Identifying Barriers to Medication Adherence in Adolescent Transplant Recipients

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Objective To create Parent and Adolescent Medication Barriers Scales (PMBS and AMBS) for assessing perceived barriers to medication adherence in adolescent transplant recipients. **Methods** These scales were developed and initially validated with 78 families. Participants responded to questions concerning perceived barriers to medication adherence. To assess validity, data on contextual factors (e.g., family functioning) and adherence measures were collected. **Results** A principal components factor analysis resulted in the following subscales for the PMBS and AMBS: (a) Disease Frustration/Adolescent Issues, (b) Regimen Adaptation/Cognitive Issues, (c) Ingestion Issues, and (d) Parent Reminder (PMBS only). Significant associations were found between barrier scale scores, contextual factors, and adherence. **Conclusions** The PMBS and AMBS are brief and psychometrically promising scales for assessing perceived barriers to adherence in adolescent transplant recipients.

Key words adherence; adolescent; measurement; medication; pediatric transplant.

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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, 3-year survival rates ranged 77– 94% for pediatric kidney transplant recipients, 66–83% for liver recipients, and 76–87% for heart 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 on a strict schedule each day for life. The degree to which patients adhere to their medication regimen varies.

The concept of adherence is defined as the ''extent to which a patient's behavior coincides with medical or health advice'' (Haynes, 1979, pp. 1–2). 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 similar rates for pediatric transplant patients (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, immunological losses, and death (Falkenstein, Flynn, Kirkpatrick, Casa-Melley, & Dunn, 2004; Meyers, Thomson, & Weiland, 1996; Ringewald et al., 2001; Shaw, Palmer, Blasey, & Sarwal, 2003; Smith, Ho, & McDonald, 2002; Watson, 2000).Palmer, Blasey, & Sarwal, 2003; Smith, Ho, & McDonald, 2002; Watson, 2000).

Research with pediatric transplant recipients and children living with other chronic medical conditions has indicated that both contextual and individual factors may be associated with adherence. Some of the contextual factors that have been associated with adherence include *demographics* (e.g., gender, age), *disease factors*

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(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). A potentially more proximal variable related to adherence involves an individual's beliefs and perceptions about the prescribed medication regimen. The adult literature has long emphasized individual beliefs and perceptions 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, although only a few studies have used this approach in the pediatric literature (e.g., Bush & Iannotti, 1990; Reikert & Drotar, 2002; Zebracki & Drotar, 2004). This investigation will develop a scale to assess perceived barriers, the facet of the Health Belief Model with the most empirical support for the prediction of medication adherence (Harrison, Mullen, & Green, 1992; Janz & Becker, 1984).

The relationship of barriers and adherence in pediatric transplant patients has not been well examined. However, in the adult transplant literature Chisholm, Lance, Williamson, and Mulloy (2005) found that higher perceived barrier scores were significantly associated with lower self-reported adherence, lower drug assay levels, and poorer prescription refill rates. In the pediatric literature, caregivers of children with HIV who reported more barriers to adherence tended to have children with lower prescription refill histories (Marhefka et al., 2004). In another study, the parents of pediatric patients with HIV who endorsed beliefs 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). Adolescents with asthma who reported having more barriers also had poorer self-reported adherence to medication, more attacks, less preventive efforts, and greater physician rated severity (Logan, Zelikovsky, Labay, & Spergel, 2003). In a study involving children with asthma, HIV, or Inflammatory Bowel Disease (IBD), more barriers were associated with lower adherence for each patient group (Riekert & Drotar, 2002). The relationship between barriers and adherence in cystic fibrosis and asthma patients was recently examined with several trends identified between parent/self-report, pharmacy refill records, diary data, electronic monitoring, and barriers to specific regimen tasks (Modi & Quittner, 2006). Unfortunately, this study lacked a sufficient sample size to obtain statistically significant results. Zelikovsky, Walsh, & Meyers (2004) examined barriers to adherence among adolescents with renal disease. They found that 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; thus providing an example of how assessing barriers translates directly into implications for intervention.

