Published in final edited form as:

Curr Opin Organ Transplant. 2010 October ; 15(5): 614–620. doi:10.1097/MOT.0b013e32833d3115.

Adherence to immunosuppressants: How can it be improved in adolescent organ transplant recipients?

Emily M. Fredericks, PhD and Dawn Dore-Stites, PhD

Department of Pediatrics, University of Michigan Health System

Abstract

Purpose of review—Nonadherence among pediatric transplant recipients is prevalent, with rates as high as 75% among adolescents. These rates are alarming given that adherence behavior has the potential to be modified. This review examines evidence from recent studies and position statements to determine the current issues related to improving medication adherence in adolescent transplant recipients.

Recent findings—To date, there are no empirically-validated treatments to promote adherence in pediatric transplant recipients. Yet, interventions in other chronic illness populations suggest that combined education and behavioral strategies are most effective in improving medication adherence. The use of technology, such as the internet and cellphones, provides a promising mechanism for delivering adherence promoting interventions to adolescents. Preliminary studies in pediatric solid organ transplant suggest that interventions focused on targeted education and behavioral cues using cellphone text messages are promising strategies for promoting medication adherence.

Summary—Strategies for promoting adherence in adolescent transplant recipients should include developmentally appropriate models and should incorporate health-related education, motivational strategies, and behavioral skills. Interventions should be tailored to meet the individual needs, and should be a collaborative effort between the adolescent, family and health care providers.

Keywords

Adherence; Pediatric Transplantation; Adolescence; Self-Management

Introduction

The prevalence of nonadherence among pediatric transplant recipients ranges from 5-80% with adolescents having the highest rates of nonadherence (1-4). These rates are striking given the potential for adverse outcomes. Nonadherence to post-transplant medications is associated with serious consequences including graft rejection, post-transplant mortality, poor health-related quality of life and increased health care costs (5-9). Moreover, medication nonadherence may negatively impact long-term health outcomes, particularly during the transition from pediatric to adult-centered care (10, 11). Given that adolescents are at high risk for nonadherence (12) and associated late graft loss (13), interventions aimed at promoting medication adherence in this population are urgently needed.

Assessment of Medication Adherence in Transplantation

Before interventions targeting adherence can be implemented, it is necessary to incorporate adherence assessment into standard clinical care. It is generally agreed that to increase the likelihood of favorable outcomes in transplantation, nearly perfect (i.e., 100%) adherence should be the goal, as minor deviations from a dosing schedule are associated with negative outcomes (14, 15). Based on a recent nonadherence consensus conference, nonadherence was defined as the “deviation from the prescribed medication regimen sufficient to influence adversely the regimen’s intended effect”(16). Yet, to date, studies of medication adherence in pediatric transplantation are limited by a lack of an accepted “gold standard” method for assessing adherence.

Medication adherence can be measured using various strategies. Patient/caregiver self-reports may be the least costly and most feasible way to monitor adherence; however, self-reported adherence is often less accurate (17). Electronic medication monitoring technology, such as the Medication Event Monitoring System (MEMS®; Aprax Corporation), is considered a recommended measure in adherence research (18). MEMS® technology provides continuous data and allows for the detection of temporal patterns of adherence. Yet, barriers associated with MEMS® technology include cost and the possibility that these devices may interfere with established adherence-promoting routines, such as the use of pillbox organizers (19).

Recent studies have attempted to measure adherence objectively using the degree of fluctuation (i.e., standard deviation, SD) of medication blood levels of tacrolimus in pediatric liver transplant recipients (5, 12, 20, 21). Higher SDs were predictive of clinical outcomes, such as biopsy-proven rejection (12, 20, 21) and hospitalizations (5). Variability in the blood levels of the immunosuppressant cyclosporine has also been associated with increased risk of rejection in pediatric heart transplant recipients (22). Blood levels of cyclosporine or tacrolimus that were out of the therapeutic range have also been shown to be indicators of poor adherence (23).

Each approach to measuring medication adherence has strengths and weaknesses, suggesting a need for a multi-method assessment strategy (24). A recent study showed that a multi-method approach which included self-report, drug assays and clinician report yielded the highest sensitivity (72%) and specificity (42%) when compared to electronic monitoring alone (25). Future studies should focus on developing a standardized method for assessing medication adherence in transplant recipients. In the meantime, it is recommended that health care providers employ strategies that can be incorporated into standard clinical care including self-report (26) and routine monitoring of the variability in immunosuppressant blood levels assays (21).

