IDENTIFYING BARRIERS TO ADHERENCE IN PEDIATRIC TRANSPLANTATION

by

LAURA E. SIMONS

Under the Direction of Ronald L. Blount

ABSTRACT

Eighty adolescent solid organ transplant recipients participated in a study designed to measure the degree to which barriers, a fundamental tenet in the Health Belief Model (HBM; Strecher & Rosenstock, 1997), predicted medication adherence. The Parent Medication Barriers Scale (PMBS) and Adolescent Medication Barriers Scale (AMBS) scales were designed to assess perceived barriers. Principle components factor analyses resulted in the following subscales for both measures: 1) Disease Frustration/Adolescent Issues, 2) Regimen Adaptation/Cognitive, 3) Ingestion Issues, and 4) Parent Reminder (parent scale only). Nomological validity was established with significant associations between disease and medication regimen variables (e.g., side effects, number of medications, time since transplant) and barrier scale scores. In addition, adolescent barrier scale scores were significantly associated with family functioning in the expected direction. Criterion validity was established with statistically significant associations between higher barrier scale scores and medication nonadherence. The predictive value of barriers on medical nonadherence was examined with adolescent issues and parent reminders significantly predicting adherence classification. This study provides a brief and valid method to assess barriers to medication adherence in adolescent transplant recipients.

INDEX WORDS: pediatric; adolescent; solid organ transplant; adherence; family functioning; health belief model

IDENTIFYING BARRIERS TO ADHERENCE IN PEDIATRIC TRANSPLANTATION

by

LAURA E. SIMONS

M.S., University of Georgia, 2004

A Dissertation Submitted to the Graduate Faculty of The University of Georgia in Partial Fulfillment of the Requirements for the Degree

DOCTOR OF PHILOSOPHY

ATHENS, GEORGIA

2006

IDENTIFYING BARRIERS TO ADHERENCE IN PEDIATRIC TRANSPLANTATION

by

LAURA E. SIMONS

Major Professor: Ronald L. Blount

Committee: Christopher Cook
Janet Frick
Amos Zeichner

Electronic Version Approved:

Maureen Grasso
Dean of the Graduate School
The University of Georgia
May 2006

DEDICATION

Mom, dad, sister, your support and love is unwavering. For the past five years my education and training have been the focus of my life, often to the neglect of those I love. Although it is difficult for those outside of the bubble that has become my life to understand the intense commitment and time demands impressed upon me, you have been forgiving, understanding, and my cheerleaders throughout. My success is truly your success. Thanks family. I love you.

And Michael, you are incredible. Thank you for listening to my rants, acknowledging my tears, and being the 1st "transplant family" I interviewed. This has been one heck of a rollercoaster and you have somehow kept me grounded, even from 2000 miles away. Love you, Love you.

ACKNOWLEDGEMENTS

I would like to acknowledge several people who made getting to this point possible. First of all there's Ron. An incredible mentor and person. I have no doubt that you were placed on my life's path to help me grow and develop as a professional and as a person. And Lisa, you didn't have a thing to do with my dissertation project, but you have been my rock. You taught me about genuine friendship and caring. You mean the world to me. Oh, and you made graduate school bearable. Thanks Ron for taking us both! I want to thank the research lab for their efforts and ideas. As for the transplant group (Grace, Dan, Megan, Jordan, Carly), you all not only made it possible for a major project to be completed in less than 9 months, you made it fun. You are a bright, dedicated, enjoyable group that I will miss.

TABLE OF CONTENTS

Page

LIST OF TABLES

Page

LIST OF FIGURES

Page

CHAPTER 1

INTRODUCTION

Pediatric transplantation, formerly considered a last option for terminally ill children, has become the treatment of choice for a number of serious medical conditions. The advent of safer and more effective immunosuppressive medications, such as cyclosporine A and tacrolimus has dramatically improved survival rates in the past 20 years (Gummert, Ikonen, & Morris, 1999). As of May 2004, the 3-year survival rates ranged from 77% to 94% for pediatric kidney transplant recipients, 66% to 83% for liver transplant recipients, and 76% to 87% for heart transplant recipients (2004 OPTN/SRTR Annual Report 1994-2003). Although these numbers are encouraging, organ transplantation is not a "cure." Rather, it is a transition from a chronic, life-threatening disease to a second chronic condition that requires living with and caring for a transplanted organ. To prevent organ rejection, a patient must take immunosuppressant medication daily for life. In addition, the patient must participate in routine medical follow-up, which involves attending clinic appointments, obtaining laboratory tests, and undergoing minor medical procedures (e.g., biopsies). Also in many cases, patients are required to follow dietary (e.g., low sodium) and exercise regimens to keep their transplanted organs and their bodies healthy. Patients follow, or adhere, to each of these medical regimen-related behaviors to varying degrees.

The concept of adherence is defined as the "extent to which a patient's behavior coincides with medical or health advice" (Haynes, 1979). Adherence has gained significant attention over the past three decades as estimates suggest that the overall treatment nonadherence

rate for pediatric populations is about 50%-55% (Rapoff, 1999), with rates in pediatric transplant ranging from 5% to 50% depending on measurement method (Rianthavorn, Ettenger, Malekzadeh, Marik, & Struber, 2004). The potential negative health consequences of transplant nonadherence are serious and include more frequent medical complications and hospitalizations, higher health care costs, increased risk for rejection, allograph loss, and immunological losses (Faulkenstein, Flynn, Kirkpatrick, Casa-Melley, & Dunn, 2004; Meyers, Thomson, & Weiland, 1996; Ringewald, Gidding, Crawford, Backer, Mavroudis, & Elfriede, 2001; Shaw, Palmer, Blasey, & Sarwal, 2003; Smith, Ho, & McDonald, 2002; Watson, 2000).

Research examining adherence with pediatric transplant recipients is limited and often preliminary in nature, but an extensive research base exists studying adherence across pediatric chronic medical conditions. Some of the contextual factors described in the literature include *demographics* (e.g., gender, age), *disease factors* (e.g., illness duration, regimen complexity, disease consequences), *child and family variables* (e.g., motivation, family support, memory), and *healthcare system variables* (e.g., doctor-patient relationship and communication) (La Greca & Bearman, 2003; Staples & Bravender, 2002). Investigators have established links between pediatric adherence and many of these contextual factors, aiding in the effort to understand adherence choices. A potentially more proximal step toward understanding adherence behavior is through assessing individual beliefs or attitudes, which are typically influenced by an individual's context or environment. The adult literature has long emphasized individual beliefs and attitudes as important predictors of treatment adherence (e.g., Bandura, 2004; Redding, Rossi, Rossi, Velicer, & Prochaska, 2000; Strecher, DeVellis, Becker, & Rosenstock, 1986) through the development of health behavior models, while the pediatric literature has generally lagged behind (Bush & Iannotti, 1990; Reikert & Drotar, 2002; Zebracki & Drotar, 2004).

Popular models of health behavior established in the adult literature include: The Health Belief Model (HBM; Strecher & Rosenstock, 1997), Theory of Reasoned Action/Planned Behavior (Montana, Kasprzyk, & Taplin, 1997), Social Cognitive Theory (Bandura, 2004), and the Transtheoretical Model (Prochaska, Redding, & Evers, 1997). These models assist in guiding our current and future understanding of health behavior, providing direction for our research and intervention development. Albeit important, they are often absent from investigations, with estimates of only 45% of adult investigations using a model to predict health behavior and 25% of pediatric studies (Bush & Iannotti, 1990). This investigation will be guided by the HBM and designed to examine the role of perceived barriers in predicting medication adherence. Although most studies examining perceived barriers to adherence have supported its predictive value (Logan, Zelikovsky, & Spergel, 2003; MacNaughton & Rodrigue, 2001; Reikert & Drotar, 2002), some studies have not (Patino, Sanchez, Eidson, & Delamater, 2005; Steele et al., 2001). Despite mixed findings, exploring the impact of perceived barriers to adherence provides the unique opportunity to translate findings directly into clinical practice, allowing for problem solving to overcome obstacles (Schafer, Glasgow, & McCaul, 1982).

Pediatric Transplantation

In the last decade, the number of solid organ transplants has steadily climbed with over 1800 performed in 2003 (2004 OPTN/SRTR Annual Report 1994-2003). As technological advances and the advent of safer and more effective immunosuppressive medications have improved survival rates dramatically in the past two decades (Gummert et al., 1999), transplantation has become the treatment of choice for end-stage liver, kidney, and heart disease. There were over 2,200 pediatric patients awaiting organ transplantation at the end of 2003, a 50% increase observed over the past decade. Among pediatric candidates, adolescents (aged 11-

17) comprise approximately half of those awaiting transplantation. As most children are not expected to live more than 6 to 12 months without transplant, life expectancy on average with transplant is usually markedly prolonged, with recent estimates of 3-year survival rates ranging from 77% to 94% for pediatric kidney transplant recipients, 66% to 83% for liver transplant recipients, and 76% to 87% for heart transplant recipients (2004 OPTN/SRTR Annual Report 1994-2003). Along with a prolonged life, quality of life is often dramatically improved as children recover quickly and are discharged from the hospital within a few weeks post-transplantation. Although quality of life is rarely commensurate with healthy same-aged peers (e.g., Qvist et al., 2004), transplantation offers a reasonable alternative to a formerly incapacitated child facing a short life expectancy. Organ transplantation is not a cure, but it is a transition from a chronic, life-threatening disease to a chronic condition that requires living with and caring for a transplanted organ.

Regimen requirements. To prevent organ rejection, a patient must take immunosuppressant medication daily for life. This medication is vital to prevent the body from rejecting the transplanted organ and typically produces a number of unwanted side effects. Cyclosporine, one of the most common immunosuppressants, causes increased blood pressure, excessive hair growth (hypertrichosis), overgrowth of the gums (gingival hyperplasia), and impaired renal function in greater than 10% of recipients (Chisholm, 2002). In addition, corticosteroids are given to recipients immediately following transplantation and are typically prescribed for approximately 1 year post-transplant, until the risk of rejection falls significantly. Corticosteroid side effects include acne, mood swings, night sweats, difficulty sleeping, growth impairment, increased appetite and weight gain, and a cushingoid appearance (mood face). Although immunosuppressants represent the most frequent medications administered, patients

are often required to take numerous other medications to combat the side effects of immunosuppressants (e.g., anti-hypertensives for elevated blood pressure).

Beyond daily medication, the patient participates in routine medical follow-up, involving clinic appointments, laboratory tests, and minor medical procedures (e.g., biopsies). In the first months following transplantation, patients are seen in clinic weekly and obtain biopsies every few weeks as the initial risk of rejection is quite high. Although often reversible, most patients develop at least one episode of rejection within the first year of transplant, despite immunosuppressive efforts (Baum & Bernstein, 1993). Transplant centers are often hours away from patient homes, necessitating reliable transportation and a considerable amount of time spent traveling to and from appointments. Patients are often required to follow dietary and exercise regimens. For example, cyclosporine increases blood pressure, which necessitates a low sodium diet (Baum & Bernstein, 1993). Taken together, pediatric transplant patients and their families must juggle complex medication regimens, extensive time commitments, and other behavioral health recommendations. Given the multi-faceted nature of these requirements, the degree to which patients adhere to each of these regimen-related behaviors varies.

Adherence. The concept of adherence is defined as the "extent to which a patient's behavior coincides with medical or health advice" (Haynes, 1979). Adherence has gained significant attention over the past three decades as estimates suggest that the overall treatment nonadherence rate for pediatric populations is about 50% (Rapoff, 1999), with rates in pediatric transplant ranging from 5% to 50% varying based on method used to measure adherence (Rianthavorn et al., 2004).The potential negative health consequences of transplant nonadherence are serious and include more frequent medical complications and hospitalizations, higher health care costs, increased risk for rejection, allograph loss, and immunological losses

(Faulkenstein et al., 2004; Meyers et al. , 1996; Ringewald et al., 2001; Shaw et al., 2003; Smith et al., 2002; Watson, 2000). In order to assess the impact of nonadherence, it is essential to be able to measure the degree to which an individual adheres. Although seemingly straightforward, this has posed a challenge not only in the area of pediatric transplantation, but also across the greater body of literature examining health behavior choices.

Medical Adherence

Operational definitions of adherence vary from categorical to continuous and unitary to multidimensional. The categorical approach has been used in many pediatric transplant adherence studies, as the number of participants is typically quite small, necessitating a dichotomous (adherent/nonadherent) approach (e.g., Meyers et al., 1996; Ringewald et al., 2001) or the use of clinical outcomes, such as acute rejection or late graft loss as a result of nonadherence (Matas, 2000). Limitations of this approach include the arbitrary nature of the cutoff criteria typically used in the dichotomous approach and the potential mitigating factors that may also contribute to negative clinical outcomes. To ameliorate some of these limitations, recent investigations have examined adherence on a continuum (Shemesh et al., 2004; Tucker et al., 2001). As caring for a transplanted organ involves multiple tasks, some have recommended combining multiple indicators (e.g., taking medication, attending clinic appointments) into an index of adherence (e.g., Becker, Drachman, & Kirscht, 1972). Although this takes into account multiple indicators of adherence behaviors, it masks the significance that some behaviors have over others, such as the life sustaining importance of taking anti-rejection medication versus merely attending clinic appointments. Therefore, the optimal approach combines examining adherence multidimensionally and continuously.

