

Non-Adherence – The Scope of the Problem

One of the most important and most impactful components of healthcare is adherence to clinicians' prescriptions and recommendations. Reflecting the degree to which a patient follows directions and complies with treatment, medications and clinical surveillance, the degree of adherence inarguably influences outcomes.

Adherence is unquestionably essential post-transplant. In large part, this is due to the natural immune system responses and the unrelenting risk of organ rejection and other consequences of non-adherence (NA). Adherence goes beyond the unflinching need for accurate self-administration of medications, which must be taken at the correct dose and correct time and for as long as needed. Adherence also requires other actions such as:

- compliance with post-transplant responsibilities surrounding infection and rejection prevention
- avoidance of the sun and other lifestyle requirements
- ongoing, long-term follow-up with appropriate clinicians

Extensively studied, NA is a significant healthcare problem, particularly in patients with chronic diseases. In a landmark publication, Osterberg and Blaschke reported that more than half of prescriptions in the United

States are not taken as directed.¹ Total direct and indirect costs of poor medication adherence have been estimated to add \$290 billion to healthcare costs per year.²

The more chronic conditions a patient has, the greater and more non-linear the economic impact of NA. In one recent study, patients with three or more chronic conditions had up to seven times more cost savings when they were adherent to their medications, compared to patients who had only one or two chronic conditions.³ This may well apply to transplantation given that post-transplant comorbidities are common. In particular, this is due to a suppressed immune system in transplant patients, and the multiple potential medication adverse effects and related medication needs to treat those effects.

“Drugs don't work in people who don't take them.”

– *Former Surgeon General C. Everett Koop*

Poor medication adherence is related to approximately 125,000 deaths and up to 25% of hospital and nursing home admissions each year.⁴ Unfortunately, the rates of poor adherence remain high.⁵

Adherence Post-Transplant

While controversial, adequate or acceptable adherence in the general patient population has been defined as taking 80% to 120% of the medication prescribed.⁶⁻⁹ In the transplant arena, however, it has been clearly established that **life-long, consistent, and accurate** adherence to a prescribed immunosuppressive regimen is a pre-requisite for sustained graft function. Thus, the definition of adequate compliance has to be 100%.

Even minor medication adherence infractions, whether intentional or accidental, consistent or occasional, have significant predictive value for worse clinical and economic outcomes in transplant recipients. Unfortunately, “minor infractions” are not clearly defined, but it is important to recognize that complete adherence is essential. Non-adherent patients experience earlier and more frequent rejection episodes, hospitalizations, late acute rejection, and graft loss before death.¹⁰⁻¹² Early post-transplant NA is associated with lower graft survival in both the short- and longer-term.¹³ In fact, evidence suggests that poor medication adherence may be the most important mediator of late acute rejection, antibody-mediated rejection, and graft failure.¹⁴⁻¹⁷

One set of authors went so far as to say that increasing the effectiveness of adherence interventions might have a far greater impact on the long-term outcomes of renal transplants than any improvement in specific medical treatments.¹⁸ Unfortunately, overall NA rates reported in the transplant population range from about 20% to 50% or more.^{17,19}

Adherence is complicated, however, in terms of defining, identifying and impacting. There is inherent difficulty in measuring non-adherence. Self-reporting has the potential to under-represent missed medication doses and

other care requirements. Measuring blood levels, while often a red flag for non-adherence, is not definitive. In one study, 54% of patients self-reported missing medication doses. They did not have blood levels drawn. In patients who did have blood levels drawn, 15% were determined to have been non-adherent based on the serum levels. These results speak to the likelihood of a significant percent of patients being non-adherent but taking their medication just before a clinic visit.¹⁷

Despite the rate of NA, 90% of patients reported knowing the consequences of not taking their medications on their graft outcomes.¹⁷ So, even when they are aware of the risks, the percent of NA in patients remains high.