Risks and Barriers to Adherence: Potential Targets for Intervention

A recent meta-analysis examining predictors of nonadherence in pediatric transplant recipients revealed very strong associations between nonadherence and psychosocial variables (e.g., psychiatric co-morbidities; child responsibility for medication) with magnitude of effect sizes ranging from large to very large (4). Indeed, medication nonadherence has been linked with inadequate regimen knowledge, depression and anxiety, poor health-related quality of life, low social support, substance abuse, life stress, barriers to medication access and poor physician-patient relationship (3, 5, 6, 27-29). Specific to adolescent transplant recipients, medication nonadherence is associated with increased disease frustration, poor regimen adaptation/cognitive issues, difficulty with ingestion (e.g., number of medications, taste), and lack of parental monitoring and involvement (30-32). Many of these predictors are modifiable and can be directly targeted through intervention.

Unfortunately, there is a lack of research investigating the impact of intervention on medication adherence in adolescent transplant recipients.

Meta-Analyses of Adherence Promoting Interventions

As demonstrated above, medication nonadherence is a complex, multifaceted problem. Thus, it is logical to assume that interventions must be multifactorial. Results from two recent meta-analyses indicate that multi-component interventions including education, parental involvement, self-monitoring, reinforcement and problem-solving have been most successful in promoting adherence to chronic regimens, subsequently leading to improved health outcomes (33, 34). These meta-analyses suggest that adherence interventions are generally successful, with small to moderate effect sizes, though the effectiveness of interventions is influenced by methodological and participant characteristics.

Of the 122 unique studies included in the above meta-analyses, only 4 included pediatric transplant recipients, reflecting the lack of interventions targeting medication adherence in this population. Further, none are considered empirically validated. Research with other pediatric populations, especially those with similar regimens, provides useful models to guide the development and implementation of interventions for adolescent transplant recipients.

Information-Motivation-Behavior Model of Health Behavior Change

The Information-Motivation-Behavior (IMB) model of health behavior change used to conceptualize adherence to antiretroviral therapy in HIV populations provides a foundation for adherence intervention that is grounded in empirical research (35). The IMB model incorporates three factors—Information, Motivation and Behavior—that are necessary, yet individually insufficient for understanding and promoting adherence behavior and health-related outcomes (36). Specifically, the IMB model posits that engaging in health promotion behavior (e.g., medication taking) is a function of the extent to which someone is well informed, motivated, and has the requisite skills and confidence to execute the behavior across various situations. The model acknowledges that the factors exist in a context of risk and resiliency at individual, family and system levels. Interventions aimed at improving information, motivation and behavioral skills are described in the following sections (Table 1).

Information and Health-related Knowledge

The Information domain relates to the content of health-related education provided to patients and their families. The overall goal of health-related education is to increase knowledge about diseases, treatments and the importance of adherence to regimens. Communication and retention of this wide array of health-related information is influenced by an individual's health literacy. Health literacy is defined as "the degree to which individuals have the capacity to obtain, process and understand basic health information and services needed to make appropriate health decisions (37)." Research suggests that low health literacy is associated with adverse health outcomes, including increased mortality, hospitalizations, poorer disease-specific knowledge and outcomes, and decreased utilization of preventive health services (38). Thus, the promotion of health education and health literacy should be considered a vital component of health care programs.

Early research in pediatric liver transplant suggests that interventions focused on targeted education are promising. Shemesh and colleagues examined the effectiveness of their clinical protocol, which involves increasing the frequency of clinic visits and adding targeted education about the importance of adherence for patients identified as being

nonadherent (39). Preliminary findings were promising and suggested that this strategy lead to significant improvements in liver function tests and a trend toward decreased rejection episodes and increased medication adherence. Larger, multi-center trials are warranted to determine if similar clinic-based education interventions can improve medication adherence and health outcomes in adolescent transplant recipients.

Motivation and Readiness for Change

The inadequacy of targeting information alone in promoting adherence has been well demonstrated (40). The role of motivation and an individual's readiness for behavior change must also be considered. Motivational Interviewing (MI) is a tailored, patient-centered approach to health behavior change that helps patients resolve ambivalence about change, build intrinsic motivation for change, and facilitate collaborative decision-making prior to implementing education and problem-solving strategies (41).

MI may be developmentally appropriate for adolescents because it promotes personal control and autonomous decision-making for change, focuses on individualized goals and values and their relation to the target behavior, and is tailored to the adolescent's readiness to change. MI strategies focus on an assessment of the current level of problem acceptance and treatment acceptance, exploration of wishes, beliefs and feelings, and options for resolving ambivalence about change or treatment (42). MI does not assume that health is the most important factor motivating the adolescent. Using MI, health care providers can collaborate to develop an adherence plan that is tailored to the adolescent's preferences and treatment needs. Techniques of MI have been shown to be effective in enacting behavior change in adolescents and adults, including adherence to chronic illness regimens (43-46).

Behavioral Skills

The Behavioral Skills domain encompasses the fundamental repertoire of skills critical to medication adherence including communication, organizational, and problem-solving skills (47-49). Previous research with other pediatric groups suggests that multi-component interventions that include behavioral skills such as self-monitoring, reinforcement and problem-solving have been most successful in promoting adherence to chronic regimens (33, 47, 50).

