Medication Barriers Predict Adolescent Transplant Recipients' Adherence and Clinical Outcomes at 18-Month Follow-up*

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*Data in this article were collected at Children's Healthcare of Atlanta in Atlanta, Georgia. Requests for copies of the Adolescent Medication Barriers Scale (AMBS) and Parent Medication Barriers Scale (PMBS) can be directed to the first author.

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Objective To prospectively validate the Parent and Adolescent Medication Barriers Scales (PMBS and AMBS) for assessing perceived barriers to medication adherence in adolescent transplant recipients by examining the relations of perceived barriers to medication adherence and clinical outcomes at 18-month follow-up. **Methods** Of the 82 adolescent recipients enrolled in the initial cohort, 66 families participated in the follow-up. Relations among barriers, adherence, and clinical outcomes were examined. **Results** Reported barriers demonstrated temporal stability over an extended span of time. Adolescent-perceived barriers of Disease Frustration/Adolescent Issues and parent-perceived barriers of Regimen Adaptation/Cognitive Issues were associated with poorer adherence to medication taking at follow-up. Interestingly, medical complications and mortality were significantly associated with both parent and adolescent-perceived ingestion issues barriers. **Conclusions** Barriers to adherence are essential to address in an effort to ameliorate adherence difficulties and potentially reduce the incidence of medical complications.

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

Transplantation has become a standard treatment option for many pediatric medical conditions. Given the increasing rates of survival in pediatric transplantation, strict adherence to complex medical regimens is a daily and lifelong responsibility for these patients. In particular, adherence to immunosuppressant medications is necessary to maintain the health of the transplanted organ and the health of the patient (Griffin & Elkin, 2001). The consequences of medication nonadherence can be quite detrimental for organ transplant recipients. Nonadherent patients can experience multiple negative health outcomes including additional medical complications, frequent hospitalizations, rejection, allograft loss, and death (Falkenstein, Flynn, Kirkpatrick, Casa-Melley, & Dunn, 2004; Shaw, Palmer, Blasey, & Sarwal, 2003). Furthermore, such outcomes not only affect the life and well-being of the patient, but can also burden the healthcare system with higher economic costs related to healthcare utilization (Cleemput, Kesteloot, & De Geest, 2002).

Unfortunately in pediatric illness populations, medication adherence rates are low, typically 50–55% (Rapoff, 2010). More specifically, studies in pediatric organ transplant have shown adherence rates to range from 5 to 50% for this population, dependent of method of adherence assessment (Dew et al., 2009; Rianthavorn, Ettenger, Malekzadeh, Marik, & Struber, 2004). Adolescents in

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particular have the least successful long-term graft survival as compared to all other pediatric age groups (Rianthavorn et al., 2004). Thus, given the medical and monetary consequences of nonadherence, investigating reasons for pediatric non-adherence is essential.

Researchers in the area of pediatric nonadherence have studied numerous disease, patient, family, and healthcare system variables for explaining nonadherence (La Greca & Mackey, 2009). One important but understudied facet of this research posits the role of health beliefs and perceptions as possible contributors to nonadherence. More specifically, the Health Belief Model emphasizes the importance of individual perceptions of benefits and barriers in explaining and predicting health behaviors, thereby providing a theoretical foundation for examining perceived barriers in relation to medication adherence (Harrison, Mullen, & Green, 1992; Janz & Becker, 1984). Additionally, support for the use of this model has been found not only in the adult literature (Bandura, 2004; Redding, Rossi, Rossi, Velicer, & Prochaska, 2000), but also within a variety of pediatric illness populations.

