Published in final edited form as:

Transplant Proc. 2007 December ; 39(10): 3081–3085.

ADHERENCE TO IMMUNOSUPPRESSION: A PROSPECTIVE DIARY STUDY

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Abstract

Immunosuppression adherence among kidney transplant recipients is essential for graft survival. However, nonadherence is common, jeopardizing graft survival. Besides skipping dosages, little is known about other forms of medication nonadherence and their underlying reasons. This study was undertaken to examine patients' extent of medication adherence over time and reasons for nonadherence. Thirty-nine new kidney transplant recipients were asked to complete a month-long medication-taking diary that included reporting medication nonadherence such as skipped medications, medications taken early or late, taking dosages greater or less than prescribed, and the reason for each occurrence of nonadherence. Of the 20 (51%) patients who completed the diary, 11 (55%) reported at least one form of nonadherence. Eleven patients reported taking their immunosuppression at least one hour later than the prescribed time, one patient reported skipping medication, but no patients reported changing the dosage on their own. Immunosuppression was taken on average 1.5 hours after the prescribed time. Of those patients who took their medications late, there were on average 3.1 occasions of taking it late. The most common reasons for this behavior included health care related issues, followed by oversleeping, being away from home, work-related barriers, and forgetting. A large minority of kidney transplant recipients took medications later than prescribed during one month. Future research should determine the clinical impact on graft function of late administration of immunosuppression. Interventions should be designed to better assist kidney recipients with taking medications on time, especially when they are away from home.

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Submitted for publication in [Transplantation Proceedings](#)

Keywords

Kidney transplantation; adherence; nonadherence; immunosuppression; medication; longitudinal research; diary methodology

Introduction

Adherence with immunosuppressants is essential for the survival of transplanted kidney grafts. Nonadherence with immunosuppressants has serious adverse effects on transplant outcome, including graft loss, rejection episodes, and consequent resumption of dialysis.¹ Nonadherence is the third leading cause of renal graft loss after simple allograft rejection and systemic infection.² Post-transplant nonadherence is common, ranging from 5% to more than 45% of patients.^{3,4}

Previous research has focused on only one type of nonadherence: not taking medications at all.⁵ Typically, these studies report that 19.3% had not taken their immunosuppressive drugs at least once within the past 4 weeks.⁶ However, other forms of medication nonadherence include: (a) changing the dose of medication taken; and (b) changing the timing of when medication is taken. Examining the reasons for nonadherence among kidney transplant recipients is important to: a) reduce nonadherence in the future, b) help physicians understand patients' clinical outcomes, c) develop a screening tool of patients most likely at risk of engaging in nonadherence, and d) design interventions to help prevent nonadherence in the patient population.

Taking less than the prescribed dose differs from not taking medications at all as patients may take fewer pills so as to stretch the medication over time. For example, patients with financial concerns will often try to "stretch" the time to a medication refill.⁷ Patients might also take larger doses of medication if they suspect they are undergoing kidney rejection. Both behaviors endanger the graft. Too little medication can cause rejection of the graft. Taking a larger dose can cause side effects and symptoms, which, if perceived as severe and/or serious, may lead patients to stop taking the medication altogether.⁸

Patients must also be consistent with the times in which they take their immunosuppressives. Not taking medication at the scheduled time can disturb immunosuppression trough levels in the blood, which disrupt the body's ability to avoid rejecting the graft. While taking immunosuppression hours later on a single occasion is generally not thought by transplant professionals to have an adverse effect upon the graft, taking medicines over an hour later than scheduled in a chronic fashion will likely have an eventual adverse effect on the graft. However, this issue has yet to be empirically examined. Compounding the problem of assessing the adverse effects of changing the timing of medication is that there is no definitively known number of hours past the scheduled time that taking medication compromises the integrity of the kidney graft.