To maximize medication adherence, it is important that adolescents have the ability to identify and problem-solve barriers to adherence. A commonly cited reason for medication nonadherence is "forgetting" (51). In a study examining medication barriers, adolescent transplant recipients and their parents indicated that cognitive barriers (e.g., poor planning/scheduling and forgetfulness) were some of the most prominent obstacles to taking medication as prescribed (30, 52). Interventions that target organizational behaviors, including the use of behavioral cues (e.g., pillboxes, reminders) are likely to be effective with this group.

A review of adherence interventions in adult populations found that the most common and effective forms of behavioral intervention were dosage simplification and repeated assessment of medication use with feedback (53). However, simplification of the treatment regimen with once-daily dosing poses challenges in a population with adherence difficulty. For example, missing a once-daily dose means 24 hours without immunosuppressant medications, whereas missing 1 dose of twice-daily regimens means only 12 hours uncovered. For nonadherent adolescents, identification and problem-solving barriers may be a more appropriate intervention with less likelihood of medication omission.

Parental Monitoring and Responsibility for Health Care Tasks

IMB addresses many of the individual (i.e. patient or parent) factors related to adherence. For adolescents, the *relationship* between parents and adolescents is also critical as there is a shift in responsibility for medical tasks from parent to adolescent which is essential to promoting adherence (54). A recent report suggests that adolescent liver transplant recipients are inconsistent with their health management tasks (55), and would likely benefit from increased monitoring and supervision during the transition of healthcare responsibility from parent to teen. Indeed, research has demonstrated that increased parental monitoring is associated with improved adherence and health outcomes in adolescents with diabetes (56, 57), HIV (58), asthma (59) and liver transplants (32). Thus, interventions should focus on the role of parental monitoring and supervision of medication related tasks as adolescents begin to demonstrate mastery of health management tasks.

Health Care Provider Behavior

In addition to family relationships, the patient/parent-provider relationship also impacts adherence and health outcomes. Most research in this area has focused on conflict between parents and health care providers (60), and has identified trust and satisfaction with psychosocial aspects of health care as related to treatment adherence (61). Unfortunately, studies exploring relationships between adolescents and their medical care providers are scarce. Those studies that do exist suggest that among adolescents, satisfaction in health care is related to provider characteristics, with trust and honesty being the most influential (62-64). Adolescents place greater trust in a physician who preserves confidentiality, remains honest and respectful and exudes competence (62). Increased trust in providers influences adherence and utilization of health care services (62, 63).

Based on a recent review of physician behavior in the management of chronic illness, parents and children have identified gaps in physician behavior and communication, which may impact medication adherence and management of chronic conditions (65). Thus, interventions aimed at improving physician communication and behavior are also warranted. Specifically, health care providers are responsible for the delivery of health-related information, fostering motivation, assisting their patients with the behavioral skills necessary for adherence, and collaborating on plans for chronic illness management. Future research should examine the impact of tailored physician communication and motivational strategies on medication adherence in adolescents.

Future Directions: The Use of Technology in the Promotion of Adherence

Adherence promoting interventions have been moderately effective in other pediatric chronic illness groups. Yet, these interventions are often time-intensive (66). Many transplant recipients do not have access to outpatient behavioral health services due to lack of trained clinicians, expense, competing work/school schedules, and travel distances as transplant centers are geographically dispersed. Also, with increased time post-transplantation, patients may return to clinic infrequently, which impacts the feasibility of a face-to-face intervention. In clinical settings, time and resource constraints demand the consideration of technology to facilitate the acquisition of the skills needed to independently manage regimen tasks. As such, internet-based and cellphone interventions ("eHealth") are increasingly being used to promote medication adherence. Thus, in developing strategies to promote adherence among adolescent transplant recipients, consideration should be given to the use of technology, as cellphones, text messaging, and the internet are ubiquitous among adolescents of all socio-economic groups (67-69).

A systematic review of health care interventions using cellphone technology revealed that enhancing standard care with reminders, disease monitoring and management, and education through the use of cellphone voice and text messaging can help improve health outcomes (70). In addition, results from a recent meta-analysis of pediatric eHealth interventions revealed that those that used behavioral methods (e.g., self-monitoring, goal setting, contingency management) produce larger effect sizes for health behaviors and their associated outcomes than interventions that only incorporate educational strategies (71). This is consistent with the findings from traditional face-to-face interventions (33, 34).

Technology-based interventions present unique opportunities for health care providers to interact with adolescents, using a means that is acceptable and continuously available to this population (72-74). Indeed, adolescent transplant recipients have reported interest in communicating with health care providers via text-messaging on cellphones or by e-mail (51). To that degree, researchers found that sending text messages that displayed reminders to administer immunosuppressant medications to the primary medication administrator significantly improved adherence to immunosuppressant medication as measured by standard deviations of serum immunosuppressant levels in pediatric liver transplant recipients (75).