With no gold standard for measuring adherence, many methods are currently used to assess this domain across the child and adult adherence literature. The most common methods include: self-report, pill counts, physician assessment, clinical outcome, pharmacy records, drug or marker level, and electronic microprocessors. Table 1 outlines advantages and disadvantages for each method of measurement. This investigation will rely on parent and adolescent report, clinical outcome, and drug levels. Although self-report relies on honesty from the respondent and often results in underreported adherence difficulties, this form of measurement can be improved by keeping the recall period short and asking detailed objective questions (La Greca & Bearman, 2003). Although clinical outcomes detect adherence difficulties only after much time has passed, particularly in the case of graft loss, evidence supporting the link between nonadherence and an increased risk of acute rejection, late acute rejection, and graft loss (Matas, 1999) highlights the importance of this objective measure of adherence. The final measure in this investigation is immunosuppressant drug levels. The frequency of laboratory visits to assess immunosuppressant drug levels vary patient to patient, but typically occur every one to 3 months. To index adherence levels, a clinician obtains the standard deviations (SDs) of consecutive blood levels of immunosuppressants in children, with a higher SD indicating more fluctuations over time and more erratic adherence (Shemesh et al., 2004).

With medical adherence definitions and methods of measurement examined, this review will turn to examining correlates to adherence. Investigations designed to pinpoint factors that may influence pediatric transplant adherence are being conducted. Unfortunately, many suffer from small sample sizes (e.g., Gerson Furth, Neu, & Fivush 2004; Lurie et al., 2000) and examine a limited scope of variables, often focusing on demographic, non-modifiable factors (Faulkenstein et al., 2004; Ringewald et al., 2000). Although adherence in pediatric transplant is

a relatively new area of inquiry, numerous medical conditions, which require frequent monitoring and care, such as diabetes, cystic fibrosis, and asthma, have inspired research examining adherence-related behaviors over the last three decades. Although each condition exerts unique and specific demands on the patient, commonalities exist, which lend clues to potentially important factors associated with adherence levels in pediatric transplant patients. This review will consider this greater body of literature investigating adherence across chronic illnesses in addition to the transplant population.

"Non-modifiable" Risk Factors

Demographics. Demographic parameters are often conceptualized as non-modifiable risk factors and the data supporting their relationship with adherence is mixed. Staples and Bravender (2002) reviewed medication compliance in adolescents across medical conditions with the majority of studies finding no difference between gender, race, and socioeconomic status. Whereas other reviews examining children with chronic illness found that families from low socioeconomic groups have more difficulty with appointment keeping and adhering to dietary and medication regimens (Fielding & Duff, 1999; Irwin, Millstein, & Ellen, 1993). Davis et al. (2001) identified black ethnicity and lower socioeconomic status as predictors of poor glycemic control in children with Type I diabetes.

In examining the transplant literature, some investigations have found that female renal transplant recipients are more adherent (Meyers et al., 1996; Tucker et al., 2001), whereas others have found no difference across gender with heart transplant (Ringewald et al., 2001), heart and heart-lung (Serrano-Ikkos et al., 1998), and liver transplant (Lurie et al., 2000). One early study found poorer adherence with female renal transplant patients (Beck, Fennell, Yost, Robinson, Geary, & Richards, 1980). Although investigators comparing pediatric heart transplant patients

with and without late rejection did not find gender differences, patients in the rejection group were more likely to be non-white and come from single parent homes (Ringewald et al., 2001). In another study, nonadherent heart and heart-lung transplant patients were more likely to come from single and reconstituted families (Serrano-Ikkos et al., 1998). In the Ringewald et al. (2001) and Serrano-Ikkos, Lask, Whitehead, and Eisler (1998) studies, investigators did not find differences based on Medicaid status, an indicator of low socioeconomic standing. An investigation conducted at the Johannesburg Hospital in South Africa assessed compliance in pediatric renal patients, finding significantly more blacks nonadherent with their regimen than other patients (Meyers et al., 1996). In a recent investigation assessing compliance in liver transplantation, Faulkenstein and colleagues (2004) identified 40 patients as non-adherent through measured drug levels. Although no statistical tests were conducted, 27 of these identified patients were receiving medical assistance, an indicator of low socioeconomic status, and 50% of the patients were from one-parent homes. Taken together, demographic results suggest that non-white, male patients from single-parent homes have the highest risk of nonadherence.

Notably, these investigations do not explore the specific barriers associated with these non-modifiable risk factors, such as the relationship between medication taking and reduced supervision provided in a one-parent home. Thus, assessing demographic risk factors should be combined with assessing barriers that could potentially explain their predictive power. Another risk factor that has gained significant attention in the literature is developmental status, as indexed by chronological age.

Adolescence. The relationship between adolescent age and decreased adherence is often found in the chronic illness literature (see reviews by Fielding & Duff, 1999; La Greca & Bearman, 2003; Staples & Bravender, 2002). In the transplant literature, this relationship has

also received support. Adolescence has been identified as a risk factor in a number of investigations, including heart (Ringewald et al., 2001) and renal transplant (Beck et al., 1980; Shaw et al., 2003). Even more striking in the Shaw et al. (2003) study is that the first documented occurrence of laboratory nonadherence was dramatically sooner in adolescents (M = 10 months) versus children (M = 2 years, 6 months). In an attempt to describe the underlying themes driving nonadherence in adolescence, Zelikovsky, Walsh, & Meyers, (2004) assessed pediatric renal patients awaiting transplant and found that older children, particularly patients ages 14 and 18, were more nonadherent than other patients. The authors concluded that age 14 (beginning high school) and age 18 (graduating high school) likely represent times of transition, where the emphasis is potentially drawn away from their regimen and toward developmental changes in the child's life.

The relationship between nonadherence and adolescent age is often interpreted as the tumultuous aspects of adolescence creating the notion of invulnerability and teenage rebellion (Nevins, 2002). Although this may be the case, there is also decreased parental support and involvement in treatment (La Greca, Auslander, Greco, Spetter, Fisher, & Santiago, 1995); thus drawing a connection between adolescent age and poor adherence is only the first step in understanding this relationship. Researchers must explore variables that may mediate the relationship between adolescent age and adherence. This can be accomplished by assessing adolescent-specific barriers that target a multitude of motives underlying poor adherence. These often encompass social and emotional issues and transition of responsibility, two areas particularly relevant to teens (e.g., I don't like how the medication makes me look; I don't want my friends to know; My parent didn't remind me). Preoccupation with peer acceptance pervades the teenage years, resulting in teens avoiding medication for the cosmetic effects (Korsh, Fine,

Negrete, 1978; Rianthavorn, 2004) or to avoid being different from peers (Kyngas, 1999). In regard to transition of responsibility, approximately 50% of pediatric transplant patients take sole responsibility for medication taking at 12 years of age (Shemesh et al., 2004). In many cases, role clarity is amiss, wherein *who* is responsible (parent, child, or both) varies based on the reporting source. Families who share the responsibilities fare best (Anderson, Auslander, Jung, Miller, & Santiago, 1990; Treadwell et al., 2005); therefore identifying families who defer responsibility to another family member (e.g., "my mother forgot to give me my medication") pinpoints an incremental barrier to adherence.

Disease and regimen. Disease parameters include illness factors (duration, course, and severity), regimen complexity, and consequences for adherence. The chronic illness literature has established links between these parameters and treatment adherence (for a review e.g., La Greca & Bearman, 2003). In the case of illness duration, Kyngas (2000) looked at compliance with 1200 children across chronic illnesses, finding that children with epilepsy and children with diabetes who had the disease for 1-3 years were more compliant than children who had the disease for more than 3 years. Interestingly, disease duration has not been supported in the transplant literature (Ringewald et al., 2001;Tucker et al., 2001), and in fact, for African American renal transplant patients, prior dialysis experience predicts better compliance (Tucker et al., 2001). Also unique to the liver and kidney transplant literature is the relationship between adherence and living or cadaveric donors. The Tucker et al. (2001) investigation found higher medication compliance in African American renal patients with cadaveric organs, although this relationship did not hold in another renal transplant study (Meyers et al., 1996) The second important factor is regimen complexity, with more than one medication and multiple doses associated with lower adherence rates (for a review e.g., Staples & Bravender, 2002). In an

investigation with HIV-infected children, 58.4% of thrice daily doses were taken 2 hours earlier or later than prescribed versus 17.3% of twice daily doses, supporting the relationship between regimen complexity and poor adherence rates. In the transplant literature, no known studies examining regimen complexity could be located. Consequences (side effects, functional impairments, pill size/taste) often represent powerful predictors of nonadherence and most readily translate into barriers to medication taking. In discussing adolescent challenges, cosmetic side effects were previously noted as being a barrier to adherence in renal transplant (Korsh et al., 1978). General side effects as well as pill size and taste have been identified as barriers to medication taking with HIV-infected children (Marhefka, Farley, Rodrigue, Sandrik, Sleasman, & Tepper, 2005), adolescents with renal disease (Zelikovsky, et al., 2004), and pediatric heart and heart-lung transplant patients (Serrano-Ikkos et al., 1998). In contrast, side effects as a barrier to adherence has not been supported with liver transplant patients (Lurie et al., 2000; Shemesh et al., 2004).

As noted with the demographic and age-related factors, disease variables can be translated into specific barriers to adherence, and in fact, the patient's perception of the impact of side effects is likely more influential that its mere presence. With demographic and disease factors reviewed, the next logical step is to examine influential child and family factors. These encompass disease knowledge, child and parental psychosocial adjustment, and familial variables such as support, communication, conflict.

Child and Family Factors

Disease Understanding. Child and parent understanding of a disease and their knowledge concerning how to manage it are incremental for adherence. In an investigation examining prophylaxis therapy for haemophilia, 44.1% of parents indicated that understanding the benefits

of prophylaxis was the most significant facilitator of compliance (Hacker, Geraghty, & Manco-Johnson, 2001). Similarly, in a study with HIV-infected children, investigators found that caregivers who could more accurately identify their child's medication had higher pharmacy refill records (Marhefka et al., 2004). In addition, medication nonadherence has also been correlated with lower levels of asthma knowledge (Bender, Milgrom, Rand, & Ackerson, 1998). Importantly, disease knowledge encompasses not only understanding the illness process, but also includes an awareness of the tasks that constitute successful treatment and the ability to execute such tasks accurately and to make adjustments when problems arise. Such tasks include fitting the regimen into the family schedule, devising organizational strategies, and committing the regimen to memory. Zelikovsky and colleagues (2004) examined rates of adherence in an adolescent renal pre-transplant population, finding that 46% of patients missed doses because they forgot, 24% were not home, and 17% indicated that it interfered with daily activities. Similar patterns have been found in other investigations. Tucker et al. (2001) found that in Caucasian renal patients, higher adherence was associated with reports of forgetting to take medication less often. Shemesh et al. (2004) found that forgetting (25.9%) was the most frequently cited reason that pediatric liver transplant patients missed a dose of immunosuppressant medication as reported by caregivers. In a renal transplant study, identified nonadherent patients knew less about their disease, allograft, and immunosuppression (Meyers et al., 1996). In addition, the nonadherent sample in this investigation forgot to take their medication more frequently, took more medication than prescribed, and knew fewer medication names.

Taken together, barriers to adherence in the domain of disease knowledge encompass little awareness of the disease process, an unclear understanding of the regimen, and the inability

to properly incorporate the course of treatment into a daily routine. Beyond disease knowledge, psychological adjustment is another important factor to consider.

Psychosocial adjustment. How a child adjusts to a chronic medical condition varies tremendously. Accordingly, numerous studies have examined the relationships between children's emotional functioning and their adherence. In general, positive psychosocial adaptation has been associated with good treatment adherence. As cited in a review by Staples & Bravender (2002) more highly adherent children with Juvenile Rheumatoid Arthritis (JRA) have been found to have better self-esteem. In an investigation with children with cystic fibrosis, those who were adherent rated themselves as more optimistic and hopeful (Abbott, Dodd, Gee, & Webb, 2001).

Conversely, children with serious emotional difficulties often have problems with adherence, although some evidence exists finding no significant relationship between psychological adjustment and adherence (Bender et al., 1998; Simoni, Asarnow, Munford, Koprowski, Belin, & Salusky, 1997). Kovacs, Goldston, Obrosky, & Iyengar (1992) followed children and adolescents for 9 years after their initial diagnosis of diabetes, finding that serious noncompliance was associated with having a major psychiatric disorder. In reference to risk taking, Logan et al. (2003) found that adolescent asthma patients who engage in more risk taking behavior report more barriers to medical adherence and have poorer responses to asthma attacks. In renal transplant, investigators found elevated levels of depression, anxiety, and anger in renal transplant patients; interestingly, only excessive anger predicted subsequently missing medication (Penkower, Dew, Ellis, Sereika, Kitutu, & Shapiro, 2003). In study of liver transplant recipients comparing severely nonadherent patients with age-matched cohorts, 100% of the severely nonadherent were diagnosed with depression, whereas 33% of the age-matched sample

had the same diagnosis (Lurie et al., 2000). Shemesh et al. (2000) examined Posttraumatic Stress Disorder (PTSD) symptoms in pediatric liver patients, finding 6 of 19 patients (32%) in the investigation met full criteria for PTSD. Three patients in this sample were identified as chronically nonadherent and each met full criteria for PTSD. Taken together, these studies suggest that although psychological distress does not always lead to adherence difficulties, those with adherence difficulties are very likely to have psychological distress. In addition, secondary behaviors such as risk taking impact adherence choices. A similar and influential construct is family functioning, which encompasses support, communication, and conflict.