Although most studies have found an association between perceived barriers and adherence (e.g., Logan et al., 2003; MacNaughton & Rodrigue, 2001; Reikert & Drotar, 2002), one study with pediatric HIV did not (Steele et al., 2001), perhaps due to the small sample size ($n = 30$). There have been no studies systematically examining perceived barriers to adherence in pediatric transplant recipients, beyond simply asking patients why they do not take their medication (e.g., Shemesh et al., 2004). The patients selected for the current investigation were adolescents who have received heart, liver, or kidney transplants. Adolescents were selected because of the prevalence of adherence difficulties within this age group (e.g., Fielding & Duff, 1999; LaGreca & Bearman, 2003; Staples & Bravender, 2002). With recent statistics from the OPTN/SRTR annual report (2004) showing lower 5-year survival rates for adolescent patients as compared to children, potential behavioral health factors that may be influencing this discrepancy warrant investigation. It is possible that lower adherence noted in adolescence may be due in part to a transition from parent to adolescent responsibility for medication intake (Le Greca et al., 1995).

The aim of this study was to develop empirically valid instruments for assessing perceived barriers to medication adherence in adolescents who have received organ transplants. To conduct a more complete assessment of barriers to adherence, both parents and adolescents participated in this study. Based on results from Logan et al. (2003) examining barriers to adherence with adolescent asthma patients, expected subscales included: (a) medication/disease understanding barriers, (b) cognitive barriers, and (c) family/adjustment barriers. We expected that higher barrier scores would be associated with lower medication adherence. We also hypothesized that pertinent contextual variables (e.g., less medication knowledge, more side-effects, family conflict) would be associated with higher barrier subscale scores and total scale scores.

Method

Participants

This study involved 78 pediatric patients between the ages of 11 and 21 ($M = 15.8$, $SD = 2.4$) who received solid organ transplants and their parents. Among transplant types, 46 patients received kidneys, 18 patients received livers, 13 patients received hearts, and 1 patient received a double lung transplant. 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-eight 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 I. Inclusion criteria for this study were 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 4 months prior to participation. If the adolescent was developmentally delayed (as judged by the parent), only the parent was interviewed, which consisted of 9% of the sample.

Table I. 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

Overview of Measures

Medical history, current medication regimen, and serum immunosuppressant assay levels obtained over the past 12 months were collected by electronic chart review for patients greater than one year post-transplant. For those who were 4–11 months post-transplant ($n = 14$), we examined records since transplantation. Other data were obtained during phone interviews with the parents and adolescents. During the phone interviews, parents and adolescents independently reported on the frequency and intensity of medication side effects, perceived barriers to taking medication, their knowledge of the prescribed medication regimen, who was responsible for medication administration, family dynamics, and the degree of adherence with the medication regimen.

Barrier Scales

The barrier scales developed in this study were based on adaptations to the PEDS-TX Survey, Version 1.0, designed by Rodrigue (2004). The PEDS-TX Survey, Version 1.0 was created by a team of pediatric transplant physicians, clinical psychologists, and trainees who specialize in pediatrics and transplantation. This measure was reviewed and underwent several revisions prior to finalization. This measure has not been used prior to inclusion in this study. For the barriers portion, each respondent is told that they will listen to ''*a list of reasons that other patients have told us make it difficult to take their medication on schedule every day. For each statement, tell me how much you agree or disagree*.'' Each participant responded on a 5-point Likert-like scale. Reliability and validity analyses for the parent and adolescent barriers measures were computed in this study for both scales. More complete descriptions of these barriers scales are included in the results section.

Validity Measures

Medical Record Review

An electronic medical record review was conducted by the principal investigator and trained research assistants to collect data on transplant type, donor type (if applicable), date of transplant, current medication regimen, and serum assay levels obtained over the past 12 months.

Parents' and Adolescents' Perceptions of Side Effects

The scales for measuring perceived side effects were also derived from the PEDS-TX Survey, Version 1.0, designed by Rodrigue (2004) and largely based on the end-stage renal disease (ESRD) Symptom Checklist — Transplant Module (ESRD-SCL; Franke et al., 1999), a scale validated for use with adults. The ESRD-SCL has demonstrated adequate internal consistency and construct validity. For each item, the respondent is asked how frequently and intensely the patient experiences 39 different side effects (e.g., changes in facial appearance, fatigue) that may be related to the transplant medications. Frequency and intensity are rated on a 5-point Likert-like scale, from *never* to *always* and *not at all* to *a lot*, respectively. The number of endorsed symptoms and the intensity ratings were summed to derive a total frequency and total intensity score. Internal consistency estimates for frequency (parent, $\alpha = 0.88$; adolescent, $\alpha = 0.91$) and intensity (parent, $\alpha = 0.88$; adolescent, $\alpha = 0.93$) of side effects were excellent in this sample.