Interventions delivered using newer technologies, such as cellphone text messages and the internet, may be a promising strategy for promoting medication adherence in adolescents. Further investigation of the sustainability and effectiveness of these innovative eHealth interventions is needed.

Conclusion

Adolescent transplant recipients have a high rate of medication nonadherence, which places them at increased risk for medical complications including rejection and graft loss. Research suggests that combined interventions incorporating health-related education, motivation and behavioral strategies are most effective in promoting medication adherence; however, there is a lack of empirically validated interventions specific to the transplant population. Using other diseases as models, it is apparent that the effectiveness of interventions is moderated by participant characteristics (e.g. motivation, health literacy). Interventions to promote medication adherence should be tailored to address individual barriers, and should be a collaborative effort between health care providers, parents and adolescents.

Acknowledgments

This review was partially supported by Grant Number # UL1RR024986 from NCRR CTSA funding to Emily M. Fredericks, PhD.

References and recommended reading

Papers of particular interest have been highlighted as:

- * of special interest
- ** of outstanding interest

1. Dobbels F, Van Damme-Lombaert R, Vanhaecke J, De Geest S. Growing pains: nonadherence with the immunosuppressive regimen in adolescent transplant recipients. *Pediatr Transplant*. 2005 Jun; 9(3):381–90. [PubMed: 15910397]
- *2. 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 Feb 28. This comprehensive review provides a systematic overview of the prevalence of nonadherence among pediatric kidney transplant recipients, including risk

factors, consequences and proposed interventions. The authors identify gaps in the literature and suggest future directions for research.

- **3. Dew MA, Dabbs AD, Myaskovsky L, Shyu S, Shellmer DA, DiMartini AF, et al. Meta-analysis of medical regimen adherence outcomes in pediatric solid organ transplantation. *Transplantation*. 2009 Sep 15; 88(5):736–46. [PubMed: 19741474] This meta-analysis evaluated the prevalence and risk factors for post-transplant nonadherence in pediatrics. Results indicated that older age, parental distress, poor family cohesion, and poor child behavioral functioning were associated with higher risk for nonadherence. These psychosocial constructs could be targeted in intervention, particularly among high risk adolescents.
4. Kahana SY, Frazier TW, Drotar D. Preliminary quantitative investigation of predictors of treatment non-adherence in pediatric transplantation: a brief report. *Pediatr Transplant*. 2008 Sep; 12(6):656–60. [PubMed: 18798360]
5. Fredericks EM, Lopez MJ, Magee JC, Shieck V, Opiari-Arrigan L. Psychological Functioning, Nonadherence and Health Outcomes After Pediatric Liver Transplantation. *Am J Transplant*. 2007; 7(8):1974–83. [PubMed: 17617862]
6. Fredericks EM, Magee JC, Opiari-Arrigan L, Shieck V, Well A, Lopez MJ. Adherence and health-related quality of life in adolescent liver transplant recipients. *Pediatr Transplant*. 2008 May; 12(3):289–99. [PubMed: 18282211]
7. Butler JA, Roderick P, Mullee M, Mason JC, Peveler RC. Frequency and impact of nonadherence to immunosuppressants after renal transplantation: a systematic review. *Transplantation*. 2004 Mar 15; 77(5):769–76. [PubMed: 15021846]
8. Griffin KJ, Elkin TD. Non-adherence in pediatric transplantation: a review of the existing literature. *Pediatr Transplant*. 2001 Aug; 5(4):246–9. [PubMed: 11472602]
- *9. Pinsky BW, Takemoto SK, Lentine KL, Burroughs TE, Schnitzler MA, Salvalaggio PR. Transplant outcomes and economic costs associated with patient noncompliance to immunosuppression. *Am J Transplant*. 2009 Nov; 9(11):2597–606. [PubMed: 19843035] Medicare pharmacy claims were used to assess patient adherence to immunosuppressant medications. Results indicated that adolescent kidney transplant recipients were most likely to be nonadherent over time. Persistent nonadherence was associated with increased risk of graft loss and higher post-transplant costs.
10. Annunziato RA, Emre S, Shneider B, Barton C, Dugan CA, Shemesh E. Adherence and medical outcomes in pediatric liver transplant recipients who transition to adult services. *Pediatr Transplant*. 2007; 11(6):608–14. [PubMed: 17663682]
11. Bell LE, Bartosh SM, Davis CL, Dobbels F, Al-Uzri A, Lotstein D, et al. Adolescent Transition to Adult Care in Solid Organ Transplantation: a consensus conference report. *Am J Transplant*. 2008 Nov; 8(11):2230–42. [PubMed: 18822088]
12. Shemesh E, Shneider BL, Savitzky JK, Arnott L, Gondolesi GE, Krieger NR, et al. Medication adherence in pediatric and adolescent liver transplant recipients. *Pediatrics*. 2004 Apr; 113(4):825–32. [PubMed: 15060234]
13. Sudan DL, Shaw BW Jr, Langnas AN. Causes of late mortality in pediatric liver transplant recipients. *Ann Surg*. 1998 Feb; 227(2):289–95. [PubMed: 9488529]
14. Nevins TE, Kruse L, Skeans MA, Thomas W. The natural history of azathioprine compliance after renal transplantation. *Kidney Int*. 2001 Oct; 60(4):1565–70. [PubMed: 11576374]
15. De Geest S, Abraham I, Moons P, Vandeputte M, Van Cleemput J, Evers G, et al. Late acute rejection and subclinical noncompliance with cyclosporine therapy in heart transplant recipients. *J Heart Lung Transplant*. 1998 Sep; 17(9):854–63. [PubMed: 9773856]
- *16. Fine RN, Becker Y, De Geest S, Eisen H, Ettenger R, Evans R, et al. Nonadherence consensus conference summary report. *Am J Transplant*. 2009 Jan; 9(1):35–41. [PubMed: 19133930] This consensus conference summary report reviews that definition, prevalence and measurement of nonadherence, as well as risk factors and impact of clinical and economical outcomes. Recommendations for intervention strategies and future research are discussed.
17. Quittner AL, Espelage DL, Ievers-Landis C, Drotar D. Measuring Adherence to Medical Treatments in Childhood Chronic Illness: Considering Multiple Methods and Sources of Information. *Journal of Clinical Psychology in Medical Settings*. 2000; 7(1):41.