Poor medication adherence may be the most important mediator of late acute rejection, antibody-mediated rejection, and graft failure.

adolescent phase presents an excellent example. Adolescence is a time to individuate, to work towards autonomy. The adolescent is looking for individual freedom rather than external control. The adolescent is sensitive to any perceived threat to social well-being and has a strong need to feel “normal”. Peer pressure is often exceedingly influential. Adolescents are concerned about appearance. Adolescence is also a time of activity and exploration. As stated by one adolescent transplant recipient, “The combination of hormones, puberty and the truly life-altering event of the kidney transplant was a lot to manage while trying to be an average teenager.”²⁵

Relationships between parents and adolescents are changing in this phase. The teenager has a need to take control of his or her actions and may do so at the expense of compliance with the prescribed care regimen. Parents often have difficulty delegating responsibility for self-management to their child, especially the child for which compliance is so critical. Some treatment regimens require complex cognitive abilities such as executive functioning or delay of gratification, behavior that may be difficult for the average adolescent.²⁵

Adolescents are typically socially active, with frequent changes in plans and schedules. Forgetfulness is one of the more common self-identified reasons for medication NA in adolescents (as well as adults), in large part due to frequent and last-minute changes in

Table 1

Factors Influencing Non-Adherence ²⁰⁻²⁴	
Category	Factors
Patient-centered factors	Demographics, e.g., age, ethnicity, gender, education, marital status
	Psychosocial factors, e.g., beliefs, motivation, attitudes
	Patient-prescriber relationship
	Patient knowledge
	Physical difficulties
	Forgetfulness
	Adherence history
	Time since transplant
Therapy-related factors	Route of administration
	Complexity of medication regimen
	Duration of the treatment period
	Medication adverse effects
Healthcare system factors	Degree of behavioral change required
	Accessibility
	Difficulty getting prescriptions filled
Social and economic factors	Cost and income
	Social support
	Change in routine
Disease factors	Disease symptoms (or lack of)

Reasons for Non-Adherence

The potential reasons for NA are as numerous and varied as are the patients themselves (see Table 1). Each patient is unique in terms of the factors, or combination of factors, that influence their decision-making. These factors may change throughout their transplant journey. Patients may be cognizant of some of the reasons for their NA; others reasons may be subconscious.

It is beyond the scope of this educational program to review each of the factors listed in Table 1, and how they might relate to transplant. But although this is not a complete list, several important factors can be called out.

Age – Particular Issues with Adolescence

Transitioning into and through the normal developmental stages, each with its unique impact and goals, is necessary and essential. Often, however, the developmental needs are in conflict with the requirements of the medical regimen. The

plans.^{24,25} Preparing patients for the likelihood of practical barriers to adherence, such as forgetfulness and missing medications when one's routine is different, is important to minimize its impact.

For example, patients should be prepared to know:

- What to do if they forget a dose of a specific medication?
 - Do they make up that forgotten dose?
 - How close together can they take the forgotten dose before the next scheduled dose?
- They should always have back-up medications in a backpack, purse, at work, in a cooler in the car, etc.
- Who they should call if they forget a dose?

Therapy Complexity

A perceived lack of time and a confusing, frequently adjusted medication schedule can affect compliance. Compliance is reportedly inversely proportional to the number of times a patient must take medications a day. For example, while not specifically related to transplant, for medication taken only once a day, the average compliance rate is a reported nearly 80%. For medications prescribed four times a day, the average drops to about 50%.²⁶ Neither rate is acceptable for the post-transplant patient.

Numerous prescribed and over-the-counter medications and supplements can alter the absorption of the patient's immunosuppressants, either lowering levels and decreasing the serum concentration or increasing levels and contributing to drug toxicity. Therefore, patients should be instructed not take anything new without consulting with their transplant team. Inadvertent or accidental noncompliance happens

if a patient takes something that does, in fact, change their serum immunosuppressant concentration.

Length of Time Since Transplant

Length of time post-transplant seems to impact compliance, with diminishing adherence the further the patient is post-transplant.^{14,23} Self-reported adherence, measured using the Basel Assessment of Adherence to Immunosuppressive Medications Scale Interview, has shown that NA significantly increased over time reaching 31% at 18 months post-transplant. Contributions to the NA included a lower perceived necessity of medication, impact of the transplant on life (consequences) and the emotional response to transplantation.²³

Knowledge

Non-adherence is significantly associated with the recipient's beliefs or concerns about immunosuppressive agents. Adherent recipients believe in the necessity of their medications more than do patients who are non-adherent. Non-adherent recipients have greater concerns about taking their medications and believe they have less control over their lives.²⁸

Depression

Depression and lesser degrees of life satisfaction may be significant risk factors for NA, particularly intentional NA. Both retrospective and prospective studies of kidney graft recipients report an association between

The word "compliance" does not even exist in the teenage language or thought process...