Parents' and Adolescents' Medication Knowledge and Regimen Responsibility

Parents' and adolescents' medication knowledge and their perception of who was responsible for administering the medication regimen were assessed based on adaptations of the Medical Adherence Measure (MAM), designed by Zelikovsky (2002). The knowledge portion of this semi-structured interview includes questions that assess: (a) the name of each medication, (b) dosage frequency, (c) dosage amount, and (d) medication purpose. Their responses were then compared with the current medication regimen in the medical chart, with a possible total score of 4 for each medication. Internal consistency estimates were good for these items in this sample (parent, $\alpha = 0.88$; adolescent, $\alpha = 0.84$). This total was then divided by the number of medications and multiplied by 100, with a higher percentage signifying greater medication knowledge. With regard to regimen responsibility, agreement and disagreement for who was primarily responsible for the medication regimen was examined between parent and adolescent report. This question consists of asking adolescents, ''*who takes primary responsibility over making sure that you take your medication?*'' and is reworded for parents. Responses were coded into three different categories: ''agreement, parent responsible'', ''agreement, child responsible'', and ''disagreement.''

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 nine 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 2-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 (Moos & Moos, 1994). It was administered to parents and adolescents separately.

Adherence Measures and Classification

Immunosuppressant Drug Assay Levels

Immunosuppressant blood levels collected during the year prior to the patient's interview date were recorded from the medical chart. From the results of the blood assays, *SDs* were calculated (for tacrolimus only). A higher *SD* suggests less consistent medication taking, and therefore, lower adherence. As medication blood levels may vary as a result of acute illness or in cases in which a more aggressive treatment is implemented, only medication blood levels that were obtained in the out patient clinic during routine visits were analyzed. Higher *SD*s have been found to be predictive of clinical outcome, such as 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 indicative of poor adherence (Chisholm et al., 2005).

Parent and Adolescent Reported adherence

For the Medical Adherence Measure Medication Module (MAM; Zelikovsky, 2002), parents and adolescents independently reported how many doses of each medication were taken late or missed in the past 7 days. Keeping the recall period short and asking detailed objective questions has been described as an effective way to obtain self-reported adherence (La Greca & Bearman, 2003). Percentage of missed and late doses was

Table II. Medication Adherence Classification System

Adherent		Nonadherent	
Adherent/stable ''genuinely adherent''	Adherent/unstable ''deniers or medically complicated''	Nonadherent/stable ''at-risk''	Nonadherent/unstable ''genuinely nonadherent''
1) All drug levels obtained are within range (no high or low levels noted)	1) A high or low drug level is noted and/or *SD* is above 3	1) All drug levels obtained are within range (no high or low levels noted)	1) A high or low drug level is noted and/or *SD* is above 3
2) *SD* of drug levels is below 3	2) Patient and parent reports missing or taking late <10% of any medication in the last 7 days	2) *SD* of drug levels is below 3	2) Patient or parent reports missing or taking late >10% of any medication in the last 7 days
3) Patient and parent reports missing or taking late <10% of any medications in the last 7 days		3) Patient or parent reports missing or taking late >10% of any medication in the last 7 days	

calculated by taking the number missed and late, divided by number prescribed, multiplied by 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.

Adherence Classification

Correlational analyses were conducted between self-reported and parent reported late and missed doses of immunosuppressant and other medications and *SDs* of serum drug levels of immunosuppressant medication. With only modest to nonsignificant correlations obtained between methods of measurement (self-report vs. immunosuppressant drug level), a composite adherence score was not used. Instead, a multidimensional adherence classification system was developed, taking into account each of these sources of data as has been suggested in the adherence literature (La Greca & Bearman, 2003). Each patient was classified into one of four categories: (a) those who report excellent adherence and had acceptable drug levels (Adherent/Stable, ''Genuinely Adherent''), (b) those who reported excellent adherence and had concerning drug levels (Adherent/Unstable, ''Deniers/Medically Complicated''), (c) those who reported nonadherence and had acceptable drug levels (Nonadherent/Stable, ''At-risk''), and (d) those who reported nonadherence and had concerning drug levels (Nonadherent/Unstable, ''Genuinely Nonadherent''), see Table II for category descriptions. This classification system retains the information provided by both self-reported data from immunosuppressant drug level data.

A Kappa coefficient was calculated between independent coders, Kappa = 0.99, indicating excellent reliability for classification. The coders were psychology trainees who were given the category descriptions and a de-identified spread sheet with the following data: (a) SD of tacrolimus, (b) presence or absence of high levels of tacrolimus or cyclosporine,(c) presence or absence of low levels of tacrolimus or cyclosporine, (d) presence or absence of adolescent reported >10% missed doses, (e) presence or absence of adolescent reported >10% late doses, (f) presence or absence of parent reported >10% missed doses, and (g) presence or absence of parent reported >10% late doses.