18. Butler JA, Peveler RC, Roderick P, Horne R, Mason JC. Measuring compliance with drug regimens after renal transplantation: comparison of self-report and clinician rating with electronic monitoring. *Transplantation*. 2004 Mar 15; 77(5):786–9. [PubMed: 15021850]
19. Shellmer DA, Zelikovsky N. The challenges of using medication event monitoring technology with pediatric transplant patients. *Pediatric Transplantation*. 2007; 11(4):422–8. [PubMed: 17493224]
20. Bucuvalas JC, Ryckman FC, Arya G, Andrew B, Lesko A, Cole CR, et al. A Novel Approach to Managing Variation: Outpatient Therapeutic Monitoring of Calcineurin Inhibitor Blood Levels in Liver Transplant Recipients. *The Journal of Pediatrics*. 2005; 146(6):744. [PubMed: 15973310]
21. Stuber ML, Shemesh E, Seacord D, Washington J, Hellemann G, McDiarmid S. Evaluating non-adherence to immunosuppressant medications in pediatric liver transplant recipients. *Pediatr Transplant*. 2008; 12(3):284–8. [PubMed: 18331387]
22. Flippin MS, Canter CE, Balzer DT. Increased morbidity and high variability of cyclosporine levels in pediatric heart transplant recipients. *The Journal of Heart and Lung Transplantation*. 2000; 19(4):343–9. [PubMed: 10775814]
23. Chisholm MA, Lance CE, Williamson GM, Mulloy LL. Development and validation of an immunosuppressant therapy adherence barrier instrument. *Nephrol Dial Transplant*. 2005 Jan; 20(1):181–8. [PubMed: 15572384]
24. Quittner AL, Modi AC, Lemanek KL, Ievers-Landis CE, Rapoff MA. Evidence-based Assessment of Adherence to Medical Treatments in Pediatric Psychology. *J Pediatr Psychol*. 2008; 33(9):916–36. [PubMed: 17846042]
25. Schafer-Keller P, Steiger J, Bock A, Denhaerynck K, De Geest S. Diagnostic accuracy of measurement methods to assess non-adherence to immunosuppressive drugs in kidney transplant recipients. *Am J Transplant*. 2008 Mar; 8(3):616–26. [PubMed: 18294158]
- **26. Dobbels F, Decorte A, Roskams A, Van Damme-Lombaerts R. Health-related quality of life, treatment adherence, symptom experience and depression in adolescent renal transplant patients. *Pediatr Transplant*. 2009 Jun 2. This study utilized a multi-method strategy for assessing medication adherence including self- and parent reports, immunosuppressant blood levels, and clinical judgment. Authors also included an assessment of adherence to other lifestyle behaviors. Rates of nonadherence were high, and may be related to number of adolescents reporting difficulty regularity of medication intake.
27. Dew MA, Roth LH, Thompson ME, Kormos RL, Griffith BP. Medical compliance and its predictors in the first year after heart transplantation. *J Heart Lung Transplant*. 1996 Jun; 15(6): 631–45. [PubMed: 8794030]
28. Bunzel B, Laederach-Hofmann K. Solid organ transplantation: are there predictors for posttransplant noncompliance? A literature overview. *Transplantation*. 2000 Sep 15; 70(5):711–6. [PubMed: 11003346]
29. Shapiro PA, Williams DL, Foray AT, Gelman IS, Wukich N, Sciacca R. Psychosocial evaluation and prediction of compliance problems and morbidity after heart transplantation. *Transplantation*. 1995 Dec 27; 60(12):1462–6. [PubMed: 8545875]
30. Simons LE, Blount RL. Identifying Barriers to Medication Adherence in Adolescent Transplant Recipients. *J Pediatr Psychol* 2007. August 1; 2007 32(7):831–44.
- *31. Simons LE, McCormick ML, Devine K, Blount RL. Medication Barriers Predict Adolescent Transplant Recipients' Adherence and Clinical Outcomes at 18-Month Follow-up. *J Pediatr Psychol*. 2010 Epub Ahead of Print. This study prospectively assessed parent and adolescent perceived barriers to medication adherence. Perceived barriers were stable over time and were related to poorer medication adherence and increased medical complications and mortality. The identification of modifiable barriers to medication administration is critical in reducing the risk of poor health outcomes in adolescent transplant recipients.
32. Fredericks EM, Dore-Stites D, Well A, Magee JC, Freed GL, Shieck V, et al. Assessment of Transition Readiness Skills and Adherence in Pediatric Liver Transplant Recipients. *Pediatric Transplantation*. in press.
- **33. Kahana S, Drotar D, Frazier T. Meta-Analysis of Psychological Interventions to Promote Adherence to Treatment in Pediatric Chronic Health Conditions. *J Pediatr Psychol*. 2008; 33(6): 590–611. [PubMed: 18192300] This meta-analysis of 70 adherence promoting interventions