Family support, communication, and conflict. Families play a critical role in the medical management of children and adolescents. DiMatteo (2004) conducted a meta-analysis examining how patient (child and adult) adherence related to social support (practical, emotional, and unidimensional) and family cohesiveness and conflict. From this analysis, he found that practical support bore the highest correlation with adherence, with the odds of adherence 3.60 times higher among those who receive practical support than those who do not, with the standardized risk for nonadherence almost twice as high among patients who do not receive practical support. Less pronounced, but significant relationships were observed for emotional support (odds of adherence 1.35 times higher) and unidimensional support (odds of adherence 1.53 times higher). In the area of family cohesiveness, which includes warmth, acceptance, family emotional health and closeness, the odds of adhering are 3.03 times higher among patients in close and cohesive families. The least robust, yet still significant finding is the role of family conflict with a 1.53 times higher risk of nonadherence if there is high conflict in the patient's family. This meta-analysis provides substantive support for the incremental importance of perceived support and family dynamics on adherence behaviors.

In a recent study examining social support, Kyngas & Rissanen (2001) collected data from over 1000 adolescents in Finland with asthma, epilepsy, JRA, and insulin-dependent diabetes mellitus, finding that support from nurses is the most powerful predictor of complying with health regimens (7.28 times more likely). In this investigation, support from physicians, parents, and friends were also significant predictors of compliance. In other single investigations, the importance of a positive family relationship has been found in children with diabetes (Hauser et al., 1990), cystic fibrosis (DeLambo, Ievers-Landis, Drotar, & Quittner, 2004), and juvenile rheumatoid arthritis (Chaney & Peterson, 1989). In addition, the detrimental effect of conflict has been found in children with diabetes on glyaemic control (Anderson, Vangsness, Connell, Butler, Goebel-Fabbri, & Laffel, 2002; Hauser et al., 1990) and in children with asthma (Bender et al., 1998). Lastly, increased family stress has been associated with poorer adherence in sickle cell disease (Treadwell et al., 2005).

Few studies in the pediatric transplant literature could be identified that examined medication adherence in relation to family functioning variables. In an early study, investigators found that family instability was associated with noncompliance, whereas parental involvement was associated with better compliance (Beck, et al., 1980). In renal transplant patients, more family stress was associated with less medication adherence (Gerson et al., 2004; Foulkes, Boggs, Fennell, & Skibinski, 1993). In sum, perceived practical, emotional, and unidimensional support from nurses, family members, and friends has a positive impact on adherence behaviors. In reference to familial dynamics, cohesive families who regularly display warmth, acceptance, and closeness have a positive influence on pediatric adherence behaviors, whereas conflictual relations and high family stress undermine adherence behaviors. Although not specifically

examined in this study, the final contextual variable that has begun to receive greater attention in recent years is the influence of the health care system.

Health Care System

In their review, La Greca and Bearman (2003) discuss personal and contextual aspects of the health care setting that have been found to influence medical adherence. These include doctor-patient rapport, perceptions of the medical provider, and providing "personal care." According to their review, patients who perceive their provider as friendly, warm, empathic, and supportive are more likely to be medically adherent. Effective strategies for improving familial involvement have included verbal support and encouragement, phone reminders for appointments, and staff support (Saylor, Elksnin, Farah, & Pope, 1990). In addition, continued contact with the same provider has been linked with better adherence. Unfortunately managed care has a detrimental impact on the ability to provide "personal care," resulting in less direct patient contact; in turn, shorter visits lead to deteriorations in communication, another challenge to adherence in the health care system. In reference to communication, regimen knowledge may be directly influenced. Patients who recall more information concerning their regimens have better adherence (e.g., Hacker et al., 2001). Unfortunately medical staff may contribute to inadequate knowledge by providing unclear instructions in technical terms or failing to repeat or rephrase instructions. In an investigation with pediatric diabetes, providers made seven recommendations on average. However, children and families recalled only two. Moreover, families recalled recommendations that were not made by health providers (Page, Verstraete, Robb, & Etzwiler, 1981).

Although the research in this area is only beginning to build momentum, these mitigating factors likely influence adherence directly or indirectly through their influence on patients'

perceptions. Thus bringing us to the final segment of this review, focusing on individual perceptions, which may serve as a more proximal step in understanding the complexities involved with the health behavior choice of medication adherence.

Beliefs and attitudes

Individual beliefs and attitudes typically spring from previous experiences within the context in which we live. Applying a perceptual filter to understanding how a myriad of variables influence individual behavioral decision-making has led to the development of a number of health behavior models to explain phenomena like adherence. Examples of these models, developed in the adult literature, include the Health Belief Model (HBM; Strecher & Rosenstock, 1997), Theory of Reasoned Action/Planned Behavior (Montana, Kasprzyk, & Taplin, 1997), Social Cognitive Theory (Bandura, 2004), and Transtheoretical Model (Prochaska, Redding, & Evers, 1997). The beneficial use of health behavior models to predict treatment adherence in the adult literature has been established and these models continue to guide research and intervention development today (e.g., Bandura, 2004; Redding, Rossi, Rossi, Velicer, & Prochaska, 2000; Strecher, DeVellis, Becker, & Rosenstock, 1986). Conversely, pediatric adherence studies are largely atheoretical, with only a handful of investigators tapping the potential of health behavior models to facilitate understanding and hypothesis generation (Bush & Iannotti, 1990; Reikert & Drotar, 2002; Zebracki & Drotar, 2004). A marked advantage to using a health behavior model to guide investigations in this area is a model's ability to assist the researcher in tying together seemingly unrelated variables. As the primary focus of this study is on perceived barriers to medication adherence, derived from the Health Belief Model (HBM; Strecher & Rosenstock, 1997), a brief overview and history of the HBM will be provided.

Health Belief Model. The HBM was initially developed in the 1950's by a group of social psychologists in the U.S. Public Health Service in an effort to explain the widespread failure of people to participate in programs to prevent or to detect disease (Rosenstock, 1974). The model was then extended to apply to people's responses to symptoms and their behavior in response to diagnosed illness, particularly their compliance with medical regimens (Rosenstock, 1974). The HBM posits that adherence to a prescribed health behavior is associated with four cognitive factors: perceived vulnerability to a consequence, perceived severity of a consequence, perceived barriers to adherence, and perceived efficacy of the health behavior. These cognitive variables are posited to exert influence over health-related behavior when activated by a cue, such as education or counseling by health care professionals. In addition, self-efficacy has been added to the original HBM as its independent influence on health behavior has been established (Strecher & Rosenstock, 1997; See Figure 1 for schematic representation). Janz and Becker (1984) conducted a review of research examining the individual and combined contributions of the four HBM tenets since its inception. Perceived barriers was found to be the most powerful single predictor among HBM dimensions. A more recent meta-analysis examining the use of the HBM with adults echo their findings (Harrison, Mullen, & Green, 1992). Taking these results in tandem with the primary goal of this investigation on identifying specific entry ways for improving individual adherence supports this study's focus on parent and patient perceived barriers.

Barrier studies. Although this study represents the first systematic examination of barriers to adherence in the pediatric transplant literature, the negative impact of barriers has been demonstrated with other populations. In the adult transplant literature, Chisholm, Lance, Williamson, & Mulloy (2005) developed an immunosuppressant therapy adherence barrier

instrument. They found that higher barrier scores were significantly associated with lower self-reported adherence, lower drug assay levels, and poorer prescription refill rates. In examining the pediatric literature, caregivers of HIV-infected children who reported more barriers to adherence tended to have children with lower prescription refill histories (Marhefka et al., 2004). In another study with the pediatric HIV population, parents who endorsed beliefs or barriers such as "It's almost impossible to get in every dose each week" and "I don't believe my child needs to take so many medications" were more likely to be nonadherent (Reddington et al., 2000). With adolescent asthma patients, more barriers correlated with poorer self-reported adherence to medication, more attacks, less preventative efforts, and greater physician rated severity (Logan et al., 2003). In a study involving children with asthma, HIV, and Inflammatory Bowel Disease (IBD), more barriers to adherence were associated with lower adherence for each disease group (Riekert & Drotar, 2002). Another investigation attempted to predict adherence to recommendations by parents of clinic-referred children. Interestingly, child behavior severity, recall of recommendations, parent satisfaction with the evaluation, and locus of control were not associated with adherence to recommendations. Instead, the number of perceived barriers was the most salient predictor of adherence, regardless of recommendation type (MacNaughton & Rodrigue, 2001). Zelikovsky and colleagues (2004) examined barriers to adherence among adolescents with renal disease. They found that patient adherence varied with the type of medication (e.g., less adherent to binders), use of an organizational strategy for taking their medication, and time of day, with bedtime doses being with the least likely to be missed. Further, the top three reasons for not taking medication were forgetting, being away from home, and being engaged in another activity. Suggestions were provided for assisting patients in how to

overcome these obstacles. This study provides a model of how assessing barriers translates directly into implications for intervention.

Rationale

This investigation pulls from three decades of research examining contextual variables that directly or indirectly influence adherence behaviors in children with medical conditions. The HBM provides a theoretical framework to integrate contextual factors with individual perceptions in an effort to better explain behavioral health decision-making, in this case, choosing to take immunosuppressant medication as prescribed. It is believed that individual perceptions may serve as a more proximal link to this decision-making process. Parent and adolescent perceived barriers to medication adherence scales were developed in this investigation. Many of the perceived barriers assessed in this study are modifiable (e.g., "can't remember to take medication"). Pinpointing these modifiable barriers translates directly into the design of treatment outcome research intended to promote adherence.

Hypotheses

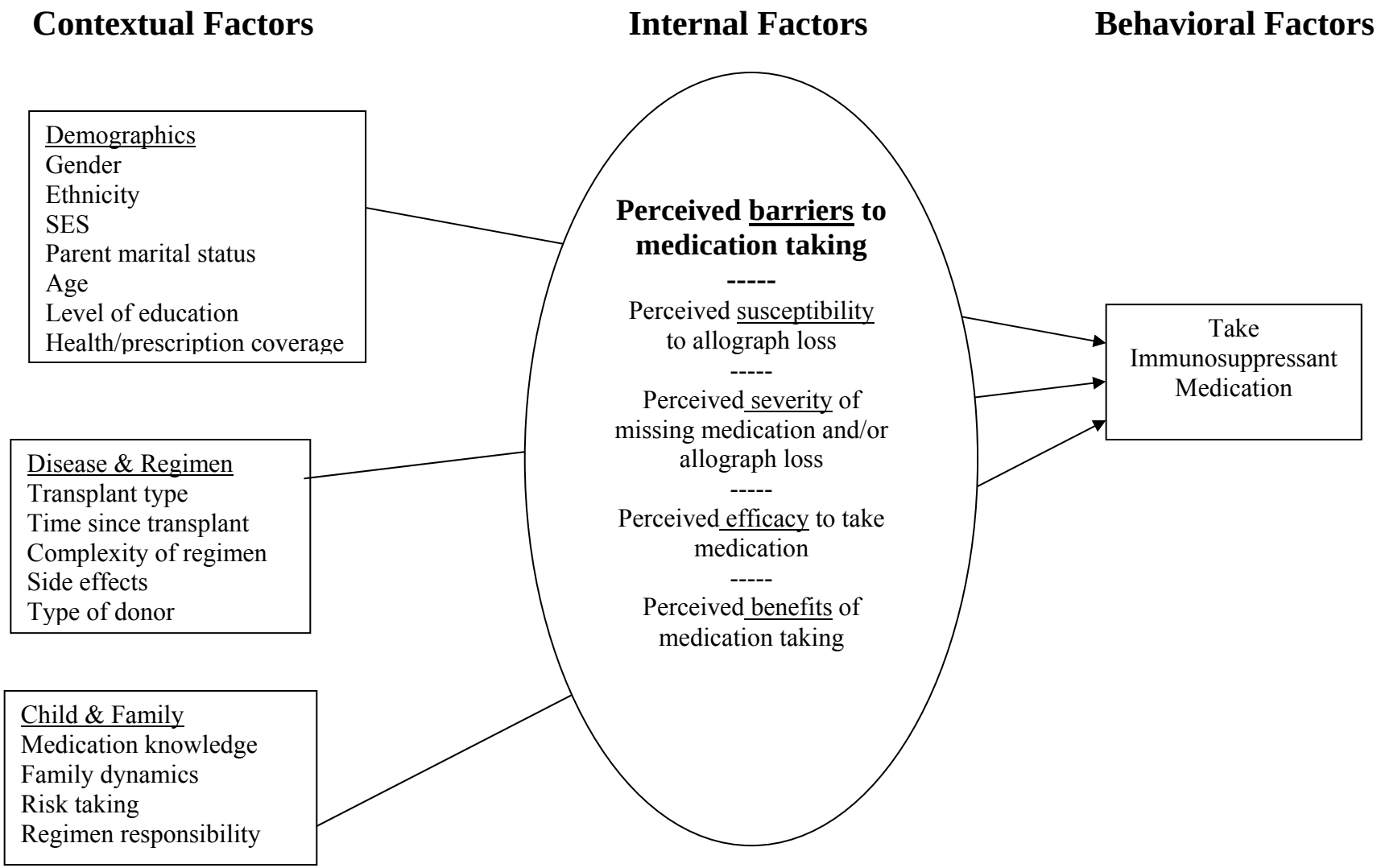
This study examines the relationship between perceived barriers and levels of medication adherence. To address this issue, parent and adolescent scales specifically designed to assess perceived barriers to medication adherence were developed. Expected subscales included: 1) medication/disease understanding barriers, 2) cognitive barriers, and 3) family/adjustment barriers. It is predicted that higher barrier subscale and total scale scores will be associated with lower medication adherence. It is hypothesized that pertinent contextual variables would be associated with higher barrier subscale and total scale scores. In reference to barrier types, it is predicted that cognitive barriers (e.g., organization, memory), or a similar construct that emerges from the factor analyses, would predict the greatest likelihood of nonadherence.