Procedure

Recruitment

Following approval from the institutional review board, eligible adolescents and parents were invited to participate. Patients and parents were initially informed of the study by the transplant coordinator at clinic or via telephone. Interested families contacted the principal investigator directly, completed an interest form, or verbally consented to have the principal investigator contact them. Of those who indicated initial interest, 8% declined participation; reasons cited included no time (3), did not want to release medical records (1), or no reason given (3). Informed consent and assent was obtained at clinic or via postal mail after initial interest was established.

Interview

The interview with each parent and adolescent consisted of verbal administration of all study measures. Each interview was conducted by research assistants or graduate students in psychology. Training involved instruction and observed practice of procedures and skills taught, including building rapport, being sensitive to parents and patients with solid organ transplants, verbally administering the questionnaires in an accurate and comfortable manner, answering participants' questions in an instructive manner that did not bias the

Table III. Frequency of Nonadherence for the Different Methods of Assessment

Transplant patients	Percentages
Adolescent self report ($n = 65$)	
Missed >10%	13.6
Late >10%	50.0
Parent report ($n = 72$)	
Missed >10%	11.0
Late >10%	42.5
SD tacrolimus ($n = 60$)	
Greater than 3.0	44.3
Tacrolimus drug levels ($n = 62$)	
Tacrolimus >17	28.6
Tacrolimus <5	50.8
Cyclosporin drug levels ($n = 8$)	
Cyclosporin >400	25.0
Cyclosporin <150	37.5

Self-report and parent report data were only collected for medications the participant could remember from the regimen. For two participants, only one blood level of Tacrolimus was collected in the past year.

research, and being culturally sensitive. The vast majority of interviews (98%) were conducted over the phone. Of the 79 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 min ($M = 55.5$, $SD = 14.4$) and adolescent interviews ranged from 24 to 66 min ($M = 42.6$, $SD = 8.2$). Twenty dollar gift cards were provided for participation. Referrals for psychological services were offered to all participants, with 30% of parents and 25% of adolescents accepting a referral. Interviews were conducted over a 5-month period.

Results

Descriptive Information and Preliminary Analyses

Descriptive statistics including means and *SD*s for each measure are detailed in Table V and Table VII. The following variables were log transformed as they were significantly skewed: parent reported cohesion, parent medication knowledge, and adolescent reported cohesion. The frequency of nonadherence for each assessment method is reported in Table III. Each patient was classified into one of the four adherence groups: ''Genuinely Adherent'' ($n = 11$), ''Deniers/Medically Complicated'' ($n = 18$), ''At-risk'' ($n = 18$), and ''Genuinely Nonadherent'' ($n = 31$), resulting in a nonadherence rate of 62.8%.

Development of the Parent Mediation Barriers Scale (PMBS)

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 principal 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 PMBS. 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 (<.40) with three factors, so it was dropped. With those items omitted, the structure held, accounting for 62.3% of the variance in responses (see Table III). The 16-item scale had a Cronbach's alpha of.87. Sample mean for the scale was 35.8 ($SD = 10.4$). 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 seven items ($\alpha = .84$). Sample mean for the subscale was 16.0 ($SD = 5.6$). This factor aligns best with the hypothesized family/adjustment domain. Factor 2, labeled Regimen Adaptation/Cognitive, contains five items ($\alpha = .82$). Sample mean for the subscale was 11.1 ($SD = 4.3$). This factor is consistent with the hypothesized cognitive barrier scale. Factor 3, labeled Ingestion Issues, contains three items ($\alpha = .69$). Sample mean for the subscale was 5.9 ($SD = 2.6$). Factor 3 partially represents 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 had little variance and therefore, were not represented in this domain. Factor 4, labeled Parent Reminder, contains one item. Sample mean for this item was 2.8 ($SD = 1.3$). 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