among chronically ill youth identified that behavioral and multi-component interventions appear to be most effective.

- **34. Graves MM, Roberts MC, Rapoff M, Boyer A. The Efficacy of Adherence Interventions for Chronically Ill Children: A Meta-Analytic Review. *J Pediatr Psychol.* 2010; 35(4):368–82. [PubMed: 19710248] This meta-analysis of 71 adherence intervention studies identified that effect sizes range from medium to large. Combined educational and behavioral interventions yielded larger effect sizes with respect to health outcomes.
35. Fisher, WA.; Fisher, JD.; Harman, JJ. The information-motivation-behavioral skills model: A general social psychological approach to understanding and promoting health behavior. In: Suls, J.; Wallston, K., editors. *Social psychological foundations of health and illness*. London: Blackwell; 2003. p. 87-106.
36. Fisher JD, Fisher WA, Amico KR, Harman JJ. An information-motivation-behavioral skills model of adherence to antiretroviral therapy. *Health Psychol.* 2006 Jul; 25(4):462–73. [PubMed: 16846321]
37. Ad Hoc Committee of Health Literacy for the Council on Scientific Affairs AMA. Health literacy: Report on the Council on Scientific Affairs. *Journal of the American Medical Association.* 1999; 281(6):552–7. [Review]. [PubMed: 10022112]
38. Nielsen-Bohlman, LT.; Panzer, A.; Kindig, D. *Health Literacy - A Prescription to End Confusion*. Washington DC: The National Academies Press; 2004.
- *39. Shemesh E, Annunziato RA, Shneider BL, Dugan CA, Warshaw J, Kerker N, et al. Improving adherence to medications in pediatric liver transplant recipients. *Pediatr Transplant.* 2008 May; 12(3):316–23. [PubMed: 18435607] This study describes a clinical intervention targeting liver transplant recipients identified as nonadherent. Increased frequency of clinic visits targeting adherence education, and increased monitoring of medication blood levels resulted in improved health outcomes.
40. Osterberg L, Blaschke T. Adherence to Medication. *N Engl J Med* 2005. August 4; 2005 353(5): 487–97.
41. Miller, WR.; Rollnick, S. *Motivational Interviewing: Preparing People for Change*. 2. New York: Guilford Press; 2002.
42. Zweben, A.; Zuckoff, A. Motivational Interviewing and Treatment Adherence. In: Miller, WR.; Rollnick, S., editors. *Motivational Interviewing: Preparing People for Change*. 2. New York: Guilford Press; 2002. p. 299-319.
43. Erickson SJ, Gerstle M, Feldstein SW. Brief Interventions and Motivational Interviewing With Children, Adolescents, and Their Parents in Pediatric Health Care Settings: A Review. *Arch Pediatr Adolesc Med* 2005. December 1; 2005 159(12):1173–80.
44. Riekert KA, Borrelli B, Bilderback A, Rand CS. The development of a motivational interviewing intervention to promote medication adherence among inner-city, African-American adolescents with asthma. *Patient Educ Couns.* 2010 Apr 3.
45. Channon SJ, Huws-Thomas MV, Rollnick S, Hood K, Cannings-John RL, Rogers C, et al. A multicenter randomized controlled trial of motivational interviewing in teenagers with diabetes. *Diabetes Care.* 2007 Jun; 30(6):1390–5. [PubMed: 17351283]
46. Naar-King S, Parsons JT, Murphy D, Kolmodin K, Harris DR. A multisite randomized trial of a motivational intervention targeting multiple risks in youth living with HIV: initial effects on motivation, self-efficacy, and depression. *J Adolesc Health.* 2010 May; 46(5):422–8. [PubMed: 20413077]
47. Creer, TL. Self-management and the control of chronic pediatric illness. In: Drotar, D., editor. *Promoting adherence to medical treatment in chronic childhood illness: Concepts, methods and interventions*. Hillsdale, NJ: Erlbaum; 2000. p. 95-129.
- **48. Rapoff M. *Adherence to Pediatric Medical Regimens, Issues in Clinical Child Psychology* (2). New York:Springer;2009 This reference provides an overview of adherence to pediatric regimens, including a critique of major adherence theories, strategies of assessment, and adherence-promoting interventions. This is an excellent resource for clinicians and researchers.
49. Kennedy A, Sloman F, Douglass JA, Sawyer SM. Young people with chronic illness: the approach to transition. *Internal Medicine Journal.* 2007; 37(8):555–60. [PubMed: 17640188]