Table I.
Methods to Assess Adherence

Method of assessment	Advantages	Disadvantages
Self-report	• Inexpensive • Readily available • Those who report noncompliance rarely lie	• Time-dependent • Dependent on patient to give an accurate assessment
Pill counts	• Inexpensive • Not time dependent	• Relies on patients to remember pill vials at clinic visits • Relies on patients not to dump or lose pills
Physician assessment	• Inexpensive	• Not objective; physician assessment has been shown to be no more accurate than a coin toss
Clinical outcome	• Inexpensive • Failure to achieve expected outcome should raise suspicions of noncompliance	• Correlation between drug dosage and clinical outcome not perfect • Potentially detects compliance too late for patient to benefit
Pharmacy records	• Inexpensive • Will not confound compliance if patient is not aware of being monitored	• No way of measuring if patient actually took medicine once filled • Time consuming to obtain
Drug or marker level	• Objective; does not rely on patient or physician assessment	• Expensive • Varies with differences in metabolism/absorption, volume of distribution, half-life of medication, and time since medication was last taken
Electronic microprocessor	• Objective • Gives information about dosing interval and other patterns of noncompliance, including drug holidays	• Expensive • May confound compliance issues by falsely elevating compliance during periods of known monitoring

Note. From Staples & Bravender, 2002.

Figure 1.
Adherence Model



Adapted from the Health Belief Model (Rosenstock, Strecher, & Becker, 1988)

CHAPTER 2

METHOD

Participants

This study involved 80 pediatric patients who received solid organ transplants, between the ages of 11 and 21 (M = 15.8, SD = 2.4). Among transplant types, 47 patients received kidneys, 18 patients received livers, 14 patients received hearts, and one patient received a double lung transplant. These numbers are representative of the proportion of adolescent patients in each organ group who are currently followed at Children's Healthcare of Atlanta (CHOA), with this sample including 53% of all transplant patients currently followed at CHOA. Time since transplant ranged from 4 months to 15.4 years (Median = 3.2 years). Among liver and kidney transplant recipients, 34.4% received organs from living donors. Fifty-seven percent of adolescent participants were male. Adolescent participants were Caucasian (62.5%), African American (30%), Asian-East Indian (1.2%), and Other (6.3%). Parent gender, marital status, level of education, work status, household income, health coverage, and prescription coverage are detailed in Table II. Inclusion criteria for this study was that the child must have had a solid organ transplant, be at least 11 years of age, live with a parent(s) in the home, be English speaking, and be transplanted at least four months prior to participation.

Contextual and Barrier Measures

Demographic information. Demographic information collected about the child included: a) child's age, b) gender, and c) ethnicity and race. Demographic information collected about the parent included: a) marital status, b) educational attainment and income, and c) health coverage.

Medical record review. A medical record review was conducted to confirm the: a) transplant type, b) date of transplant, c) immunosuppressant regimen, and d) all medications that the child is currently taking.

PEDS-TX Survey, Parent and Adolesent Version 1.0. The PEDS-TX Survey (Rodrigue, 2004) is a measure specifically designed for this investigation. It includes questions: 1) about the child's transplant (e.g., type of donor), 2) side effects from the medication (listed below) and 3) perceived barriers (listed below). This measure was created with the expertise of a clinical team comprised of pediatric transplant physicians, clinical psychologists and trainees who specialize in pediatrics and transplantation, and from examination of the research literature on adherence difficulties across medical conditions, and more specifically, with transplant patients. As the PEDS-TX Survey, Parent Version 1.0 was created for this study; no psychometric data exist for this measure. Parents and adolescents provided responses to this inventory.

Perceived side effects. Derived from the PEDS-TX Survey (Rodrigue, 2004), the side effects portion of this measure asks how frequently and intensely the patient experiences 39 side effect (e.g., changes in facial appearance, fatigue) that they believe may be related to their transplant medications. Frequency and intensity are rated on a 5-point likert-like scale. All symptoms are summed to derive a total frequency and total intensity score.

Perceived barriers. Derived from the PEDS-TX Survey (Rodrigue, 2004), this section includes perceived barrier statements to taking immunosuppressant medication. Each participant responded to a list of barriers using a 5-point likert-like scale, "*strongly disagree*" to "*strongly agree."* Parent and adolescent versions exist for this inventory. Reliability and validity analyses were conducted in this study for this scale.

Medication knowledge. Derived from the Medical Adherence Measure (MAM; Zelikovsky, 2002), the knowledge portion of this semi-structured interview includes questions concerning: 1) the name of each medication, 2) dosage frequency, 3) dosage amount, and 4) medication purpose. Each participant (parent and patient) receive a point for each domain they answer correctly for each medication (possible total of 4 points per medication). This total is then divided by the number of medications and multiplied by 100, with a higher percentage signifying greater medication knowledge.

Regimen responsibility. Derived from the Medical Adherence Measure (MAM; Zelikovsky, 2002), the responsibility portion of this semi-structured interview includes questions concerning: 1) who refills prescriptions, 2) which family members oversee medication taking, and 3) who has primary responsibility for overseeing medication taking. Degree of agreement and disagreement was examined between parent and adolescent responses.

Family Relationship Index. The Family Relationship Index (FRI; Moos & Moos, 1994) is a subset of the Family Environment Scale (FES), consisting of 3 of the 10 subscales: Conflict, Expressiveness, and Cohesion. Each subscale contains 9 true-false items, and the combined 27-item index is used to assess the overall quality of family relationships. Internal consistencies of .78, .69, and .85, and two-month test-retest reliabilities of .86, .73, and .85, respectively, have been reported for the three subscales of the FRI (Moos, 1990). When comparing normal and distressed families, distressed families are lower on cohesion and expressiveness and higher on conflict, with these differences evident after controlling for socioeconomic and family background characteristics (Moos & Moos, 1994).

Adolescent Risk Taking Survey. The Adolescent Risk Taking Survey (ARTS; Alexander, Kim, Ensminger, Johnson, Smith, & Dolan, 1990) is a 6-item scale to assess the risk-

taking propensity among adolescents. This scale is completed by the adolescents. The scale showed good reliability, as indicated by coefficient alpha and factor analyses (Alexander et al., 1990). In terms of validity, 8th-grade adolescents who scored higher on the risk-taking scale were more likely to initiate sexual activity and substance use in 9th grade than those who scored lower (Alexander et al., 1990).

Adherence Measures

Immunosuppressant drug assay levels. Immunosuppressant blood levels collected during the one year period prior to the patient's interview date were recorded from the medical chart. From the results of the blood assays, standard deviations (SD) were calculated. A higher SD signifies a higher degree of difference between individual levels, which suggests less consistent medication taking, and therefore, lower adherence. However, it is important to note that medication blood levels may vary as a result of acute illness or in cases in which a more aggressive treatment is implemented. Therefore, only medication blood levels that were obtained in the outpatient clinic during routine visits were analyzed. Higher SDs have been found to be predictive of clinical outcome (e.g., biopsy-proven rejection) (Shemesh et al., 2004). Blood levels of cyclosporine (outside of 150-400 ng/ml) or tacrolimus (outside of 5-17 ng/ml) that were out of the therapeutic range were also considered to be indicators of poor adherence (Chisholm et al., 2005).

Medical Adherence Measure. The Medical Adherence Measure (MAM; Zelikovsky, 2002) is a semi-structured interview to assess adherence behaviors in different domains of medical care that are typically expected of pediatric patients and their families. Although multiple modules for this measure exist, this investigation only included the Medication Module. This module includes questions concerning 1) medication taken late or missed in the past 7 days

and 2) the last missed dose prior to the past 7 days (ranging from 2 weeks ago to greater than a year ago). Percentage of missed and late doses is calculated by taking the number of prescribed minus number missed, divided by number prescribed, times 100. This measure has been used as a self-report measure with patients 11 years or older and with parents. The MAM was administered separately to each parent and patient. Validity and reliability studies are currently being conducted at Children's Hospital of Philadelphia (CHOP).

Clinical outcome (part of the PEDS-TX Survey, Parent Version 1.0 and derived from the medical record). During the interview clinical outcome data were obtained on: a) number of rejection episodes in the past 6 months, b) number of infections in the past 6 months, c) number of hospitalizations in the past six months, d) number of days hospitalized in the past 6 months. These data were confirmed by examining the medical chart. Acute rejection has been found to be associated with low immunosuppressant drug levels and subsequent chronic rejection (Feinstein, Keich, Becker-Cohen, Rinat, Schwartz, & Frishberg, 2005).

Adherence classification. Correlational analyses were conducted with self-reported and parent reported late and missed doses of immunosuppressant and other medications as well as standard deviations of serum drug levels of immunosuppressant medication. None of the correlations were found to be .50 or greater, with many of the correlations nonsignificant. For this reason, a composite adherence score was not used. Instead, a multidimensional adherence classification system was developed, taking into account each of these sources of data. Each patient was classified into one of four categories: Adherent/Stable, Adherent/Unstable, Nonadherent/Stable, Nonadherent/Unstable, and (see Table III for category descriptions). A Kappa coefficient was calculated between independent coders, Kappa = 0.99, indicating excellent reliability for classification.

Procedure

All parents of eligible adolescents were invited to participate. To recruit participants for the proposed study, patients were initially contacted by the transplant coordinator at clinic or via telephone to solicit interest. Interested families contacted the principle investigator directly, completed an interest form, or verbally consented to have the principle investigator contact them. Of those approached, 8% declined participation; reasons cited included no time (3), not comfortable with release of medical records (1), or none specified (3). Informed consent and assent were obtained at clinic or via postal mail.

Interview. The interview with each parent consisted of verbal consent and verbal administration of the MAM, the PEDS-TX Survey, Parent Version 1.0, the FRI, and demographic questions. The interview with each participating adolescent consisted of verbal assent and verbal administration of the MAM, the PEDS-TX Survey, Adolescent Version 1.0, the ARTS, and the FRI. Each interview was conducted by research assistants and/or graduate students in psychology. Interviewers were trained in all research procedures by the principle investigator. Training included observed practice of procedures and skills taught, focused on building rapport with and being sensitive to parents and patients with solid organ transplants, verbally administering the assessment questionnaires in an accurate and comfortable manner, giving answers to questions from parents and patients in an instructive manner that does not bias the research, and being culturally and socioeconomically sensitive when greeting and interviewing families. The vast majority of interviews (98%) were conducted over the phone. Of the 80 families recruited, 2 parents did not complete interviews (contacted repeatedly, but never available) and 10 adolescents did not complete interviews, reasons included: significant developmental delay (7), too shy (2), and not available after repeated attempts (1). Parent

interview length ranged from 29 to 114 minutes (M = 55.5, SD = 14.4) and adolescent interviews ranged from 24 to 66 minutes (M = 42.6, SD = 8.2). Twenty dollar gift cards were provided for participation. Referrals for psychological services were offered and made, with 30% of parents and 25% of adolescents requesting referrals. Interviews were conducted over a 5 month period.

Power Analyses. Within the adolescent sample of 70 participants, with power set at 0.80 and significance level set at .05, two-tailed tests, effects of .33 or greater are detectable. Within the parent sample of 78 participants, with power set at .80 and significance level set at .05, two-tailed tests, effects of .31 or greater are detectable. The average effect sizes for studies examining barriers to medication adherence and health behavior choices range from 0.35 to 0.375, respectively (e.g., Brownlee-Duffeck, Peterson, Simonds, Goldstein, Kilo, & Hoette, 1987; Chisholm, Lance, Williamson, & Mulloy, 2005; Dutton, Johnson, Whitehead, Bodenlos, & Brantley, 2005; Kloeblen & Batish, 1999; Mirotznik, Ginzler, Zagon, & Baptiste, 1998).

Table II
Demographic Information

Transplant study (n = 78)	Percentages
Parent gender	
Female	93.6
Male	6.40
Marital status	
Married	61.5
Single	14.1
Divorced	14.1
Separated	6.4
Widowed	2.6
Life partner	1.3
Level of education	
Did not complete high school	15.4
High school graduate	23.1
Some college	25.6
College graduate	23.1
Professional degree	12.8
Household income	
$0-$9,999	14.1
$10,000-$24,999	15.4
$25,000-$49,999	26.9
$50,000-$74,999	12.8
$75,000-$99,999	7.7
$100,000-$149,999	9.0
$150,000 +	11.5
Health coverage	
Medicare/Medicaid	46.2
Private insurance	32.1
No coverage	3.8
Medicare/Medicaid and private	7.7
Other	10.3
Prescription drug coverage	
Full covered	59.0
Small co-pay	24.4
Moderate co-pay	12.8
Out-of-pocket	2.6
Other	1.3

Table III

Medication Adherence Classification System

Adherent		**Nonadherent**	
Adherent/Stable	**Adherent/Unstable**	**Nonadherent/Stable**	**Nonadherent/Unstable**
1) All drug levels obtained are within range (no high or low levels noted) 2) Standard deviation of drug levels is below 3 3) Patient/parent reports missing/taking late < 10% of any medications in the last *7 days* 4) Patient/parent reports not missing a dose within the past *2 weeks*	1) A high or low drug level is noted and/or standard deviation is above 3 2) Patient/parent reports missing/taking late < 10% of any medication in the last *7 days* 3) Patient/parent reports not missing a dose within the past *2 weeks*	1) All drug levels obtained are within range (no high or low levels noted) 2) Standard deviation of drug levels is below 3 3) Patient/parent reports missing/taking late > 10% of any medication in the last *7 days* and/or patient/parent reports missing a dose within the past *2 weeks*	1) A high or low drug level is noted and/or standard deviation is above 3 2) Patient/parent reports missing/taking late > 10% of any medication in the last *7 days* and/or patient/parent reports missing a dose within the past *2 weeks*

Note. The two higher-order adherence groups were used for analyses to conduct point-biserial correlations between barriers and adherence.