Table IV. Summary of Factor Loadings for PMBS

Item	Factor loading			
	Disease frustration/ adolescent issues	Regimen adaptation/ cognitive	Ingestion issues	Parent reminder
1. My child feels that it gets in the way of his/her activities.	**.65**	.25	.06	−.02
2. My child does not want other people to Notice him/her taking the medication.	**.73**	.05	.23	−.07
3. My child sometimes feels sick and can't take the medication.	**.55**	.26	.33	−.07
4. My child doesn't like what the medication does to his/her appearance.	**.61**	.25	.08	.40
5. My child is tired of taking medicine.	**.53**	.49	.27	.30
6. My child is tired of living with a medical condition.	**.77**	.18	.03	−.05
7. My child believes the medicine has too many side-effects.	**.72**	.00	.07	.18
8. My child is forgetful and doesn't remember to take his/her medication every time.	.03	**.79**	.11	.18
9. My child is not very organized about when and how he/she takes his/her medication.	.10	**.76**	−.05	.29
10. My child is very busy with other things that get in the way of taking the medication.	.23	**.73**	.22	−.32
11. My child finds it hard to stick to a fixed medication schedule.	.21	**.69**	.17	.30
12. I am not always there to remind my child to take his/her medication.	.28	**.68**	−.07	−.00
13. My child has a hard time swallowing the medicine.	.17	.09	**.79**	−.17
14. My child has too many pills to take.	.28	.11	**.69**	.16
15. My child does not like how the medicine tastes.	.00	.00	**.80**	.18
16. My child relies on me to remind him/her when to take his/her medication.	.03	.24	.10	**.80**
Eigen value	3.33	3.22	2.09	1.34
% Variance	20.80	20.13	13.05	8.35

Boldface indicates highest factor loadings.

Table V. Intercorrelations, Means, and *SDs* for PMBS

Variable	1	2	3	4	5	6	7	8	9	10	11	12	13	14	*M*	*SD*
PMBS																
1. Total score	–	**.88****	**.79****	**.59****	**.43****	−.13	.17	**.26***	**.24***	−.21	−.10	−.10	−.05	−.03	35.8	10.3
2. Disease frustration/Adol. iss.		–	**.53****	**.41****	**.23***	−.13	.16	**.35****	**.34****	**−.27***	−.12	−.12	−.12	−.07	16.0	5.5
3. Regimen adaptation/Cog. iss.			–	**.24***	**.32****	.00	.01	.10	.09	.06	.01	−.07	.17	.06	11.1	4.2
4. Ingestion issues				–	.18	**−.25***	**.22***	.08	.08	**−.27***	.00	−.07	**−.22***	−.04	5.9	2.6
5. Parent reminder					–	−.01	**.22***	.06	.05	−.14	**−.29***	.08	−.02	.01	2.8	1.3
Disease & Regimen																
6. Time since transplant						–	**−.29***	−.03	−.07	.22	−.06	.06	.14	.18	57.0	53.0
7. Number of medications							–	**.33****	**.31****	**−.43****	**−.36****	.07	−.07	−.15	6.43	3.20
8. Frequency of side-effects (p)								–	**.92****	.03	−.16	.06	.04	−.14	62.2	16.8
9. Intensity of side effects (p)									–	.01	−.15	.04	.01	−.13	49.4	13.8
Child & Family																
10. Medication knowledge (p)										–	**.33****	−.13	**.31****	.17	−1.0	.70
11. Medication knowledge (c)											–	−.09	**.27***	−.15	58.4	25.9
12. Cohesion (p)												–	**−.27***	**.34****	0.25	.24
13. Expression (p)													–	−.09	6.12	1.68
14. Conflict (p)														–	2.51	1.94

Correlations are two-tailed. All significant associations are in boldface. *$p < 0.05$, **$p < 0.01$. (p) = parent report; (c) = child report.

ownership of regimen responsibility. All of the factors were significantly intercorrelated except for Parent Reminder and Ingestion Issues (see Table V). Following item selection and factor analyses, construct and criterion validity were examined for the PMBS total score and subscale scores.

PMBS Construct Validity with Demographic, Disease, and Regimen Factors

One-way ANOVA were conducted to examine differences in the number of barriers reported across categorical demographic and disease and regimen factors. No significant differences were detected across age, developmental delay, gender, race, income, and parent educational background. 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, or transplant type.

Results for Pearson Product Moment correlation analyses between barriers and time since transplant, number of medications, and frequency and intensity of side effects are displayed in Table V. 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 scores and higher Disease Frustration/Adolescent Issues subscale scores.

PMBS Construct Validity with Child and Family Factors

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 (Table V). Lower parent medication knowledge was significantly associated with higher PMBS Disease Frustration/Adolescent Issues scores and higher 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 ($M = 7.90$, $SD = 1.39$, original value prior to log transformation) and low levels of conflict ($M = 2.51$, $SD = 1.94$), 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).