– Transplant recipient reflecting on teenage years²⁵

When I first came home, I was taking six prescription medications. Some of them I took four times a day, some I took two times a day. For some, I need to take four tablets. Others I took two tablets or one tablet. Altogether, I was taking about 27 or 28 pills a day at first. The good news is that you only have to take some of those pills for a couple of months. Now, I only take three prescription medications: two anti-rejection pills and one blood pressure pill because the anti-rejection medicine has made my blood pressure go up. So, now I only take seven pills each day — four in the morning and three at night.²⁷

– Patricia, liver transplant recipient

NA and depression.²⁹⁻³¹ However, the impact of sociodemographic factors must also be considered.²⁴

Measuring Non-Adherence

As stated above, measuring and monitoring NA is challenging for several reasons including logistics, costs, and being able to recognize underlying patient-specific influences. For example, direct observation of medication self-administration would be accurate – but impractical at best. Measuring trough levels can provide some objective information, but only on recent adherence. If the patient missed doses but took them the day of or before serum testing, the missed doses might not be evident. In addition, multiple factors can influence serum levels so it is difficult to discern cause for abnormal levels without trending.

One can evaluate prescription fills/refills, or monitor use via electronic pill bottle caps that record the opening of the bottle. However, such efforts can only assume compliance or that the patient is actually taking the medication.

It is helpful for patients to bring their pill box to each clinic visit. This provides opportunity to see just what the patient is taking and if any errors in their dosing are happening. This should include over-the-counter medications and supplements as well.

Creating a judgment free environment is also critical. Patients should be assured that there is no wrong answer, and that it is important that they be truthful about any non-adherence, for any reason. This allows the clinicians to address their risk, conduct a root cause analysis, and work to develop interventions that will support their adherence.

Immunosuppressant Therapy Adherence Scale (ITAS)

The Immunosuppressant Therapy Adherence Scale (ITAS), an instrument developed to measure adherence to immunosuppressive regimens, is considered a reliable and valid tool.^{32,33} The four-point scale asks:

In the past three months, how often:

1. Did you forget to take your immunosuppressant medications?
2. Were you careless about taking your immunosuppressant medications?
3. Did you stop taking your immunosuppressant medications because you felt worse?
4. Did you miss taking your immunosuppressant medications for any reason?

Response choices were:

- 0% of the time
- 1-20% of the time
- 21-50% of the time
- > 50% of the time

While important and informative, self-reporting may be limited by inaccurate recall and/or an over-estimates of adherence depending in part on the patient's willingness to be transparent.

Interventions to Prevent Non-Adherence

Just as there are so many dynamic factors impacting a patient's adherence throughout their transplant journey, so are there potential ways to intervene. Careful evaluation of key patient-specific factors, including the recipient's demographics, beliefs, psychosocial state, cognitive abilities, adherence history and co-morbidities are critical. Patient education, with emphasis on and restatement of the need for absolute adherence, and risks of NA, is an essential foundation. Patients typically have every intention to adhere, but intention may well play only a minor role in ultimate adherence.³⁰ Multidimensional interventions are required.

A study by Chisolm-Burns et al detailed the positive clinical and economic impact of a multifactorial approach with appropriately designed multidimensional interventions. Interventions that are informational (review the consequences of NA), behavioral (identify routines, tools or strategies to increase adherence), and emotional (enhanced patient motivation) are associated with a higher adherence rate.¹² Similarly positive is the impact of an education program — above and beyond the standardized transplant training by the transplant

physicians and nurses — with intensified patient counseling by a dedicated clinical pharmacist, often both prior to discharge and for several months during transplant clinic visits.