CHAPTER 3

RESULTS

Analyses for this study involved multiple steps. Descriptive statistics were examined with corrections made for significantly skewed variables. An adherence classification system was designed to encompass subjective and objective adherence methods. This system will be described and its validity presented. Item selection and factor analyses for the development of parent and adolescent barrier scales will then be reviewed. The validity of the two barrier scales were examined by determining their association with contextual factors and then with the patients' adherence classification. The contribution of the various barriers was examined as predictors of adherence.

Descriptive Information and Preliminary Analyses

Descriptive statistics including means and standard deviations for each measure are detailed in Table VII and Table XI. The following variables were log transformed as they were significantly skewed: parent reported cohesion, parent reported overall family functioning, parent medication knowledge, and adolescent reported cohesion. Standard deviations of tacrolimus levels were rank-ordered, as some outliers were present. The magnitude of the correlations among adherence measures did not justify creating a composite rating. Alternatively, an adherence classification system was established (see Table III). This system classified patients into one of four groups: (1) those who report excellent adherence and had acceptable drug levels (Adherent/Stable; n = 11), (2) those who reported excellent adherence and had concerning drug levels (Adherent/Unstable; n = 15), (3) those who reported nonadherence and had acceptable

drug levels (Nonadherent/Stable; n = 19), and (4) those who reported nonadherence and had concerning drug levels (Nonadherent/Unstable; n = 35). For barrier analyses, the four categories were collapsed into two higher-order groups, Adherent (Adherent/Stable and Adherent/Unstable, *n* = 26) and Nonadherent (Nonadherent/Stable and Nonadherent/Unstable, *n* = 54). Analyses were then conducted to determine the effect of adherence categorization on the contextual variables of disease and regimen factors. In addition, analyses were conducted to examine the association between adherence classification and clinical outcomes.

Adherence Classification

Adherence categories and disease and regimen factors. Using one-way ANOVA and Chi-Square analyses to examine disease and regimen factors that may differ across the four adherence groups, no differences were found for time since transplant, number of medications, type of transplant, and living vs. cavearic donor recipients. An analysis of variance showed that the effect of adherence group was significant for frequency of side effects reported by parents $F(3,74) = 4.79$, $p = .004$ and frequency of side effects reported by adolescents $F(3,66) = 2.74$, $p = .05$. Tukey HSD post hoc analyses indicated that the frequency of parent reported side effects was significantly higher in the nonadherent/unstable ($M = 66.9$, $SD = 16.7$) and nonadherent/stable groups ($M = 67.3$, $SD = 17.9$) than in the adherent/stable ($M = 53.6$, $SD = 3.40$) and adherent/unstable groups ($M = 52.0$, $SD = 12.7$). For adolescent report, those classified as nonadherent/unstable ($M = 69.0$, $SD = 22.6$) and nonadherent/stable group ($M = 68.1$, $SD = 19.7$) reported more side effects than those classified as adherent/stable ($M = 50.1$, $SD = 12.6$) and adherent/unstable group ($M = 55.7$, $SD = 15.8$), but it did not reach statistical significance in post hoc analyses. It is interesting to note that parent and adolescent-perceived frequency of side effects appeared to function independently of erratic drug assay levels, as the nonadherent groups

(nonadherent/unstable and nonadherent/stable) were more similar in their level of perceived side effects than the two groups with erratic drug assays (nonadherent/unstable and adherent/unstable).

Validity of adherence classification. The occurrence of a rejection episode in the past 6 months was assessed for patients in each of the four adherence categories. Twenty individuals had one or more rejection episodes in the past six months. Of those individuals, one was classified as adherent/stable (5% of individuals who had a rejection episode, 9% of those in the adherent/stable group), four were classified as adherent/unstable (20% of rejection episodes, 27% of adherent/stable group), one was classified as nonadherent/stable (5% of rejection episodes, 5% of nonadherent/stable group), and fourteen were classified as nonadherent/unstable (70% of rejection episodes, 40% of nonadherent/unstable group). A chi-square test of independence was performed. The relation between the occurrence of a rejection episode in the past six months and membership in the nonadherent/unstable group was significant, χ^2 (3, N = 80) = 9.65, p =.022. No significant results were found between membership in an adherence category and number of hospital admissions, number of days spent in the hospital, and number of infections in the past six months. After establishing initial validity for the adherence classification system, analyses were conducted to determine item selection, initial reliability, and initial validity of the parent and adolescent barriers to medication adherence scales.

Development of the Parent Mediation Barriesr Scale (PMBS)

Item selection and factor analyses of the PMBS will be presented. This will be followed by examining the associations between PMBS total and subscale scores and the various contextual factors. The association between the PMBS and the patients' adherence categorization will then be determined.

Parent scale item selection and factor analysis. Each of the 39 original items was examined to determine its contribution to the scale. All items that were endorsed as "strongly disagree" or "disagree" at the 90th percentile, suggesting that they were rarely to never endorsed as barriers, were dropped from the scale. This resulted in eliminating 19 items. Next, item-total correlations were conducted, with one item dropped ($r < .25$; criteria outlined by DeVellis, 2003; see Table IV). The remaining items were entered into a principle components factor analysis (PCA) with Varimax rotation. The joint criteria of eigen values > 1 and Cattell's elbow criteria on the scree plot (DeVellis, 2003) indicated that four factors best explained the structure of the Parent Medication Barrier Scale. Two items were omitted from the factor analyzed subscales as they had overall loading < .40 and did not conceptually fit with any of the factors. When the structure was re-run, one item significantly loaded (above .40) with 3 factors, so it was dropped. With those items omitted, the structure held, accounting for 62.3% of the variance in their responses (see Table V). The 16-item scale had a Cronbach's alpha of .87 (see Table VI). Sample mean for the scale was 35.76 (SD = 10.3). Two items had loading of .40 or above on two factors.

The results are consistent with the hypothesized subscales, with slight revision. Factor 1, labeled Disease Frustration/Adolescent Issues, contains 7 items (α = .84). This factor aligns best with the hypothesized family/adjustment domain. Items suggestive of a behavioral power struggle between the parent and adolescent were dropped early in the analysis as they were not endorsed by parents (e.g., "*My child refuses to take his/her medication"*). Factor 2, labeled Regimen Adaptation/Cognitive, contains 5 items (α = .82). This factor is consistent with the hypothesized cognitive barrier scale. Factor 3, labeled Ingestion Issues, contains 3 items (α = .69), partially representing the hypothesized medication/disease understanding subscale. Items

that represented lack of understanding for the importance of the medication and feeling that the medication was unnecessary were not endorsed and therefore not represented in this domain. Factor 4, labeled Parent Reminder, contains 1 item; therefore an alpha coefficient was not calculated. This item was retained in the factor analysis, as it contributed significantly to the explanatory power of the scale (8.4%) and provides useful information concerning ownership of regimen responsibility. All of the factors were significantly intercorrelated except for Parent Reminder and Ingestion Issues (see Table VII). Following item selection and factor analyses, the construct and criterion validity was examined for the PMBS total scale score and subscale scores.

PMBS construct validity with demographic, disease, and regimen factors. One-way ANOVA and Pearson Product Moment correlation coefficients were conducted to examine differences in the number of barriers reported across demographic factors and disease and regimen factors. No significant differences were detected across age, developmental delay, gender, race, income, and parent educational background. In reference to disease and regimen factors, among parents of patients who received living or cadaver organs, parents of living donor recipients ($M = 40.4$, $SD = 9.38$) had a significantly higher PMBS total scale score $F(1, 56) = 6.12$, $p = .02$ than cadaveric donor recipient parents ($M = 33.5$, $SD = 10.6$). Parents of living donor recipients ($M = 13.6$, $SD = 4.66$) also had higher Regimen Adaptation/Cognitive barrier scores $F(1, 56) = 13.8$, $p < .00$ than cadaveric donor recipient parents ($M = 9.63$, $SD = 3.46$). No significant differences were found for health care coverage, prescription drug coverage, and transplant type. Correlation analyses for time since transplant, number of medications (i.e., an indicator of regimen complexity), and frequency and intensity of side effects are displayed in Table VI. Less time since transplant was significantly associated with higher Ingestion Issues

subscale scores. A greater number of medications were significantly associated with higher Ingestion Issues scores and Parent Reminder scores. More frequent and intense side effects were associated with higher PMBS total scale scores and higher Disease Frustration/Adolescent Issues subscale scores.

PMBS construct validity with child and family factors. Associations between the PMBS and child and family contextual variables were examined with correlational and one-way ANOVA analyses. With regard to regimen responsibility, an analysis of variance showed that the effect of the person who was primarily responsible for the patient's medication regimen was significant, $F(3,57) = 8.46$, $p = .00$. As expected, using Tukey HSD post hoc analyses the PMBS Parent Reminder scores were significantly lower when the parent and child agreed that the child was primarily responsible for their medication regimen ($M = 1.90$, $SD = 0.97$), compared to when they agreed that the parent was responsible ($M = 3.16$, $SD = 1.43$) or when they disagreed ($M = 3.17$, $SD = 0.99$). All other relationships were examined using correlation analyses (see Table VI). Lower parent medication knowledge was significantly associated with higher PMBS total scale scores, higher Disease Frustration/Adolescent Issues scores, and Ingestion Issues scores. Higher scores on the PMBS Parent Reminder scale were also associated with lower adolescent knowledge scores. Parent reported family functioning was not associated with barrier scores, with the exception of higher expressiveness scores being associated with lower scores on the Ingestion Issues subscale. The lack of significant correlations for the family variables may be due to a restricted range of scores for the parent completed measures of family functioning. Parents reported high levels of cohesion ($M = 7.90$, $SD = 1.39$) and low levels of conflict ($M = 2.56$, $SD = 1.94$), with mean scores more favorable than was found in a normative sample (cohesion $M = 6.73$, $SD = 1.47$; conflict $M = 3.18$, $SD = 1.91$; Moos & Moos, 1994).

PMBS criterion validity with adherence. To assess criterion validity of the PMBS, associations between barrier scale scores and adherence was examined. Since predicting nonadherence was the purpose of this analysis, the four adherence categories were collapsed into the two higher-order factors of Adherent and Nonadherent. Point-biserial correlations were conducted between barrier scales and adherence (see Table VII). Higher PMBS total scale scores, Disease Frustration/Adolescent Issues scores, and Regimen Adaptation/Cognitive scores were significantly associated with poor adherence.

Development of the Adolescent Medication Barriers Scale (AMBS)

The same series of steps that was used to develop and assess the validity of the PMBS was used for the AMBS. Item selection and factor analyses were followed by an examination of the associations between the AMBS total and subscale scores and contextual factors. This was followed by determining the association between the AMBS and the patients' adherence classification.

Adolescent scale item selection and factor analysis. Similar to the Parent Medication Barrier Scale, each of the 29 original items were examined to determine its contribution to the scale. All items that were endorsed as "strongly disagree" or "disagree" at the 90th percentile, suggesting that they were rarely to never endorsed as barriers, were dropped from the scale. This resulted in eliminating 8 items. Next, item-total correlations were conducted ($r < .25$; criteria outlined by DeVillis, 2003; see Table VIII). One item met this criterion ("*I rely on my parent to remind me to take my medication*") and was dropped from the subsequent factor analysis, a departure from the PMBS. The remaining items were plugged into a principle components factor analysis (PCA) with Varimax rotation. The joint criteria of eigen values > 1 and Cattell's elbow criteria on the scree plot (DeVellis, 2003) indicated that three factors best explained the

structure of the Adolescent Medication Barrier Scale. Three items were omitted from the factor analyzed subscales as they had overall loading < .40 and did not conceptually fit with any of the factors. With those items omitted from the factors, the structure held, accounting for 54.7% of the variance in their responses (see Table IX). The overall 17-item scale has a Cronbach's alpha of .86 (see Table X). Sample mean for the scale was 37.9 (*SD* = 10.8). Five items had loading of .40 or above on two separate factors.

Similar to the PMBS, results parallel the hypothesized subscales with some revision. Factor 1, labeled Disease Frustration/Adolescent Issues, contains 7 items (α = .84). This factor aligns best with the hypothesized family/adjustment domain. Consistent with the PMBS, items suggestive of a behavioral power struggle between the parent and adolescent were dropped early in the analysis as they were not endorsed (e.g., "*I believe that I can get out of taking the medication if I stall"*). Factor 2, labeled Ingestion Issues, contains 5 items (α = .70), partially representing the hypothesized medication/disease understanding subscale. Items that represented lack of understanding for the importance of the medication and feeling that the medication was unnecessary were not endorsed and therefore not represented in this domain. Factor 3, labeled Regimen Adaptation/Cognitive, contains 5 items (α = .76). This factor is consistent with the hypothesized cognitive barrier scale. Unlike the PMBS, there wasn't a forth factor. All factors were significantly intercorrelated (see Table XI). Following item selection and factor analyses, construct and criterion validity were examined for the AMBS total scale score and subscale scores.

AMBS construct validity with demographic, disease, and regimen factors. To examine the variability of AMBS scores across demographic, disease, and regimen factors, one-way ANOVA and Pearson Product Moment correlational analyses were conducted. No significant differences

in adolescent barrier scores were detected for age, gender, race, and income. An analysis of variance showed that the effect of parent relationship status was significant, $F(4,62) = 3.05$, $p = .023$ for adolescent reports of Disease Frustration/Adolescent Issues barriers. Post hoc analyses using the Tukey HSD post hoc test indicated that the average number of Disease Frustation/Adolescent Issues barriers was significantly higher for separated families ($M = 22.6$, $SD = 7.27$) than married ($M = 15.5$, $SD = 5.18$) and divorced families ($M = 12.6$, $SD = 3.44$). An analysis of variance showed that the effect of parent educational background was significant, $F(4,63) = 2.93$, $p = .028$ with the Tukey HSD post hoc test indicating that adolescents of high school educated parents ($M = 13.3$, $SD = 3.35$) reported more Ingestion Issue barriers than adolescents of parents who received a professional degree ($M = 8.38$, $SD = 2.45$). No significant differences were found for health care coverage, prescription drug coverage, transplant type, and donor type.