Development of the Adolescent Medication Barriers Scale (AMBS)

Adolescent Scale Item Selection and Factor analysis

Similar to the PMBS, each of the 29 original items on the adolescent scale 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 eight items. Next, item-total correlations were conducted, with items that correlated less than .25 with the total score being dropped. (Criteria outlined by DeVillis, 2003). The remaining items were entered into a principal components factor analysis 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 (Table VI). The overall 17-item scale has a Cronbach's alpha of .86. Sample mean for the scale was 38.1 ($SD = 10.7$). 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 eight items ($\alpha = .84$). Sample mean for the subscale was 15.7 ($SD = 5.9$). Factor 2, labeled Ingestion Issues, contains five items ($\alpha = .70$). Sample mean for the subscale was 11.2 ($SD = 3.9$). Factor 3, labeled Regimen

Table VI. Summary of Factor Loadings for AMBS

Item	Factor loading		
	Disease frustration/ adolescent issues	Ingestion issues	Regimen adaptation/ cognitive
1. I don't want to take the medicine at school.	**.54**	.46	.01
2. I feel that it gets in the way of my activities.	**.60**	.26	.02
3. I am forgetful and I don't remember to take the medicine every time.	**.50**	−.15	.42
4. I do not want other people to notice me taking the Medicine.	**.69**	.25	.12
5. I sometimes just don't feel like taking the medicine.	**.73**	.10	.10
6. I don't like what the medication does to my appearance.	**.63**	−.01	.19
7. I am tired of taking medicine.	**.75**	.14	.05
8. I am tired of living with a medical condition.	**.78**	.18	.08
9. I believe that the medicine is hard to swallow.	−.09	**.81**	.03
10. I believe that I have too many pills to take.	.28	**.61**	−.13
11. I don't like how the medicine tastes.	.23	**.62**	.09
12. I believe the medicine has too many side-effects.	.35	**.58**	.12
13. I get confused about how the medicine should be taken (with or without food, with or without water, etc.).	−.08	**.57**	.45
14. I am not organized about when and how to take the medicine.	.03	.06	**.82**
15. I find it hard to stick to a fixed medication schedule.	.43	−.03	**.64**
16. Sometimes I don't realize when I run out of pills.	.47	−.04	**.56**
17. Sometimes its hard to make it to the pharmacy to pick up the prescription before the medicine runs out.	−.00	.24	**.82**
Eigen value	4.19	2.56	2.55
% Variance	24.64	15.04	14.98

Boldface indicates highest factor loadings.

Table VII. Intercorrelations, Means, and *SDs* for AMBS

Variable	1	2	3	4	5	6	7	8	9	10	11	12	13	*M*	*SD*
AMBS															
1. Total score	–	**.89****	**.70****	**.70****	.04	.01	**.31****	**.32****	−.07	−.06	−**.32****	−**.27***	**.33****	38.1	10.7
2. Disease frustration/Adol. iss.		–	**.47****	**.48****	.09	.03	**.33****	**.36****	.02	−.03	−**.32****	−**.27***	**.32****	15.7	5.9
3. Ingestion issues			–	**.23***	.03	.15	.10	.07	−**.33****	−**.23***	−**.25***	−.22	**.29***	11.2	3.9
4. Regimen adaptation/Cog.				–	.05	−.13	**.24***	**.28***	.12	.10	−.15	−.12	.13	11.2	3.8
Disease & Regimen															
5. Time since transplant					–	−**.29***	−.06	−.04	.06	.22	−.13	−.19	−.19	57.9	53.0
6. Number of medications						–	.13	.09	−**.36****	−**.43****	.11	.13	−.11	6.4	3.2
7. Freq of side effects (c)							–	**.93****	−.09	.01	−.16	−.08	.23	64.7	20.9
8. Intensity of side effects (c)								–	−.07	−.02	−.10	−.12	**.24***	48.5	16.3
Child & Family															
9. Med knowledge (c)									–	**.33****	.09	.21	−.15	−1.0	.70
10. Med knowledge (p)										–	.10	.05	−.09	58.4	25.9
11. Cohesion (c)											–	**.38****	−**.42****	−.37	.26
12. Expression (c)												–	−**.47****	4.66	1.70
13. Conflict (c)													–	2.93	1.97

Correlations are two-tailed. All significant associations are in boldface. *$p < 0.05$, **$p < 0.01$. (p) = parent report; (c) = child report.

Adaptation/Cognitive, contains four items ($\alpha = .76$). Sample mean for the subscale was 11.2 ($SD = 3.8$). Unlike the PMBS, there was not a fourth factor. All factors were significantly intercorrelated (Table VII). Following item selection and factor analyses, construct and criterion validity were examined using the AMBS total and subscale scores.