Specific barriers identified in pediatric groups have ranged from disease severity, regimen complexity, and forgetfulness (Bond, Aiken, & Somerville, 1992; Lemanek, Kamps, & Chung, 2001; Modi & Quittner, 2006; Witherspoon & Drotar, 2006) to beliefs about treatment undesirability or medication ineffectiveness (La Greca & Bearman, 2003). Furthermore, the number and types of barriers endorsed has been found to be associated with measures of nonadherence, including missed and late doses of medication (Bond et al., 1992; Zelikovsky, Schast, Palmer, & Meyers, 2008). However, despite our knowledge that perceived barriers are related to current adherence behaviors, the research has yet to establish enduring and prognostic qualities of barriers over time as they relate to adherence and other health outcomes. As a first step, the development of reliable and valid assessment measures is needed not only to further unearth the nature of perceived barriers, but also in order to integrate such research into medical practice and inform possible interventions. Prior research by our group has sought to create such tools with pediatric organ transplant recipients and their families in mind. In particular, we developed measures to assess barriers to medication taking (Simons & Blount, 2007). The Parent and Adolescent Medication Barriers Scales (PMBS and AMBS) are brief, factor analytically derived, multidimensional screening tools for examining barriers to medication adherence in adolescent transplant recipients. Initial findings revealed that adolescent- and parent-reported barriers were significantly and inversely associated with medication adherence, as well as being associated with pertinent medical regimen, disease, child, and family factors. These findings support the construct and criterion validity of the measures, making them the first psychometrically sound and valid barrier scales in the pediatric transplant literature (Simons & Blount, 2007).

The current study sought to extend the research in this area beyond a cross-sectional understanding of barriers to adherence by longitudinally evaluating the psychometric properties and validity of the AMBS and PMBS. This investigation examined the temporal stability and predictive validity of these measures through follow-up assessments of the original study participants. More specifically, we examined the temporal stability of the barriers over time, as well as the association between barriers identified at the original assessment and medical adherence and health outcomes 18 months later. For the AMBS and PMBS, we hypothesized that (1) both scales will demonstrate adequate stability over time and will be associated with concurrent measures of adherence at Time 2, (2) higher barrier scores at Time 1 will be associated with more nonadherence at Time 2, and (3) higher barriers scores at Time 1 will be associated with negative clinical outcomes at Time 2. Individual barrier items reflect behaviors (e.g., forgetful, not organized), beliefs (e.g., believe medicine is hard to swallow), and emotions (e.g., I am tired of taking medication). Based on the widely accepted maxim that the best predictor of future behavior is past behavior, we expect that barriers reflective of these observable, cognitive, and emotional behaviors will be fairly stable over time, barring any systematic interventions. As the items on the AMBS and PMBS are face valid and clinically relevant, a secondary aim of this study is to explore the association between specific barriers with negative medical outcomes 18 months later (i.e., medication nonadherence, rejections, hospitalizations, and death). Identifying individual barriers provides targets for intervention. Thus, identification of those barriers which are associated with long-term adherence and health outcomes is crucial for informing treatment design and evaluating the clinical utility of these measures.

Method

Participants

Initial Sample

Our initial sample at Time 1 included 82 adolescent patients between the ages of 11 and 20 years ($M = 15.8$,

$SD = 2.4$) who received solid organ transplants. In total, 80 parents and 71 adolescents participated in the study, with a total of 68 parent–child dyads. Forty-six patients had received a kidney transplant, 18 had received a liver, 13 had received a heart, and 1 patient had received a double lung transplant. Among liver and kidney transplant recipients, 34.8% received their organ from a living donor. Adolescent participants were Caucasian (61%), African American (32%), and other races (7%). Fifty-six percent of adolescent participants were male. Additional demographic information is detailed in table format in the study by Simons & Blount (2007). Inclusion criteria for the original study were that the adolescent had received a solid organ transplant, was at least 11 years of age, lived with at least one parent, was English speaking, and was transplanted at least 4 months prior to participation. For developmentally delayed adolescents (as determined by the parent), only the parent was interviewed. These adolescents consisted of 9% of the original sample ($n = 7$).