Another study showed that by combining educational, behavioral, and motivational interventions, the applied multifactorial pharmaceutical care was associated with an improvement of drug adherence in the intervention group (91% vs. 75%).³⁴ Additional research points to the benefit of targeting adherence interventions to patients based on their adherence history and co-morbidities.³

References

1. Osterberg L, Blaschke T. Adherence to medication. *NEJM*. 2005; 353(5):487-497.
2. Healthcare Intelligence Network. 2010 Benchmarks in Improving Medication Adherence. *HIN*. N.p., May 2010. Web. Feb. 2011. http://store.hin.com/2010-Benchmarks-in-Improving-Medication-Adherence_p_4006.html#. Accessed August 17,2016.
3. Kymes SM, Pierce RL, Girdish C, Matlin OS, Brennan T, Shrank WH. Association among change in medical costs, level of comorbidity, and change in adherence behavior. *Am J Manag Care*. <http://www.ajmc.com/journals/issue/2016/2016-vol22-n8/Association-Among-Change-in-Medical-Costs-Level-of-Comorbidity-and-Change-in-Adherence-Behavior>. Published online August 22, 2016. Accessed August 22, 2016.
4. Fleming WK. Pharmacy management strategies for improving drug adherence." *J Managed Care Pharmacy*. 14.6-b Supplement (2008):n. pag. Web. Feb. 2011. http://www.amcp.org/data/jmcp/JMCPSuppB_S16-S20.pdf.
5. Honigberg R, Gorden M, Wisniewski AC. Supporting patient medication adherence: ensuring coordination, quality and outcomes. *URAC*. 2011. http://adhereforhealth.org/wp-content/uploads/pdf/URAC-MedAdherence_WP.pdf. Accessed January 4, 2014.
6. Sackett DL, Haynes RB, Gibson ES, Hackett BC, Taylor DW, Roberts RS, Johnson AL. Randomised clinical trial of strategies for improving medication compliance in primary hypertension. *Lancet*.1975;1:1205-1207.