AMBS Construct Validity with Demographic, Disease, and Regimen Factors

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 Frustration/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 VII. 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

There were no significant differences in AMBS scores based on who was responsible for medication administration. For the correlational analyses, 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 and lower Disease Frustration/Adolescent Issues scores. Lower Ingestion Issues scale scores were associated with higher cohesion and lower conflict.

PMBS and AMBS Criterion Validity with Adherence Categories

To assess criterion validity of the PMBS and AMBS, differences across adherence categories for each barrier scale score were examined using Independent T-tests. No significant differences were detected within the two adherent groups (''Genuinely Adherent'' and ''Deniers/Medically Complicated'') or within the two nonadherent groups (''At Risk'' and ''Genuinely Nonadherent''). Several significant differences were detected between the adherent and nonadherent groups and are detailed in Table VIII. Overall, adolescents classified as ''Deniers/Medically Complicated'' reported the fewest barriers according to parent and adolescent report. Scores on the PMBS total, cognitive, and adolescent issues scales were significantly lower for these adolescents as compared to adolescents classified in the ''At-Risk'' and ''Genuinely Nonadherent'' categories. This general pattern persisted for scores on the AMBS with some exceptions. The ''Deniers/Medically Complicated'' group showed a trend reporting fewer AMBS cognitive barriers to medication taking when compared to the ''At-Risk'' group. There was no significant difference between the ''Deniers/Medically Complicated'' group and the ''Genuinely Nonadherent'' group on the AMBS Cognitive barrier subscale scores. In addition, unlike the PMBS, there was a trend for adolescents in the ''Deniers/Medically Complicated'' group to report fewer Ingestion barriers when compared to the adolescents classified as ''Genuinely Nonadherent''.

For adolescents who were classified as ''Genuinely Adherent'', trends between this group and the two nonadherent groups were detected. When comparing the ''Genuinely Adherent'' and ''At-Risk'' group, differences were detected at the trend level for the PMBS Adolescent Issues subscale, the AMBS Cognitive Issues barriers subscale, and the AMBS Adolescent Issues subscale. For each comparison, the ''Genuinely Adherent'' group reported fewer barriers than the ''At-Risk'' group. In examining differences between the ''Genuinely Adherent'' and ''Genuinely Nonadherent'' groups, for the PMBS there were trends for adolescents classified as ''Genuinely Adherent'' to have lower scores on the PMBS total score, Cognitive Issues subscale, and Ingestion Issues subscale when compared to the ''Genuinely Nonadherent'' group. For the AMBS, no

Table VIII. PMBS scores and AMBS scores across the four adherence classification groups

	Adherent		Nonadherent	
	Deniers/medically complicated Mean ± SD	Genuinely adherent Mean ± SD	At-risk Mean ± SD	Genuinely nonadherent Mean ± SD
PMBS	(n = 18)	(n = 10)	(n = 18)	(n = 30)
Total	30.2 ± 11.4[a,b]	32.4 ± 8.3[d†]	38.3 ± 10.9[a]	38.7 ± 9[b,d†]
Cognitive	8.7 ± 3.3[a,b]	9.8 ± 3.7[d†]	12 ± 4.8[a]	12.4 ± 4.1[b,d†]
Adolescent issues	12.8 ± 5.5[a,b]	14.7 ± 4.2[c†]	17.9 ± 6[a,c†]	17.2 ± 5.1 [b]
Ingestion issues	5.8 ± 3.2	5 ± 1.3[d†]	5.7 ± 1.9	6.3 ± 2.9[d†]
Parent reminder	2.9 ± 1.6	2.9 ± 1.4	2.7 ± 1.3	2.7 ± 1.1
AMBS	(n = 12)	(n = 8)	(n = 18)	(n = 30)
Total	32.8 ± 10.5[a,b]	38.4 ± 9.3	43.7 ± 7.8[a]	41.2 ± 11.4 [b]
Cognitive	9.7 ± 4.7[a†]	10.1 ± 2.5[c†]	12.6 ± 3.7[a†,c†]	11.1 ± 3.5
Adolescent issues	11.8 ± 4.2[a,b]	13.6 ± 4.4[c†]	17.6 ± 4.9 [a†,c†]	16.2 ± 6.5[b]
Ingestion issues	9.4 ± 3[b†]	12.4 ± 4.1	10.8 ± 3.6	11.7 ± 4.1 [b†]

No significant differences were detected within the two adherent groups or within the two nonadherent groups. Stand-alone superscripts are differences at the $p < .05$ level. Superscripts accompanied by a † signify differences at the $p < .10$ level.

[a]Deniers/Medically Complicated versus At-Risk.