Although medication adherence is critical to graft survival, little is known about the reasons why patients do not adhere to their immunosuppression regimens. Studies that have addressed the reasons for post-transplant nonadherence have identified the following: forgetting, high costs of medications, unpleasant side effects, difficulty preparing medications, and their low palatability.^{9,10} The few studies examining nonadherence in-depth by race/ethnicity found that: African American and Hispanic American patients are more likely than European American patients to believe that: a) the kidney graft was functioning so well that immunosuppressants were not needed, b) immunosuppressants remain active in the body for

several days, and c) immunosuppressants were no longer needed when the dosage was reduced.^{11,12}

The studies to date, while important, are not definitive. Most are retrospective in nature and have only small sample sizes. Moreover, because these studies used closed-ended interview questions, it is not clear if there remain undisclosed problems that can only be elucidated using more formative research methods. Finally, without having examined nonadherence over time, previous research has been limited by not capturing the ebb and flow of contextual factors on patients' lives, e.g., the impact of work or clinic schedules or other life events that may disrupt patients' medication-taking routines. The development of effective interventions will need to address the specific beliefs and perceptions that are associated with nonadherence behavior. A qualitative approach can provide a better understanding of the specific patterns of nonadherence emerging over time and the causes for nonadherence.

This report is part of a larger study of kidney recipients' post-transplant self-care to prospectively and qualitatively examine patients' extent of medication adherence over time and their reasons for nonadherence. The purpose of this study component is to examine medication adherence over time and the factors associated with adherence/nonadherence using a longitudinal diary method.

Methods

This study recruited new adult kidney transplant recipients within on average 6 weeks of their transplant and the diary was sent to patients within 14 months of recruitment (mean = 8 months; range = 2.25–14 months) after their transplant. All kidney transplant recipients were asked to keep an immunosuppression medication diary for four consecutive weeks.

Diaries refer to an annotated chronological record commissioned by the investigator.¹³ Diaries hold great promise for ascertaining routine self-management behavior. Since kidney transplant recipients are already required to systematically record daily information about their weight, blood pressure, and temperature, the diary fits easily into the patient's routine. Moreover, dialysis patients' dietary patterns have been studied successfully through their use of diaries.¹⁴

The diary booklet was mailed to study participants along with instructions, a list of their medications, and a stamped, self-addressed envelope for returning the booklet. Transplant recipients were asked daily to record: a) whether or not they skipped a dose of medication; b) changed the dose by specifying if more or fewer pills were taken; c) changed the time they took the dose by specifying how many hours earlier or later than they routinely take their medications; and d) reasons for each type of medication nonadherence practiced. A week after mailing the diaries, the research team called each patient to review the instructions and answer questions. Efforts undertaken to encourage diary completion included: a) reassuring participants that data would be kept confidential and not shared with transplant professionals; b) offering \$20 for completing the diary; and c) establishing rapport with patients during prior interviews. All subjects provided written informed consent to the study, which was approved by the Institutional Review Board at Loyola University Medical Center.

Statistical Analysis

Inferential statistics were used to analyze the data. Responses to open- and closed-ended questions were coded and entered into a statistical software database (SPSS 15.0 for Windows, Chicago, IL). The two-sample t-test was used to test differences between means for measures including, number of hours medication was taken late and patient age. Differences in proportions were tested using Chi-square test or Fisher's exact test. All tests were two-sided

and $P < 0.05$ was considered statistically significant. Changes made in the medication, dosage, or timing due to a physicians' updated prescription were not included in the analysis. For the purpose of analysis, patients taking their medications at least 1 hour before or after their scheduled time were considered nonadherent.

Qualitative Analysis

Two investigators (EJG & MPG) independently reviewed and coded open-ended responses as part of thematic analysis.¹⁵ Thematic analysis entails the systematic search for themes and repetitions emergent from the data. The investigators then together reviewed the two sets of codes for inconsistencies, and revised the codes to ensure categorical fit.

Results

A total of 20 (51.3%) diaries were completed out of 39 sent for completion over two separate occasions. There were significant demographic differences between responders and nonresponders to the diary by gender ($p < 0.05$; chi-square = 4.74), and race ($p < 0.05$; chi-square = 5.07). Most respondents were female (55%), European American (75%), older (average age 51), and better educated (average 14 years). Most nonresponders were male (79%), racially split among African American (42%), European American (37%), or other/unknown (21%), younger (average age 48), and less educated (average 13.6 years).