7. Monane M, Bohn RL, Gurwitz JH, Glynn RJ, Levin R, Avorn J. Compliance with antihypertensive therapy among elderly Medicaid enrollees: the roles of age, gender, and race. *Am J Public Health*.1996;86:1805–1808.
8. Avorn J, Monette J, Lacour A, Bohn RL, Monane M, Mogun H, LeLorier J. Persistence of use of lipid-lowering medications: a cross national study. *JAMA*.1998;279:1458–1462.
9. Hope CJ, Wu J, Tu W, Young J, Murray MD. Association of medication adherence, knowledge, and skills with emergency department visits by adults 50 years or older with congestive heart failure. *Am J Health Syst Pharm*. 2004;61:2043–2049.
10. Nevins TE, Thomas W. Quantitative patterns of azathioprine adherence after renal transplantation. *Transplantation*.2009;87:711–718.
11. Pinsky BW, Takemoto SK, Lentine KL, Burroughs TE, Schnitzler MA. Transplant outcomes and economic costs associated with patient noncompliance to immunosuppression. *Am J Transplant*.2009;9:2597–2606.
12. Chisholm-Burns MA, Spivey CA, Graff Zivin J, Lee JK, Sredzinski E, Tolley EA. Improving outcomes of renal transplant recipients with behavioral adherence contracts: a randomized controlled trial. *Am J Transplant*.2013;9:2364–2373.
13. Tiele M, van Exel J, Laging M, Beck DK, Khemai R, van Gelder T, et al. Attitudes to medications after kidney transplantation and their association with medication adherence and graft survival: a 2-year follow-up study. *J Transplant* 2014.doi 10.1155/2014/675301. Ihttp://www.ncbi.nlm.nih.gov/pmc/articles/PMC4020188/Epublished April 28, 2014. Accessed June 10, 2016.
14. Gaynor JJ, Ciancio G, Guerra G, et al. Graft failure due to noncompliance among 628 kidney transplant recipients with longterm follow-up: a single-center observational study. *Transplantation*.2014;97(9):925–933.
15. Sellares J, de Freitas DG, Mengel M, et al. Understanding the causes of kidney transplant failure: the dominant role of antibodymediated rejection and nonadherence. *Am J Transplant*.2011;12(2):388–399.
16. Dobbels F, Ruppert T, De Geest S, Decorte A, Van Damme-Lombaerts R, Fine RN. Adherence to the immunosuppressive regimen in pediatric kidney transplant recipients: a systematic review. *Pediatr Transplant*.2010;14(5): 603–613.
17. Prendergast MB, Gaston RS. Optimizing medication adherence: an ongoing opportunity to improve outcomes after kidney transplantation. *Clin J Am Soc Nephrol*.2010;5(7):1305–1311.
18. Moreso F, Torres IB, Costa Requena G, Seron D. Nonadherence to immunosuppression:challenges and solutions. *Transplant Res Risk Mgmt*.2015;2015(7):27–34.
19. Laederach-Hofman K, Bunzel B. Noncompliance in organ transplant recipients: a literature review. *Gen Hosp Psychiatry*.2000;22(6):412–414.
20. Jing J, Sklar GE, Oh, VMS, Li SC. Factors affecting therapeutic compliance: a review from the patient’s perspective. *Clin Risk Manag*.2008;4(1):269–286.
21. Serper M, Patzer RE, Reese PP, Przytula K, Koval R, Ladner DP, et al. Medication misuse, nonadherence, and clinical outcomes among liver transplant patients. *Liver Transp*. 2015;21(1):22–28.
22. Hugon A, Roustit M, Lehmann A, Saint-Raymond C, Borrel E, Hilleret MN, et al. Influence of intention to adhere, beliefs and satisfaction about medicines on adherence in solid organ transplant recipients. *Transplantation*.2014;98(2):222–228.
23. Massey EK, Tielen M, Laging M, Timman R, Beck DK, Khemai R, et al. Discrepancies between beliefs and behavior: a prospective study into immunosuppressive medication adherence after kidney transplantation. *Transplantation*.2015;99(2):375–380.
24. Weng FL, Chandwani S, Kurtyka KM, Zacker C, Chisolm-Burns MA, Demissie K. Prevalence and correlates of medication non-adherence among kidney transplant recipients more than 6 months post-transplant: a cross-sectional study. *BMC Nephrology*.2013;14:261–270.
25. Wu MH. Medication compliance. National Kidney Foundation website. https://www.kidney.org/transplantation/transaction/TC/summer11/TCsummer_11_MedicationCompliance. Accessed June 10, 2016.
26. Claxton AJ, Cramer J, Pierce C. A systematic review of the associations between dose regimens and medication compliance. *Clin Ther*.2012;23:1296–1310.
27. <http://www.uchospitals.edu/specialties/transplant/stories/patricia.html>. Accessed August 30, 2016.
28. Chisolm-Burns, Hugon, Massey, Sellares J, de Freitas DG, Mengel M, et al. Understanding the causes of kidney transplant failure: the dominant role of antibodymediated rejection and nonadherence. *Am J Transplant*.2011;12(2):388–399.
29. Chilcot J, Spencer BWJ, Maple H, Mamode N. Depression and kidney transplantation. *Transplantation*. 2014;97:717–772.
30. Griva K, Davenport A, Harrison M, Newman SP. Non-adherence to immunosuppressive medications in kidney transplantation: intent vs forgetfulness and clinical markers of medication intake. *Ann Behav Med*.2012;44:85–93.
31. Chisolm-Burns M, Pinsky B, Parker G, Johnson P, Arcona S, Buzinec P, et al. Factors related to immunosuppressant medication adherence in renal transplant recipients. *Clin Transplant*.2012;26(5):706–713.
32. Chisolm MA, Lance CE, Williamson GM, Mulloy LL. Development and validation of the immunosuppressant therapy adherence instrument (ITAS). *Patient Educ Couns*.2005;59(1):13–20.
33. Wilks SE, Spivey CA, Chisolm-Burns MA. Psychometric re-evaluation of the immunosuppressant therapy adherence scale among solid-organ transplant recipients. *J Eval Clin Pract*.2010;16(1):64–68.
34. Joost R, Dörje F, Schvittulla J, Eckardt KU, Hugo C. Intensified pharmaceutical care is improving immunosuppressive medication adherence in kidney transplant recipients during the first post-transplant year: a quasi-experimental study. *Nephrol Dial Transplant*. 2014;29(8):1597–1607.

Self-Assessment Quiz: Non-Adherence – The Scope of the Problem

LEARNING GOAL

Gain an appreciation for the clinical and economic impact non-adherence in the post-transplant recipient.