[b]Deniers/Medically Complicated versus Nonadherent.

[c]Adherent versus At-Risk.

[d]Adherent versus Nonadherent.

differences were detected between the ''Genuinely Adherent'' group and the ''Genuinely Nonadherent'' group.

Discussion

Factor analytic procedures were used to develop both parent and adolescent completed scales for assessing barriers to medication adherence in pediatric patients who have received solid organ transplants. 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 was supported by significant associations between barriers scale scores and relevant disease, medical regimen, child, and family factors. Further, total and subscale scores were significantly different between adherent and nonadherent categories. 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). It is possible that these parents feel greater responsibility for the success of the transplant if they were the donor, and are therefore more hypervigilant of the child's medication taking behavior. These dynamics may consequently increase tension within the child/parent relationship. A protective factor seemed to emerge from the results with the Parent Reminder subscale. Parents provided more prompts to their adolescents to take medication if their adolescents were prescribed a greater number of medications or were less knowledgeable about their regimen. 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. Alternatively, 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. Knowledge is malleable, and should be assessed routinely during clinic visits.

In examining PMBS and AMBS barrier scores, several significant differences were found between the adherent groups and the nonadherent groups on Total, Disease Frustration/Adolescent Issues, and Regimen Adaptation/Cognitive scale scores. In addition, no significant differences were found within the two adherent groups (''Genuinely Adherent'' and ''Deniers/Medically Complicated'') and within the two nonadherent groups (''At-Risk'' and ''Genuinely Nonadherent''). The lack of findings within the adherence groups provides preliminary support for both the adherence system and the barrier scales. Among the findings, adolescents and parents in this sample indicated that cognitive barriers (e.g., ''not organized'', ''forgetting'') and adolescent issues (e.g., ''tired of taking medication'', ''too many side effects'') were the most prominent obstacles to taking medication as prescribed. Targeting these two themes will likely contribute to improved adherence levels. Taken together, 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 clinical utility being indicated.

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). The new classification system permits both sources of data to be considered. Two of the adherence classification groups pose several new questions. The ''Deniers/Medically Complicated'' group is worthy of further attention, clinically and in the research realm. These patients generally endorsed very few barriers. It is possible that including a social desirability scale in future studies would help to tease apart those classified in the adherent/unstable group into ''Deniers'' and the truly ''Medically Complicated''. This group must be monitored closely as these patient families do not verbalize difficulties. In addition, the ''At-Risk'' group did not have recorded erratic immunosuppressant drug levels, but reported nonadherent behavior. This may mean that they are ''at-risk'' for future erratic levels and would benefit from preventative efforts prior to experiencing compromised health as a result of nonadherence.

The implications of these findings are clear. These scales can serve as brief screening tools for healthcare providers to determine the most prominent issues that may be interfering with adherence. After barriers are identified, healthcare providers and patients can collaboratively create treatment plans that may involve implementing behavioral cues or making referrals for psychotherapy. The barriers identified in this study can also easily inform the development of interventions. Prominent components of the intervention would include coping with side effects, increasing medication knowledge, and appropriate parental responsibility.

There are also limitations to the current study. Over half of the patients in this sample were kidney transplant recipients; therefore the results may better characterize this population. However, the sample used in this investigation is representative of the pediatric transplant literature, as adolescent kidney recipients are the largest group of adolescent transplant 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. For this study, only English speaking families were recruited. This is a limitation and as our country continues to diversify, it will become increasingly important to develop multilingual assessment measures. We do believe that the PMBS and AMBS could be translated into Spanish for use, but this must be tested.

In relation to the factor analytic 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. However, we should also note that the sample size in this investigation is large for the pediatric transplant literature (e.g., Gerson Furth, Neu, & Fivush 2004; Lurie et al., 2000). Although we

attempted to control for some of the medical influences on erratic drug assay levels by only using outpatient samples, it is likely that other medical and biological factors could have influenced the patient's drug level, thus providing further evidence for closely monitoring the ''deniers/medically complicated'' adherence group. 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 versions of the parent and adolescent scales that will allow them to note any barriers not previously assessed.

There are a number of areas for future research in this area of pediatric healthcare. First, the parent and adolescent barrier scales 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 efforts prior to transplantation to head off adherence difficulties. Another important step for future research and clinical work is using the information provided by an assessment of barriers to guide the design of treatment intervention programs. Both the PMBS and AMBS 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. Ongoing assessment of barriers and intervention are crucial for pediatric transplant patients, given the life and death issues involved. The barrier scales developed in this study can aid in this endeavor.

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