Of the 20 diaries returned, 11 (55%) reported at least one form of nonadherence. Among all diaries returned, there was no significant difference in patient demographics between those who did and did not report any nonadherence.

Only two types of nonadherence were reported: 1) skipping a dose of medication because of having forgotten it ($n = 1$), and 2) changing the time the medication was taken ($n = 11$). This paper focuses on this latter form of nonadherence. Although one patient reported that she had changed the dose of their medication, this was based on orders given by their transplant nurse, and thus not included for analysis.

Changing the time of medication-taking

Eleven patients reported changing the timing in which medications were taken. Of these patients' diaries, there were 32 occasions of taking the medications at least 1 hour later than prescribed. There were also 7 occasions reported by 2 different people of taking the medications at least 1 hour earlier than prescribed. Specific information about: a) the average number of hours that immunosuppression was taken at least one hour earlier or later from the prescribed time, b) the longest time span that medication was taken from the prescribed time, and c) the average number of occasions in which immunosuppression was taken at least 1 hour earlier or later from the prescribed time is presented in Table 1. The data for Table 1 are based on the total number of occasions reported. As these data show, kidney recipients are more likely to be late in taking their medicines than early, take their medications on average 1.5 hours later than the prescribed time, and have a range of 1 to 4 hours of delay in taking immunosuppressive drugs. One patient reported taking immunosuppressives 4 hours late. Patients were late taking their medications on average on 3.1 occasions.

The reasons for taking medications late or early varied (see Table 2). In total, 35 reasons were provided for nonadherence. These reasons were categorized into 5 content areas: healthcare structural factors, sleeping/slept in, being away from home, work-related barriers, and forgot/inattention. The most common reason reported for taking medications late related to structural features of the health care delivery system. Examples of this category include the fact that patients underwent medical procedures, or were at their doctors' appointments, undergoing

laboratory tests that required patients to not take their medications for 1–2 hours prior to their blood work. As one patient stated, “One time a month I am late taking meds in the morning because I have my blood work done for the transplant.” The second most common reason for taking medications late was oversleeping or sleeping in on the weekend. Being away from home refers predominantly to social occasions like being at a BBQ or at church where patients forgot to bring their medications, and even confusion with time changes when traveling.

The two least commonly reported reasons for taking medications late pertained to work-related barriers wherein patients had to work late or be in a meeting; and forgetting to take their medications on time, wherein patients simply forgot, did not watch the time, or became distracted by other events. As one patient reported, “[I] took [my] son to [the] doctor[’s] appointment. [I] forgot to take medication before I left.” Two patients reported taking medication early due to having to start work early at 6:30 am or undergoing a medical procedure.

All patients who received the diary had previously participated in a semi-structured interview that asked questions about different forms of adherence to their anti-rejection medicines. Of these patients, 12 (31%) reported at least one form of nonadherence; six of these patients completed the diary. Major forms of nonadherence include: being in a situation that prevented them from taking their medications (13%); changing the dose of their medicines (10%); ‘stretching’ medicines (5%); and taking medicine at different times each day (3%). There were no significant differences in these patient-reported forms of medication nonadherence between those who completed the diary and those who did not.

Discussion

The findings show that a large minority of kidney transplant recipients took their medications later than prescribed in the course of one month. Unlike other studies that report high frequencies of skipping medications,¹⁶ this diary study observed very little skipping in the course of one month. The interview data support this finding, and dispel the possibility that nonadherent patients did not complete the diary.

The rates of nonadherence reported among those completing the diaries are likely to be lower than the rates found among study participants not completing the diaries and possibly among kidney recipients in general. Self-monitoring through the diary could increase medication adherence, and those who returned the diaries are likely, in general, more compliant than those who did not. This is because the data collection method constitutes a built-in model for behavior change. In other words, the act of completing the diaries likely fosters medication adherence because it entails self-monitoring. Despite this fact, many patients still reported nonadherence in the timing of medication taking, suggesting that this phenomenon may be more common than clinicians or scholars recognize.