LEARNING OBJECTIVES

After reviewing this publication, each participant should be able to:

1. Describe the clinical and economic impact of non-adherence in the post-transplant patient population.
2. Identify 3 key risk factors for non-adherence post-transplant.
3. Describe factors to be considered to promote adherence when developing a transplant recipient care plan.

SELF-ASSESSMENT QUESTIONS

In the Quiz Answers section on the next page, circle the correct answer for each question. To obtain two (2.0) contact hours toward CE credit, the passing score is 100%. Return your Self-Assessment Quiz to Coram via email, fax or mail. See the next page for details on how to return to your quiz. Please allow approximately seven days to process your test and receive your certificate upon achieving a passing score.

1. All of the following statements are true EXCEPT
 - a. Adherence refers only to the post-transplant patient's prescribed medication regimen.
 - b. Non-adherence has a significant predictive value of worse outcomes.
 - c. Non-adherence may be unintentional.
 - d. Intermittent non-adherence can negatively impact long-term transplant success.
2. _____ conditions are more likely to influence adherence.
 - a. Acute
 - b. Chronic
3. Adherence has been shown to be _____ the more frequently medication dosing is required.
 - a. Greater
 - b. Lesser
4. Self-reporting adherence may _____-represent missed medication doses.
 - a. Over
 - b. Under
5. Potential risk factors for non-adherence in the adolescent population include:
 - a. Developmental need for autonomy
 - b. Forgetfulness
 - c. Peer pressure
 - d. Cognitive abilities
 - e. All of the above
 - f. A, B, and C
6. The degree of adherence tends to improve over time (post-transplant).
 - a. True
 - b. False
7. Potential risk factors for non-adherence in the post-transplant population include:
 - a. Depression
 - b. Forgetfulness
 - c. Socioeconomic factors
 - d. Patient perception of medication benefits
 - e. All of the above
 - f. A, B, and C
8. Reasons for adherence throughout the transplant journey
 - a. Tend to remain the same for patients since patient's don't tend to change much
 - b. Tend to change as patient factors change
 - c. Are predictable
9. Intent to adhere is a strong predictor of post-transplant adherence.
 - a. True
 - b. False
10. Multi-dimensional interventions associated with greater adherence incorporate all of the following EXCEPT
 - a. Information
 - b. Behavior
 - c. Punishment
 - d. Emotion

Non-Adherence – The Scope of the Problem

QUIZ ANSWERS

Fill in the key below with the correct answers to receive 2.0 Continuing Education credits.*

- 1.
- 2.
- 3.
- 4.
- 5.
- 6.
- 7.
- 8.
- 9.
- 10.

*Accreditation Information

- Provider approved by the California Board of Registered Nursing, Provider Number 15200 for 2.0 contact hours.
- Coram CVS Specialty Infusion Services is approved by the Delaware Board of Nursing, Provider Number DE-14-010517.
- Coram CVS Specialty Infusion Services is approved by The Commission for Case Manager Certification to provide continuing education credit to CCM® board certified case managers.
- Coram CVS Specialty Infusion Services is an approved provider for the American Board for Transplant Certification (ABTC). Coram CVS Specialty Infusion Services will grant one Continuing Education Point for Transplant Certification (CEPTC) for this offering. Provider Number 147.

© 2017 Coram LLC | COR16069-0117

To obtain Continuing Education credits, please complete this information in full. Please print clearly.

Name: _____

Address: _____

City: _____ State: _____ Zip: _____

License Number (required to receive CEs): _____

RN LPN Certified Case Manager

Employer: _____

Work Phone: _____

Coram Representative: _____ Date: _____

Was this material:

Useful in your practice? Yes No

Comprehensive enough? Yes No

Well organized? Yes No

Certificate delivery:

I would like my certificate mailed to the address provided above.

I would like my certificate emailed to me at: _____
(ex: john.smith@coramhc.com)

RETURN THIS PAGE TO CORAM VIA:

Mail: Coram's CE Department
12600 E Arapahoe Road, Suite A
Centennial, CO 80112

Fax: 949.462.8990

SUBMIT FORM VIA EMAIL: CEDept@coramhc.com