For other disease and regimen variables, correlation analyses for time since transplant, number of medications (i.e., an indicator of regimen complexity), and frequency and intensity of side effects are detailed in Table XI. No significant associations were noted for time since transplant and number of medications. Adolescents' reports of more frequent and intense side effects were associated with higher AMBS total scale scores, Disease Frustration/Adolescent Issues scores, and Regimen Adaptation/Cognitive scores.

AMBS construct validity with child and family factors. Although no relationship between regimen responsibility and adolescent barriers was found, a number of other associations were noted in the child and family domain (see Table XI). Lower adolescent and parent knowledge were associated with higher Ingestion Issues scores. Associations between family functioning and barriers scales were consistent with hypotheses, wherein higher cohesion, more

expressiveness, and lower conflict scores were associated lower AMBS total scale scores, lower Disease Frustration/Adolescent Issues scores, and lower Ingestion Issues scores. There were no significant associations found between adolescent risk taking and barrier scores.

AMBS criterion validity with adherence. As described for the PMBS, the four adherence categories were collapsed into the two higher-order factors of Adherent and Nonadherent. Point-biserial correlations were conducted between barrier scales and adherence (see Table XI). Consistent with the PMBS, higher AMBS total scale scores, Disease Frustration/Adolescent Issues scores, and Regimen Adaptation/Cognitive scores were significantly associated with lower adherence. With the initial psychometric properties for each barrier scale reviewed, the contribution of specific types of barriers to the prediction of adherence was examined.

Barriers as predictors of adherence.

Parent barriers and adherence. To examine the predictive power of barriers on adherence, logistic regressions were conducted with the binary categorical variable of adherent/nonadherent. Parent barriers and adolescent barriers were examined separately. Each parent barrier subscale was simultaneously entered into the regression model, with non-significant subscales trimmed from the model to generate the most parsimonious predictive model of adherence group membership. As listed in Table XII, significant predictors of adherence group membership were the Disease Frustration/Adolescent Issues barriers subscale and Parent Reminder subscale. Membership in the nonadherent group was 1.3 times more likely for adolescents whose parents reported more Disease Frustration/Adolescent Issue barriers. More frequent parent reminders served as a protective factor, yielding an odds ratio of only .62 for nonadherent classification.

Adolescent barriers and adherence. An analogous procedure was conducted for adolescent barrier subscales, with all three subscales simultaneously entered into a logistic regression. Only one barrier subscale, Disease Frustration/Adolescent Issues significantly predicted membership in the nonadherent category, with higher scores on this subscale increasing the likelihood of nonadherence.

Table IV
Parent Medication Barriers Scale (PMBS)

Items (Responses)	*M*	*SD*	Corrected item-total correlation	Alpha if item deleted
Disease Frustration/Adolescent Issues				
1. My child feels that it gets in the way of his/her activities	1.96	1.01	.51	.86
2. My child does not want other people to notice him/her taking the medication	2.13	1.12	.50	.86
3. My child sometimes feels sick and can't take the medication	2.13	1.04	.55	.86
4. My child doesn't like what the medication does to his/her appearance	2.59	1.24	.59	.85
5. My child is tired of taking medicine	2.54	1.22	.75	.84
6.My child is tired of living with a medical condition	2.55	1.12	.52	.86
7. My child believes the medicine has too many side effects	2.09	.98	.46	.86
Regimen Adaptation/Cognitive				
8. My child is forgetful and doesn't remember to take his/her medication every time	2.28	1.34	.51	.86
9. My child is not very organized about when and how he/she takes his/her medication	2.09	.98	.50	.86
10. My child is very busy with other things that get in the way of taking the medication	2.21	1.08	.53	.86
11. My child finds it hard to stick to a fixed medication schedule	2.08	1.10	.62	.85
12. I am not always there to remind my child to take his/her medication	2.42	1.24	.49	.86
Ingestion Issues				
13. My child has a hard time swallowing the medicine	1.63	.94	.36	.86
14. My child has too many pills to take	2.10	1.22	.48	.86
15. My child does not like how the medicine tastes	2.18	1.17	.28	.87
Parent Reminder				
16. My child relies on me to remind him/her when to take his/her medication	2.78	1.31	.31	.87

Table V
Summary of Factor Loadings for PMBS

Item	Factor Loading			
	Disease Frustration/ Adolescent Issues	Regimen Adaptation/ Cognitive	Ingestion Issues	Parent Reminder
1	**.65**	.25	.06	-.02
2	**.73**	.05	.23	-.07
3	**.55**	.26	.33	-.07
4	**.61**	.25	.08	.40
5	**.53**	.49	.27	.30
6	**.77**	.18	.03	-.05
7	**.72**	.00	.07	.18
8	.03	**.79**	.11	.18
9	.10	**.76**	-.05	.29
10	.23	**.73**	.22	-.32
11	.21	**.69**	.17	.30
12	.28	**.68**	-.07	-.00
13	.17	.09	**.79**	-.17
14	.28	.11	**.69**	.16
15	.00	.00	**.80**	.18
16	.03	.24	.10	**.80**
Eigenvalue	3.33	3.22	2.09	1.34
% Variance	20.80	20.13	13.05	8.35

Note. Boldface indicates highest factor loadings.

Table VI
Means, Standard Deviations, and Alpha Internal Consistency Values for PMBS Four Subscales and Total Scale Score

Subscale	Number of Items	*M*	*SD*	Alpha
Disease Frustration/ Adolescent Issues	7	15.99	5.52	.84
Regimen Adaptation/Cognitive	5	11.08	4.24	.82
Ingestion Issues	3	5.91	2.63	.69
Parent Reminder	1	2.78	1.31	--
Total Scale	16	35.76	10.35	.87

Table VII

Intercorrelations, Means, and Standard Deviations for PMBS

Variable	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	*M*	*SD*
PMBS																	
1. Total score	---	**.88****	**.79****	**.59****	**.42****	-.13	.17	**.25***	**.24***	-.21	-.1	-.10	-.06	-.03	**.37****	35.8	10.3
2. Disease Frustration/AI		---	**.53****	**.41****	**.23***	-.13	.16	**.35****	**.33****	**-.27***	-.12	-.12	-.06	-.03	**.39****	16.0	5.5
3. Regimen Adaptation/C			---	**.24***	**.32****	.00	.01	.10	.09	.06	.01	-.07	.17	.06	**.33****	11.1	4.2
4. Ingestion Issues				---	.17	**-.26***	**.22***	.07	.08	**-.27***	-.00	-.08	**-.23***	-.06	.17	5.9	2.6
5. Parent Reminder					---	.01	**.22***	.07	.05	-.14	**-.29***	.08	.01	-.02	-.14	2.8	1.3
Disease & Regimen																	
6. Time since transplant						---	**-.29***	-.02	-.06	.22	-.06	.07	.16	.20	.08	57.9	53.0
7. Number of medications							---	**.33****	**.31****	**-.43****	**-.36****	.07	-.07	-.15	.00	6.43	3.20
8. Frequency of side effects (p)								---	**.91****	.03	-.16	.06	.06	-.11	**.40****	62.4	16.8
9. Intensity of side effects (p)									---	.01	-.15	.04	.02	-.12	**.40****	49.4	13.8
Child & Family																	
10. Medication knowledge (p)										---	**.33****	-.13	**.31****	.17	.13	-1.0	.70
11. Medication knowledge (c)											---	-.09	**.27***	-.15	.09	58.4	25.9
12. Cohesion (p)												---	**-.26***	**.34****	-.09	0.25	.24
13. Expression (p)													---	-.05	.08	6.15	1.68
14. Conflict (p)														---	.02	2.56	1.94
Adherence																	
15. Nonadherence															---	0.67	.47

Note. Correlations are two-tailed. (p) = parent report; (c) = child report.

Table VIII
Adolescent Medication Barriers Scale (AMBS)

Items (Responses)	*M*	*SD*	Corrected item-total correlation	Alpha if item deleted
Disease Frustration/Adolescent Issues				
1. I don't want to take the medicine at school	2.28	1.32	.54	.85
2. I feel that it gets in the way of my activities	1.84	.99	.54	.85
3. I am forgetful and I don't remember to take the medicine every time	2.70	1.24	.42	.85
4. I do not want other people to notice me taking the medicine	1.97	1.11	.64	.84
5. I sometimes just don't feel like taking the medicine	2.07	1.06	.57	.85
6. I don't like what the medication does to my appearance	2.24	1.14	.48	.85
7. I am tired of taking medicine	2.51	1.36	.56	.84
8. I am tired of living with a medical condition	2.60	1.24	.65	.84
Ingestion Issues				
9. I believe that the medicine is hard to swallow	2.03	1.11	.25	.86
10. I believe that I have too many pills to take	2.51	1.33	.41	.85
11. I don't like how the medicine tastes	2.48	1.27	.41	.85
12. I believe the medicine has too many side effects	2.30	1.06	.53	.85
13. I get confused about how the medicine should be taken (with or without food, with or without water, etc.)	1.90	.85	.33	.85
Regimen Adaptation/Cognitive				
14. I am not organized about when and how to take the medicine	1.94	.90	.38	.85
15. I find it hard to stick to a fixed medication schedule	2.10	.99	.55	.85
16. Sometimes I don't realize when I run out of pills	2.40	1.15	.50	.85
17. Sometimes its hard to make it to the pharmacy to pick up the prescription before the medicine runs out	1.99	.96	.41	.85

Table IX
Summary of Factor Loadings for AMBS

	Factor Loading		
Item	Disease Frustration/ Adolescent Issues	Ingestion Issues	Regimen Adaptation/Cognitive
1	**.54**	.46	.01
2	**.60**	.26	.02
3	**.50**	-.15	.42
4	**.69**	.25	.12
5	**.73**	.10	.10
6	**.63**	-.01	.19
7	**.75**	.14	.05
8	**.78**	.18	.08
9	-.09	**.81**	.03
10	.28	**.61**	-.13
11	.23	**.62**	.09
12	.35	**.58**	.12
13	-.08	**.57**	.45
14	.03	.06	**.82**
15	.43	-.03	**.64**
16	.47	-.04	**.56**
17	-.00	.24	**.82**
Eigenvalue	4.19	2.56	2.55
% Variance	24.64	15.04	14.98

Note. Boldface indicates highest factor loadings.

Table X
Means, Standard Deviations, and Alpha Internal Consistency Values for AMBS Four Subscales and Total Scale Score

Subscale	Number of Items	*M*	*SD*	Alpha
Disease Frustration/ Adolescent Issues	8	18.21	6.51	.84
Ingestion Issues	5	11.21	3.86	.70
Regimen Adaptation/Cognitive	4	8.47	3.07	.76
Total Scale	17	40.16	11.00	.86

Table XI
Intercorrelations, Means, and Standard Deviations for AMBS

Variable	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	*M*	*SD*
AMBS																	
1. Total score	---	**.88****	**.68****	**.72****	.05	.01	**.32****	**.33****	-.03	-.08	**-.30****	**-.27***	**.33****	.05	**.31****	40.4	10.9
2. Disease Frustration/AI		---	**.46****	**.48****	.03	.00	**.33****	**.35****	-.03	.02	**-.31****	**-.27***	**.32****	.05	**.30****	15.7	5.9
3. Ingestion Issues			---	**.23***	.02	.15	.10	.08	**-.23***	**-.33****	**-.25***	-.22	**.29****	.05	.09	11.2	3.9
4. Regimen Adaptation/C				---	.06	-.13	**.24***	**.27***	.10	.12	-.15	-.12	.13	.01	**.28***	11.2	3.8
Disease & Regimen																	
5. Time since transplant					---	**-.29****	-.06	-.05	.22	-.06	-.12	-.18	.19	.07	.08	57.9	53.0
6. Number of medications						---	.13	.09	**-.43****	**-.36****	.11	.13	-.11	-.06	-.01	6.4	3.2
7. Freq of side effects (c)							---	**.93****	.01	-.09	-.16	-.08	**.23***	.02	**.33****	64.7	20.9
8. Intensity of side effects (c)								---	-.02	-.07	-.10	-.12	**.23***	.02	**.35****	48.5	16.3
Child & Family																	
9. Med knowledge (p)									---	**.33****	.09	.21	-.15	.02	.09	-1.0	.70
10. Med knowledge (c)										---	.10	.05	-.09	-.09	.13	58.4	25.9
11. Cohesion (c)											---	**.38****	**-.41****	-.03	-.20	-.37	.26
12. Expression (c)												---	**-.47****	-.06	-.04	4.66	1.70
13. Conflict (c)													---	**.32****	.18	2.93	1.97
14. Risk Taking														---	.16	8.60	2.07
Adherence																	
15. Nonadherence															---	.68	.47

Note. Correlations are two-tailed. (p) = parent report; (c) = child report.

Table XII
Logistic Regression Analyses for Parent and Adolescent Barriers Predicting Adherence

Variable	Odds ratio	95% CI lower/ upper	β	SE	Wald test	d.f.	Sig level	R^2
Parent Barrier Model								.29
Disease Frustration/ Adolescent Issues	1.26	1.10/1.44	.23	0.07	11.69	1	.001	--
Parent Reminder	.62	0.40/0.96	.48	0.23	4.51	1	.034	--
Adolescent Barrier Model								.14
Disease Frustration/ Adolescent Issues	1.14	1.03/1.29	.14	0.06	5.68	1	.017	--

Note. R^2 is the Nagelkerke R square and is calculated for the full model, rather than for each predictor.