Patients reported numerous valid reasons for delaying taking their medications, including both extenuating circumstances and situations presumably under their control. By having to take their medications at routine, set times during the day, kidney transplant recipients are expected to constantly attend to the time. Many of patients’ reasons suggest that patients may desire not to have medication time schedules orient their lives, including their sleeping habits and social interactions.

An underlying motif that emerged in the analysis of the reasons for taking medications late was that taking medication while away from home is difficult. This finding suggests that interventions enabling kidney recipients to take their medications on time generally, and specifically while away from home must be developed. Timely medication adherence is important to ensure that the body has a consistent level of medication in the bloodstream.

Encouraging patients to carry pill boxes wherever they go may be a start, however, there may be concerns about taking medications in social situations, for which many occasions away from home reflected. Interventions that develop cues to prompt, timely medication-taking may help patients.

Other research supports these findings. A study of adherence among new kidney recipients who were given medicines at no cost found that adherence declined after the first year, suggesting that cost-factors do not completely explain patients' nonadherence behavior with immunosuppressants.¹⁷

As with investigations of nonadherence behavior among other patients using diaries, diaries enable a much-needed prospective examination of nonadherence behavior among kidney transplant recipients.¹⁸ These data show, contrary to expectation, that nonadherent patients will adhere to completing the diaries. Moreover, but not unexpectedly, patients reporting nonadherence did not always report nonadherence in their in-depth interviews, reflecting inconsistency in reporting. This finding indicates that patients are more candid and/or attentive to this issue in the diary data collection method, lending much value to their use as a more accurate data collection method for future research in adherence.¹⁹

Future research should systematically examine the impact of delaying medication-taking on kidney transplant recipients' graft outcomes. Consideration of the drug half-lives may be essential to determining the actual impact of delayed medication-taking on graft outcomes. Such information could be used to better educate patients about precise parameters of necessary medication-taking practice.

To further understand patients' reasons for engaging in nonadherence, future research should consider cultural factors shaping their self-care management. For example, people's understanding of time may influence when they take medicine: while some ethnic and cultural groups emphasize the present time, others focus on future time.²⁰ Similarly, ethnic and cultural groups vary in the value placed on self-care: while the individual takes responsibility for self-care among many groups, in many others, family members are highly involved in ensuring the well-being of the patient.²¹ Cultural attitudes about time and self-care may influence kidney recipients' readiness to adhere to the time frames established by transplant professionals for the new immunosuppression regimen.

A limitation of this study is the absence of external measures to validate adherence assessments. Additionally, the small sample size and single institutional experience limits generalizability of research findings. Further, the small response rate of 51% may be the result of nonadherent patients not completing the diary. Future research should replicate this research and compare diary reports by the same individuals over repeated monthly periods to longitudinally ascertain whether patterns of nonadherence emerge within individuals over time and establish causal relationships²² with graft outcomes.

Acknowledgements

Supported by grant DK063953 from the National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda, MD.

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Table 1

Taking medications earlier or later than prescribed

	Mean number of hours Ia taken from prescribed time	Longest span of time from prescribed time	Mean number of occasions Ia taken >1 hour from prescribed time
Earlier	1.0 hour	1.5 hours	3.5
Later	1.5 hours	4.0 hours	3.1

Table 2

Reasons for taking medications later than prescribed by frequency within occasion and individual*

Reasons	Occasions Reported N = 32 n (%)	Individuals Reported N = 11 n (%)
Healthcare structural factors	10 (31.3)	7 (63.6)
Sleeping/Slept in	8 (25.0)	5 (45.5)
Away from home	6 (18.8)	4 (36.4)
Work-related barriers	4 (12.5)	3 (27.3)
Forgot/Inattention	4 (12.5)	2 (18.2)

* Percentages add up to more than 100 because respondents took medications later on more than one occasion.