50. Lemanek KL, Kamps J, Chung NB. Empirically supported treatments in pediatric psychology: regimen adherence. *J Pediatr Psychol*. 2001 Jul-Aug; 26(5):253–75. [PubMed: 11390568]
51. Bullington P, Pawola L, Walker R, Valenta A, Briars L, John E. Identification of medication non-adherence factors in adolescent transplant patients: The patient's viewpoint. *Pediatr Transplant*. 2007; 11(8):914–21. [PubMed: 17976128]
- *52. Simons LE, McCormick ML, Mee LL, Blount RL. Parent and patient perspectives on barriers to medication adherence in adolescent transplant recipients. *Pediatr Transplant*. 2009 May; 13(3): 338–47. [PubMed: 18433413] This study found that nonadherence was more common when adolescents, versus parents, were responsible for medication administration. This lends support for the role of parental monitoring and supervision in promoting medication adherence.
53. Kripalani S, Yao X, Haynes RB. Interventions to Enhance Medication Adherence in Chronic Medical Conditions: A Systematic Review. *Arch Intern Med* 2007. March 26; 2007 167(6):540–9.
54. Annunziato RA, Emre S, Shneider BL, Dugan CA, Aytaman Y, McKay MM, et al. Transitioning health care responsibility from caregivers to patient: A pilot study aiming to facilitate medication adherence during this process. *Pediatr Transplant*. 2008; 12(3):309–15. [PubMed: 18435606]
55. Annunziato RA, Parkar S, Dugan CA, Barsade S, Arnon R, Miloh T, et al. Brief Report: Deficits in Health Care Management Skills Among Adolescent and Young Adult Liver Transplant Recipients Transitioning to Adult Care Settings. *J Pediatr Psychol*. 2009 Dec 7.
56. Ellis DA, Templin TN, Podolski CL, Frey MA, Naar-King S, Moltz K. The parental monitoring of diabetes care scale: development, reliability and validity of a scale to evaluate parental supervision of adolescent illness management. *J Adolesc Health*. 2008 Feb; 42(2):146–53. [PubMed: 18207092]
57. Horton D, Berg CA, Butner J, Wiebe DJ. The role of parental monitoring in metabolic control: effect on adherence and externalizing behaviors during adolescence. *J Pediatr Psychol*. 2009 Oct; 34(9):1008–18. [PubMed: 19420225]
58. Naar-King S, Montepiedra G, Nichols S, Farley J, Garvie PA, Kammerer B, et al. Allocation of family responsibility for illness management in pediatric HIV. *J Pediatr Psychol*. 2009 Mar; 34(2): 187–94. [PubMed: 18586756]
59. Walders N, Drotar D, Kercsmar C. The allocation of family responsibility for asthma management tasks in African-American adolescents. *J Asthma*. 2000 Feb; 37(1):89–99. [PubMed: 10724302]
60. Kazak, A.; Rourke, M.; Navsaria, N. Families and other systems in pediatric psychology. In: Roberts, MC.; Steele, RG., editors. *Handbook of pediatric psychology*. 4. New York: Guilford Press; 2009. p. 656–71.
61. DiMatteo MR, Lepper HS, Croghan TW. Depression is a risk factor for noncompliance with medical treatment: meta-analysis of the effects of anxiety and depression on patient adherence. *Arch Intern Med*. 2000 Jul 24; 160(14):2101–7. [PubMed: 10904452]
62. Klostermann BK, Slap GB, Nebrig DM, Tivorsak TL, Britto MT. Earning trust and losing it: adolescents' views on trusting physicians. *J Fam Pract*. 2005 Aug; 54(8):679–87. [PubMed: 16061053]
63. Britto MT, DeVellis RF, Hornung RW, DeFries GH, Atherton HD, Slap GB. Health care preferences and priorities of adolescents with chronic illnesses. *Pediatrics*. 2004 Nov; 114(5): 1272–80. [PubMed: 15520107]
64. Shaw KL, Southwood TR, McDonagh JE. Young people's satisfaction of transitional care in adolescent rheumatology in the UK. *Child Care Health Dev*. 2007 Jul; 33(4):368–79. [PubMed: 17584391]
- **65. Drotar D. Physician behavior in the care of pediatric chronic illness: association with health outcomes and treatment adherence. *J Dev Behav Pediatr*. 2009 Jun; 30(3):246–54. [PubMed: 19525719] This review includes a model of physician behavior in chronic illness management that includes contextual influences, physician behavior and targets for intervention, and clinically relevant outcomes. Results of this review emphasize the importance of physician communication, support and decision-making with respect to treatment adherence and health outcomes.
66. Haynes RB, Yao X, Degani A, Kripalani S, Garg A, McDonald HP. Interventions for enhancing medication adherence. *Cochrane Database of Systematic Reviews*. 2005; (4) Art. No.: CD000011. 2005 Contract No.: Document Number1. 10.1002/14651858.CD000011.pub2

