transplant follow-up.

A study by Cukor et al¹³ in 2008 was the first study to investigate a correlation between depression and adherence to immunosuppressant medications in kidney transplant recipients. This study found higher levels of depression correlated with missing more medication doses. Jindal et al¹² using the United States Renal Data Service data in 2009, conducted a retrospective cohort study of 32,757 Medicare primary renal transplant recipients. A strong association between depression and nonadherence was found using this database, regardless of whether the depression was diagnosed pre or post-transplant. The results of our study with regard to the kidney transplant population are consistent with the findings in these two previous reports.

Only one study to date, from 2009 in Portuguese liver transplant candidates, has been designed to determine whether there is an association between adherence and personality.

Table 6 Adherence correlated for liver transplant recipients

Correlate	Odds ratio and confidence interval	P-value
Age	1.07 (1.00–1.14)	0.04

This is a study in pre-liver transplant candidates. The authors measured adherence by a Multidimensional Adherence Questionnaire developed and validated by them. They found that multidimensional adherence positively correlated with the personality trait of agreeableness. In our study we found that a low level of openness was associated with nonadherence to medications in the kidney transplant recipients.

No prior studies have been conducted to determine the association between quality of life and nonadherence in the adult transplant population. In our study, possibly due to the small sample size, we did not find an association between quality of life and adherence to immunosuppressant medications in the liver or kidney transplant population.

From the available data it is clear that depression and personality traits are associated with nonadherence to immunosuppressant medications. Strategies need to be incorporated to address these factors. Physicians need to be advised to screen for pre and post-transplant depression, as this may affect adherence and therefore transplant outcomes. Diagnosed depression needs to be treated appropriately, and patients need to be monitored. Depressed patients need to receive special attention by transplant clinic health care providers to facilitate the development of good medication-taking behaviors. For example, extensive medication adherence counseling and use of a medication adherence tool could be administered to these at-risk individuals. There is only one previously published study that evaluated the association of personality traits with adherence.¹⁴ That study and ours indicate an association between low agreeableness or low openness and nonadherence. Consideration should be given to administration of a pretransplant personality assessment to facilitate identification of individuals with personality traits associated with medication nonadherence. More studies are needed to determine whether quality of life is associated with adherence to immunosuppressant medications. This association has been demonstrated only in studies of adolescent patients.^{10,27}

It is important to identify targeted interventions to improve adherence rates so that costs resulting from nonadherence can be reduced or avoided. Previous adherence research has led to several different strategies for increasing adherence to medications in patients with chronic disease states.

Identification of these patients will allow appropriate resource allocation to ensure intensive patient education and medication adherence monitoring.

Medication nonadherence is a significant problem in the transplant populations. Enhanced understanding of the

impact of personality traits, depression, and quality of life on medication-taking behaviors is an important step in the development of novel strategies to improve medication adherence and, ultimately, patient outcomes.

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Disclosure

The authors report no conflicts of interest in this work.

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