CHAPTER 4

DISCUSSION

Factor analytic procedures were used to develop both parent and adolescent completed scales for assessing barriers to medication adherence. The scales were designed to be multidimensional, emphasizing areas of difficulty observed in adolescent patients. The factors that emerged for both measures were disease frustration/adolescent issues, regimen adaptation/cognitive issues, and ingestion issues. Unique to the parent scale, there was a one item parent reminder subscale. The validity of these brief, easily completed measures is supported by significant associations between barriers scale scores and relevant disease, medical regimen, child, and family factors. Further, total and subscale scores were significantly associated with the patients' medical adherence classification. These assessment measures represent the first psychometrically sound and valid barrier scales in the pediatric transplant literature.

The validity of the parent and adolescent subscales was established by examining their associations with contextual factors and adherence. Among the findings for the parent barrier scale, parents of living donor recipients reported higher PMBS Total barrier scores and Regimen Adaptation/Cognitive barriers. Given that living donors are often family members, whereas cadaveric donors are unknown individuals, the interpersonal dynamics involved may be much more complicated for both the donors and recipients. Similar results were found in a study with pediatric African American renal transplant patients (Tucker et al., 2001). These two studies suggest a need to further examine the influence of beliefs, attributions, and other family dynamics on outcomes in living donor recipients and their families. A protective factor seemed

to emerge from the results with the Parent Reminder subscale. Parents of adolescents who were taking a greater number of medications and who were also less knowledgeable about their regimen provided more prompts to their children to take their medication. It is likely that parents were recognizing and responding to the adolescents' need for assistance.

For the AMBS, the Total scale and the Disease Frustration/Adolescent Issues and Ingestion Issues subscales were associated in the expected direction with adolescents' reports of cohesion, expressiveness, and conflict. Medication taking could potentially be a battle ground for parent-adolescent conflict. Similarly, adolescent difficulties related to medication taking could strain familial relationships. Regardless of directionality, these findings underscore the importance of examining family functioning with pediatric transplant recipients.

Medical factors were related to both PMBS and AMBS scales. For both parents and adolescents, the frequency and intensity of side effects were related to Total barriers and to the subscales of Disease Frustration/Adolescent Issues. Perceived side effects were also associated with Regimen Adaptation/Cognitive factors for the adolescent patients. This suggests that healthcare providers should be especially attuned to the negative impact of medication side effects on the patients' health behavior choices and outcome. Although side effects may be difficult to eliminate, efforts to address their psychological impact are warranted. In considering other medical factors, parents and adolescents who had greater knowledge of the adolescents' medication regimen reported fewer perceived barriers. Unlike side effects, knowledge is malleable. Perhaps ongoing assessment of medication knowledge could identify those who are at risk for nonadherence.

For both the AMBS and PMBS, the Total score, Disease Frustration/Adolescent Issues and Regimen Adaptation/Cognitive subscales were found to be associated with nonadherence.

Parent Reminders was also found to be associated with better adherence. These findings support the validity and clinical utility of these two measures in this important area of pediatric health care. The scales appear to be psychometrically sound and are correlated in the expected direction with contextual factors and adherence, with further research investigating their utility indicated.

The implications of these findings are clear. These scales can serve as brief screening tools to determine the most prominent issues that may be interfering with adherence. From this, individualized treatment plans can be developed for transplant patients that may involve implementing behavioral cues or making referrals for psychotherapy. The key issues that surfaced in this study can easily inform the development of group interventions targeting adolescent transplant recipients. Prominent components of this intervention would include addressing adjustment issues that surface when living with a transplanted organ (e.g., coping with side effects). This would likely be best accomplished in a group format where peer-to-peer contact could provide a normalizing experience and social support. With some of the implications considered, this study must be viewed in light of its limitations.

In addition to the development of barriers measures, a novel medication adherence classification was designed. A difficulty in this area of research has been that measures of immunosuppressant blood levels and subjective reports of adherence often do not correspond (e.g., Chisholm et al., 2005). In this investigation, a multidimensional categorization of adherence was created that takes into account the standard deviation of immunosuppressant medications, out-of-range drug levels, and parent and adolescent reports of doses missed or taken late. From these biological and subjective measures, patients were assigned to one of four categories: adherent/stable, adherent/unstable, nonadherent/stable, and nonadherent/unstable. For determining patients' adherent/nonadherent classification, parent and adolescent reports were

used. Reports of missing or taking medication late were considered accurate, regardless of the patients' lab reports, given that these reports were contrary to socially desirable responding. The majority of the patients (67.5%) reported missing or taking late > 10% of their doses, and therefore were classified as nonadherent. Within the adherent groups, there are those who had stable and therapeutic drug assay levels (13.8% of sample) and were likely to be true positives for adherence behaviors. However, in the adherence group also were those who had either nontherapeutic levels or high standard deviations for their assays, yet deny missing or taking any medications late (19% of sample). These reports are potentially suspect. They may have been inaccurate reporters or may have been experiencing medical complications that contribute to their undesirable blood levels. The adherent/unstable group is in need of further investigation.

The validity of the classification system is supported by the results of analyses examining medication side effects and rejection episodes for each group. According to parent reports and trends based on adolescents' reports, the two adherent groups of patients reported the fewest medication side effects. With regard to clinical outcomes, 40% of individuals in the nonadherent/unstable and 27% of the adherent/unstable group experienced a rejection episode in the past 6 months. Only 9% of the patients in the adherent/stable and 5% of the patients in the nonadherent/unstable group experienced a rejection episode in that same time frame.

There are also limitations in the study that deserve mention. Over half of the patients in this sample were kidney transplant recipients; therefore the results may better characterize this population. However, the constituency of the sample used in this investigation is representative of the pediatric transplant literature, as adolescent kidney recipients are the largest group of adolescent patients nationwide. In addition, this sample was recruited from one major transplant center in the southeastern United States. These findings must be tested by replicating this

research at other major medical institutions and at other geographic locations. With regard to the findings in this study, perceived side effects played a prominent role in relation to barriers to medication adherence and adherence behavior itself. Unfortunately, objective measures of side effects were not included in this study to determine the degree of overlap between medically documented and subjective experiences. It is not clear that this added information would provide any further understanding of its relationship to adherence behavior, but could be explored in future investigations.

In relation to statistical procedures, the number of patients in this study is at the lower end of acceptability for conducting factor analyses; therefore the factor structure may differ slightly if conducted on another transplant sample. The limitation of small sample size is characteristic of much of the research in pediatric psychology and reflects the difficulty in conducting research with children living with rare conditions. But notably, the sample size in this investigation is one of the largest in the pediatric transplant literature (e.g., Gerson Furth, Neu, & Fivush 2004; Lurie et al., 2000). In reference to the predictive power of the barrier measure, it shows promise as a predictor of adherence outcomes, but long term follow-up is necessary. Currently, a follow-up study is planned for this sample to examine adherence and clinical outcomes at one-year, two-year, and five-year intervals. Lastly, it is possible that there are other relevant barriers than the ones assessed in this study. An open-ended question will be included on the final parent and adolescent scales that will allow them to note any barriers not previously assessed. With limitations considered, there are several directions for future research.

The results in this study support examining adherence issues across solid organ groups. This is important for the area of pediatric transplant as most studies include a very small number of patients. Conducting research across organ groups will further test the potential

generalizability of findings and increase statistical power. In relation to clinical research, the parent and adolescent barrier scales were designed to be implemented as part of routine clinical assessment. These measures could be administered to both pre- and post-transplant patients. Conducting research to examine the predictive power of these barriers scales in the pre-transplant population could potentially lead to preventative efforts to head off adherence difficulties prior to transplantation.

An important step for future research and clinical work is using the information provided by the barrier scales to improve adherence. The barrier scale items are face valid and clinically relevant. Simply examining items endorsed by parents and/or adolescents could provide healthcare professionals with an indication of the need for further assessment or intervention. These interventions would target the most prominent concerns and barriers (e.g., coping with side effects) and other challenges associated with adapting to the regimen. Assessment and intervention to monitor and improve adherence are important in any area of pediatrics. However, for pediatric transplant patients it is critical, given the life and death issues involved. The barrier scales developed in this study can aid in this endeavor.

CHAPTER 5

REFERENCES

2004 Annual Report of the U.S. Organ Procurement and Transplantation Network and the Scientific Registry of Transplant Recipients: Transplant Data 1994-2003. Department of Health and Human Services, Health Resources and Services Administration, Healthcare Systems Bureau, Division of Transplantation, Rockville, MD; United Network for Organ Sharing, Richmond, VA; University Renal Research and Education Association, Ann Arbor, MI.

Abbott, J., Dodd, M., Gee, L., & Webb, K. (2001). Ways of coping with cystic fibrosis: Implications for treatment adherence. *Disability and Rehabilitation, 23*, 315-324.

Alexander, C.S., Kim, Y.J., Ensminger, M., Johnson, K.E., Smith, B.J., & Dolan, L.J. (1990). A measure of risk taking for young adolescents: Reliability and validity assessments. *Journal of Youth and Adolescents, 19*, 559-569.

Anderson, B.J., Auslander, W.F., Jung, K.C., Miller, J.P., & Santiago, J.V. (1990). Assessing family sharing of diabetes responsibilities. *Journal of Pediatric Psychology, 15*, 477-492.

Anderson, B.J., Vangsness, L., Connell, A., Butler, D., Goebel-Fabbri, A., & Laffel, L.M.B. (2002). Family conflict, adherence, and glycaemic control in youth with short duration Type 1 diabetes. *Diabetic Medicine, 19*, 635-642.

Bandura, A. (2004). Health Promotion by Social Cognitive Means. *Health Education and Behavior, 31*, 143-164.

Baron, R.M., & Kenny, D.A. (1986). The moderator-mediator variable distinction in social

psychological research: Conceptual, strategic, and statistical considerations. J*ournal of Personality and Social Psychology, 52*, 1173-1182.

Baum, D. & Bernstein, D. (1993). Heart and lung transplantation in children. In I.H.Gessner & B.E. Victoria (Eds.), *Pediatric cardiology: A problem oriented approach (pp. 245-252.* Philadelphia: W.B. Saunders.

Beck, D.E., Fennell, R.S., Yost, R.L., Robinson, J.D., Geary, D., Richards, G.A. (1980). Evaluation of an educational program on compliance with medication regimens in pediatric patients with renal transplants, *Journal of Pediatrics, 96*, 1094-1097.

Becker, M.H., Drachman, R.H., & Kirscht, J.P. (1972). Predicting mothers' compliance with pediatric medical regimens. *Journal of Pediatrics, 81*, 843-854.

Bender, B., Milgrom, H., Rand, C., & Ackerson, L. (1998). Psychological factors associated with medication nonadherence in asthmatic children. *Journal of Asthma, 35,* 347-353.

Brownlee-Duffeck, M., Peterson, L., Simonds, J.F., Goldstein, D., Kilo, C., & Hoette, S. (1987). The role of health beliefs in the regimen adherence and metabolic control of adolescents and adults with diabetes mellitus. *Journal of Consulting and Clinical Psychology, 55,* 139-144.

Bush, P.J. & Iannotti, R.J. (1990). A children's health belief model. *Medical Care, 28*, 69-86.

Chaney, J.M. & Peterson, L. (1989). Family variables and disease management in juvenile rheumatoid arthritis. *Journal of Pediatric Psychology, 14,* 389-403.

Chisholm, M.A. (2002). Issues of adherence to immunosuppressant therapy after solid-organ transplantation. *Drugs, 62,* 567-575.

Chisholm, M.A., Lance, C.E., Williamson, G.M., & Mulloy,L.L. (2005). Development and validation of an immunosuppressant therapy adherence barrier instrument. *Nephrology Dialysis Transplantation, 20,* 181-188.

Christensen , D.B., Williams, B., Goldberg, H.I., Martin, D.P., Engelberg, R., & LoGerfo, J.P. (1997). Assessing compliance to antihypertensive medications using computer-based pharmacy records. *Medical Care, 35*, 1164-1170.

Davis, C.L., Delamater, A.M., Shaw, K.H., La Greca, A.M., Eidson, M.S., Perez-Rodriguez, J.E., & Nemery, R. (2001). Parenting Styles, Regimen Adherence, and Glycemic Control in 4- to 10-Year-Old Children With Diabetes. *Journal of Pediatric Psychology*, *26*, 123-129.

DeLambo, K.E., Ievers-Landis, C.E., Drotar, D., & Quittner, A.L. (2004). Association of observed family relationship quality and problem-solving skills with treatment adherence in older children and adolescents with cystic fibrosis. *Journal of Pediatric Psychology, 29*, 343-353.

DeVellis, Robert F. (2003). *Scale Development: Theory and Applications, 2nd Edition*. Newbury Park, CA: SAGE Publications.

DiMatteo, M.R. (2004). Social support and patient adherence to medical treatment: A meta-analysis. *Health Psychology, 23*, 207-218.

Dutton, G.R., Johnson, J., Whitehead, D., Bodenlos, J.S., & Brantley, P.J. (2005). Barriers to physical activity among predominantly low-income African American patients with type 2 diabetes. *Diabetes Care, 28,* 1209-1210.

Falkenstein, K., Flynn, L., Kirkpatrick, B., Casa-Melley, A., & Dunn, S. (2004). Non-

compliance in children post-liver transplant. Who are the culprits? *Pediatric Transplantation 8*, 233-236.

Feinstein, S., Keich, R., Becker-Cohen, R., Rinat, C., Schwartz, S.B., & Frishberg, Y. (2005). Is noncompliance among adolescent renal transplant recipients inevitable? *Pediatrics, 115,* 969-973.