67. Lenhart, A.; Ling, R.; Campbell, S.; Purcell, K. Teens and Mobile Phones. 2010. [updated 2010 April 20, 2010; cited]; Available from: <http://pewinternet.org/Reports/2010/Teens-and-Mobile-Phones.aspx>
68. Lenhart, A.; Purcell, K.; Smith, A.; Zickuhr, K. Social Media & Mobile Internet Use Among Teens and Young Adults. 2010. [updated 2010; cited]; Available from: <http://www.pewinternet.org/Press-Releases/2010/Social-Media-and-Young-Adults.aspx>
69. Taylor A, Harper R. The gift of the gab?: a design oriented sociology of young people's use of mobiles. *Journal of Computer Supported Cooperative Work (JCSCW)*. 2003; 12(3):267–96.
70. Krishna S, Boren SA, Balas EA. Healthcare via cell phones: a systematic review. *Telemed J E Health*. 2009 Apr; 15(3):231–40. [PubMed: 19382860]
- *71. Cushing CC, Steele RG. A Meta-Analytic Review of eHealth Interventions for Pediatric Health Promoting and Maintaining Behaviors. *J Pediatr Psychol*. 2010 Apr 27. This meta-analysis evaluating the impact of technology-based (eHealth) interventions revealed that interventions that incorporated behavioral strategies produced larger effect sizes for health behaviors and related outcomes than interventions that only incorporated educational strategies.
72. Stinson J, Wilson R, Gill N, Yamada J, Holt J. A Systematic Review of Internet-based Self-Management Interventions for Youth with Health Conditions. *J Pediatr Psychol*. 2008 Nov 23.
73. van der Meer V, van Stel HF, Detmar SB, Otten W, Sterk PJ, Sont JK. Internet-based self-management offers an opportunity to achieve better asthma control in adolescents. *Chest*. 2007 Jul; 132(1):112–9. [PubMed: 17400674]
74. Gerber BS, Solomon MC, Shaffer TL, Quinn MT, Lipton RB. Evaluation of an internet diabetes self-management training program for adolescents and young adults. *Diabetes Technol Ther*. 2007 Feb; 9(1):60–7. [PubMed: 17316099]
- **75. Miloh T, Annunziato R, Arnon R, Warshaw J, Parkar S, Suchy FJ, et al. Improved adherence and outcomes for pediatric liver transplant recipients by using text messaging. *Pediatrics*. 2009 Nov; 124(5):e844–50. [PubMed: 19822583] This innovative study evaluated the effectiveness of sending cell phone text messages to the primary medication administrator (patient or caregiver) for pediatric liver transplant recipients. Results indicated that this technology-based intervention was associated with improved medication adherence, as measured by standard deviations of tacrolimus blood levels, and a reduction in episodes of a rejection.

Table 1**Intervention Strategies Based on the IMB Model for Health Behavior Change**

Domain	Concept	Intervention
Information	• Disease-specific knowledge	• Health education
	• Health literacy	• Promote the "Ask Me Three" approach: http://www.npsf.org/askme3 (What is my main problem? What do I need to do? Why is it important for me to do this?)
Motivation	• Readiness for change	• Motivational Interviewing
Behavioral Skills	• Problem identification, goal setting	• Self-Management Training
	• Communication skills	• Communication skills training
	• Cues to action	• Emotional support: coping strategies
	• Incentives/rewards	
	• Stress	
Risk Factors	• Emotional distress	• Refer to community level resources, such as mental health agencies, school districts and job training centers
	• Family conflict	
	• Psychiatric Disorders	
	• Learning disabilities	
	• Developmental delay	