Fielding, D. & Duff, A. (1999). Compliance with treatment protocols: Interventions for children with chronic illness. *Archives of Disease in Childhood, 80*, 196-200.

Foulkes, L.M., Boggs, S.R., Fennell, R.S., Skibinski, K. (1993). Social support, family variables, and compliance in renal transplant children. *Pediatric Nephrology, 7,*185-188.

Gerson, A.C., Furth, S.L., Neu, A.M., & Fivush, B.A. (2004). Assessing associations between medication adherence and potentially modifiable psychosocial variables in pediatric kidney transplant recipients and their families. *Pediatric Transplantation, 8*, 543-550.

Gummert, J.F. Ikonen, T. & Morris, R.E. (1999). Newer immunosuppressive drugs: A review. *Journal of the American Society of Nephrology, 10*, 1366-1380.

Hacker, M.R., Geraghty, S., & Manco-Johnson, M. (2001). Barriers to compliance with prophylaxis therapy in haemophilia. *Haemophilia, 7*, 392-396.

Harrison, J.A., Mullen, P.D., & Green, L.W. (1992). A meta-analysis of studies of the health belief model with adults. *Health Education Research, 7,* 107-116.

Hauser, S.T., Jacobson, A.M., Lavori, P., Wolfdorf, J.I., Herskowitz, R.D., Milley, J.E., Bliss, R., Wertleib, D., & Stein, J. (1990). Adherence among children and adolescents with insulin dependent diabetes mellitus over a four-year longitudinal follow-up: II. Immediate and long-term linkages with the family milieu. *Journal of Pediatric Psychology, 15*, 527-542.

Haynes, R.B. (1979). Introduction. In R.B. Haynes, D.W. Taylor, & D.C. Sakett (Eds.), *Compliance in healthcare* (pp. 1-7). Baltimore: John Hopkins University Press.

Irwin, C.E.Jr., Millstein, S.G., Ellen, J.M. (1993). Appointment-keeping behavior in adolescents: factors associated with follow-up appointment-keeping. *Pediatrics, 92,*20-23.

Janz, N.K. & Becker, M.H. (1984). The Health Belief Model: a decade later. *Health Education Quarterly, 11,*1-47.

Kloeblen, A.S. & Batish, S.S. (1999). Understanding the intention to permanently follow a high folate diet among a sample of low-income pregnant women according to the Health Belief Model. *Health Education Research: Theory and Practice, 14,* 327-338.

Korsh, B.M., Fine, R.N., &Negrete, V.F. (1978). Noncompliance in children with renal transplants. *Pediatrics, 61*, 872-876.

Kovacs, M., Goldston, D., Obrosky, D.S., & Iyengar, S. (1992). Prevalence and predictors of pervasive noncompliance with medical treatment among youths with insulin-diabetes mellitus. *Journal of the American Academy of Child and Adolescent Psychiatry, 31*, 1112-1119.

Kyngas, H.A. (1999). Compliance of adolescents with asthma. *Nursing and Health Sciences, 1*, 195-202.

Kyngas, H.A. (2000). Compliance of adolescents with chronic disease. *Journal of Clinical Nursing, 9*, 549-556.

La Greca, A.M. & Bearman, K.J. (2003). Adherence to pediatric treatment regimens. In M.C. Roberts (Ed.), *Handbook of Pediatric Psychology*. (pp. 119-140). New York: The Guilford Press.

La Greca, A.M., Auslander, W.F., Greco, P., Spetter, D., Fisher, E.B., Jr., & Santiago, J.V. (1995). I get by with a little help from my family and friends: Adolescents' support for diabetes care. *Journal of Pediatric Psychology, 20*, 449-476.

Logan, D., Zelikovsky, N., Labay, L., & Spergel, J. (2003). The illness management survey: Identifying adolescent perceptions of barrier to adherence. *Journal of Pediatric Psychology, 28,* 383-392.

Lurie, S., Shemesh, E., Sheiner, P.A., Emre, S., Tindle, H.L., Melchionna, L., & Shneider, B.L. (2000). Non-adherence in pediatric liver transplant recipients – an assessment of risk factors and natural history. *Pediatric Transplantation, 4*, 200-206.

MacNaughton, K.L. & Rodrigue, J.R. (2001). Predicting adherence to recommendations by parents of clinic-referred children. *Journal of Consulting and Clinical Psychology, 69*, 262-270.

Marhefka, S.L., Farley, J.J., Rodrigue, J.R., Sandrik, L.L., Sleasman, J.W., & Tepper, V.J. (2004). Clinical assessment of medication adherence among HIV-infected children: examination of the Treatment Interview Protocol (TIP). *AIDS Care, 16*, 323-337.

Matas, A.J. (1999). Noncompliance and late graft loss: Implications for long-term clinical studies. *Transplantation Review, 13,* 78-82.

Matas, A.J. (2000). Impact of acute rejection on development of chronic rejection in pediatric rejection in pediatric renal transplant recipients. *Pediatric Transplantation, 4*, 92-99.

Meyers, K.E.C., Thomson, P.D, & Weiland, H. (1996). Noncompliance in children and adolescents after renal transplantation. *Clinical Transplantation, 62*, 186-189.

Mirotznik, J., Ginzler, E., Zagon, G., & Baptiste, A. (1998). Using the health belief model to explain clinic appointment keeping for the management of a chronic disease condition. *Journal of Community Health, 23*, 195-210.

Montaño, D.E., Kasprzyk D., & Taplin S.H. (1997). The theory of reasoned action and theory of planned behavior. In K. Glantz, F.M. Lewis, B.K. Rimer, (Eds.) *Health Behavior and Health Education: Theory, Research, and Practice, 2nd ed*. (pp. 85-112). San Francisco, CA: Jossey-Bass, Inc.

Moos, R.H. (1990). Conceptual and empirical approaches to developing family-based assessment procedures: Resolving the case of the Family Environment Scale. *Family Process, 29,* 199-208.

Moos, B. R., & Moos, B. S. (1994). *The Family Environment Scale manual* (3rd ed.). Palo Alto, CA: Consulting Psychologists Press.

Nevins, T.E. (2002). Non-compliance and its management in teenagers. *Pediatric Transplantation, 6*, 475-479.

Organ Transplant Recipient (OTR) Network. Database retrieved on 9/20/05.

Page, P., Verstraete, D.G., Robb, J.R., & Etzwiler, D.D. (1981). Patient recall of self-care recommendations in diabetes. *Diabetes Care, 4*, 96-98.

Patino, A.M., Sanchez, J., Eidson, M., & Delamater, A. (2005). Health beliefs and regimen adherence in minority adolescents with type 1 diabetes. *Journal of Pediatric Psychology, 30,503-512.*

Penkower, L., Dew, M.A., Ellis, D., Sereika, S.M., Kitutu, J.M.M. & Shapiro, R. (2003). Psychological distress and adherence to the medical regimen among adolescent renal transplant recipients. *American Journal of Transplantation, 3*, 1418-1425.

Prochaska J.O., Redding C.A., & Evers, K. (1997). The transtheoretical model and stages of change. In K. Glantz, F.M. Lewis, B.K. Rimer, (Eds.) *Health Behavior and Health Education: Theory, Research, and Practice, 2nd ed*. (pp. 60-84). San Francisco, CA: Jossey-Bass, Inc.

Qvist, E., Narhi, V., Apajasalo, M., Ronnholm, K., Jalanko, H., Almqvist, F., Holmberg, C. (2004). Psychosocial adjustment and quality of life after renal transplantation in early childhood. *Pediatric Transplantation, 8,* 120-125.

Rapoff, M.A. (1999). *Adherence to pediatric medical regimens.* New York: Kluwer Press.

Redding, C.A., Rossi, J.S., Rossi, S.R., Velicer, W.F., Prochaska, J.O. (2000). Health Behavior Models. *The International Electronic Journal of Health Education, 3,*180-193.

Reddington, C., Cohen, J. M., Baldillo, A., Toye, M., Smith, D., Kneut, C., et al. (2000). Adherence to medication regimens among children with human immunodeficiency virus infection. *Pediatric Infectious Diseases*, *19,* 1148–1153.

Rianthavorn, P. Ettenger, R.B., Malekzadeh, M., Marik, J.L., & Struber, M. (2004). Noncompliance with immonsuppressive medications in pediatric and adolescent patients receiving solid-organ transplants. *Transplantation, 77,* 778-782.

Riekert, K.A. & Drotar, D. (2002). The beliefs about medication scale: Development, reliability, and validity. *Journal of Clinical Psychology in Medical Settings, 9*, 177-184.

Ringewald, J.M., Gidding, S.S., Crawford, S.E., Backer, C.L., Mavroudis, C., & Elfriede, P. (2001). Non adherence is associated with late rejection in pediatric heart transplant receipients. *Journal of Pediatrics, 139*, 75-78.

Rosenstock, I.M. (1974). Historical origins of the Health Belief Model. *Health Education Monographs, 2*, 328-335.

Saylor, C.F., Elksnin, N., Farah, B.A., & Pope, J.A. (1990).Depends on who you ask: What maximizes participation of families in early intervention programs. *Journal of Pediatric Psychology, 15*, 557-569.

Schafer, L.C., Glasgow, R.E., & McCaul, K.D. (1982). Adherence to IDDM regimens: Relationship to psychosocial variables and metabolic control. *Diabetes Care, 6*, 493-498.

Serrano-Ikkos, E., Lask, B., Whitehead, B., & Eisler, I. (1998). Incomplete adherence after pediatric heart and heart-lung transplantation. *Journal of Heart and Lung Transplantation, 17*, 1177-1183.

Shaw, R.J., Palmer, L., Blasey, C., & Sarwal, M. (2003). A typology of non-adherence in pediatric renal transplant recipients. *Pediatric Transplantation, 7*, 489-493.

Shemesh, E., Lurie, S., Stuber, M.L., Emre, S., Patel, Y., Vohra, P., et al. (2000). A pilot study of posttraumatic stress and nonadherence in pediatric liver transplant recipients. *Pediatrics, 105*, 1-7.

Shemesh, E., Shneider, B.L., Savitzky, J.K., Arnott, L., Gondolesi, G.E., Kreiger, N.R., et al. (2004). Medication adherence in pediatric and adolescent liver transplant recipients. *Pediatrics, 113,* 825-832.

Sherman, J., Hutson, A., Baumstein, S., & Hendeles, L. (2000). Telephoning the patient's pharmacy to assess adherence with asthma medications by measuring refill rate for prescriptions. *Journal of Pediatrics, 136*, 532-536.

Simoni, J.M., Asarnow, J.R., Munford, P.R., Koprowski, C.M., Belin, T.R., & Salusky, I.B. (1997). Psychological distress and treatment adherence among children on dialysis. *Pediatric Nephrology, 11*, 604-606.

Smith, J.M. Ho, P.L., McDonald, R.A. (2002). Renal transplant outcomes in adolescents: A

report of the North American Pediatrics Renal Transplant Cooperative Study. *Pediatric Transplantation, 6*; 493-499.

Staples, B. & Bravender, T. (2002). Drug compliance in adolescence: Assessing and managing modifiable risk factors. *Pediatric Drugs, 4,*503-513.

Steele, R.G., Anderson, B., Rindel, B., Dreyer, M.L., Perrin, K., Christensen, R., Tyc, V., & Flynn, P.M. (2001). Adherence to antiretroviral therapy among HIV-positive children: examination of the role of caregiver health beliefs. *AIDS Care, 13*, 617-629.

Steiner, J.F. & Prochazka, A.V. (1997). The assessment of refill compliance using pharmacy records: Methods, validity, and applications. *Journal of Clinical Epidemiology, 50*, 105-116.

Strecher, V.J., DeVellis, B.M., Becker, M.H., & Rosenstock, I.M. (1986). The role of self-efficacy in achieving health behavior change. *Health Education Quarterly, 13*, 73-91.

Strecher, V.J. & Rosenstock, I.M. (1997). The health belief model. In K. Glantz, F.M. Lewis, B.K. Rimer, (Eds.) *Health Behavior and Health Education: Theory, Research, and Practice, 2nd ed*. (pp. 41-59). San Francisco, CA: Jossey-Bass, Inc.

Treadwell, M.J., Law, A.W., Sung, J., Hackney-Stevens, E., Quirolo, K., Murray, E., et al. (2005). Barriers to adherence of deferoxamine usage in sickle cell disease. *Pediatric Blood Cancer, 44*, 1-8.

Tucker, C.M., Peterson, S., Herman, K.C., Fennell, R.S., Bowling, B., Pedersen, T., & Vosmik, J.R. (2001). Self-regulation predictors of medication adherence among ethnically different pediatric patients with renal transplants. *Journal of Pediatric Psychology, 26*, 455-464.

Wardle, J., Sutton, S., Williamson, S., Taylor, T., McCaffery, K., Cuzick, J., Hart, A., Atkins, W. (2000). Psychosocial influences on older adults' interest in participating in bowel cancer screening. *Preventative Medicine, 31*, 323-334.

Watson, A.R. (2000). Non-compliance and transfer from paediatric to adult transplant unit. *Pediatric Nephrology, 14,* 469-472.

Zebracki, K. & Drotar, D. (2004). Outcome expectancy and self-efficacy in adolescent asthma self-management. *Children's Health Care, 33,*133-149.

Zelikovsky, N. (2002). Medication Adherence Measure (MAM). *Unpublished manual.*

Zelikovsky, N., Walsh, A.P., & Meyers, K.E.C. (2004, April). *Understanding barriers to adherence among adolescents with renal disease.* Poster presented at the Society of Pediatric Psychology National Conference on Child Health Psychology, Charleston, SC.