18-Month Follow-up

The follow-up sample at Time 2 included 66 adolescent and young adult recipients and their families from the original sample. Recipients were between the ages of 12 and 22 years ($M = 17.1$, $SD = 2.4$). The sample consisted of 63 parents (62 mothers) and 51 adolescent participants for a total of 49 parent–child dyads. Within this sample, 39 received a kidney transplant, 16 received a liver, 10 received a heart, and one received a double-lung transplant. Approximately 31% received transplants from living donors. This sample was 62% Caucasian, 29% African American, and 9% other races. Fifty-five percent of adolescents were male. Similar to initial interviews, only parents were interviewed for developmentally delayed adolescents, making up 8% of the sample ($n = 5$). Taking this into account, the difference in the number of parents or adolescents interviewed from the 66 follow-up families was due to our inability to contact these individuals after repeated attempts (adolescents $n = 10$; parents $n = 3$). Overall, from the initial sample to the 18-month follow-up 16 complete families did not participate. Of these, seven participant families passively declined after repeated attempts to contact, five patients died before the re-enrollment phase, two families could not be contacted due to a disconnected phone number, and two participant families were no longer followed at this medical institution, resulting in 87% retention rate for enrollable families. There were no significant differences on demographic or medical factors between follow-up participant families ($n = 66$) and those who did not participate ($n = 16$). For the 66 families who participated, the time lapse between initial and follow-up interviews ranged from 12 to 20 months ($M = 16.5$, $SD = 1.5$).

Overview of Measures

Medical histories, serum immunosuppressant assay levels, and clinical outcomes (i.e., hospitalizations, rejection episodes, and mortality) were obtained through electronic chart review. Using structured interviews, patients and parents reported on barriers to medication taking and degree of adherence to these regimens.

Barriers to Adherence

PMBS

The PMBS (Simons & Blount, 2007) is designed to assess parent perceived barriers to their child's medication taking. Each item is rated on a 5-point Likert-like scale from ''strongly disagree'' to ''strongly agree.'' The PMBS consists of 16 items with a maximum score of 80. The Cronbach's alpha of the total scale was .87 indicating strong internal consistency. There are four factor-analytically derived subscales: Disease frustration/adolescent issues with seven items ($\alpha = .84$), regimen adaptation/cognitive with five items ($\alpha = .82$), Ingestion Issues with three items ($\alpha = .69$), and parent reminder with one item. For criterion-related validity, adolescents with solid organ transplants who were classified as non-adherent had significantly higher barrier scores than those classified as adherent (Simons & Blount, 2007).

AMBS

The AMBS assesses adolescent-perceived barriers to their prescribed medication taking. All items are rated on a 5-point Likert-like scale from ''strongly disagree'' to ''strongly agree.'' The AMBS consists of 17 items with a maximum score of 85. The Cronbach's alpha of the total scale was .86 indicating strong internal consistency. There are three factor-analytically derived subscales: disease frustration/adolescent issues with eight items ($\alpha = .84$), ingestion issues with five items ($\alpha = .70$), and regimen adaptation/cognitive with four items ($\alpha = .76$). The AMBS has demonstrated good construct validity, as frequency and intensity of perceived side effects was significantly associated with the AMBS total score, Disease frustration/adolescent issues score, and regimen adaptation/cognitive issues score, whereas lower parent and adolescent medication knowledge was associated with higher ingestion issue scores (Simons & Blount, 2007). For family functioning,

greater conflict and lower family cohesion was associated with higher barrier scores on the total AMBS scale score, the disease frustration/adolescent issues, and the ingestion issue score. Adolescents with solid organ transplants who have been classified as non-adherent had significantly higher AMBS barrier scores than those classified as adherent (Simons & Blount, 2007).

Clinical Outcomes

Data were obtained from medical records on: (1) occurrence of a rejection episode, (2) occurrence of a transplant-related hospitalization, and (3) mortality since the initial interview date. Each of these outcomes was measured in a dichotomous fashion (i.e., presence/absence). Acute rejection has been found to be associated with low immunosuppressant drug levels and subsequent chronic rejection (Feinstein et al., 2005). Self- and proxy- reported non-adherence has been associated with mortality and greater immunosuppressant drug variability has been associated with rejection episodes ($r = .49$, $p < .00$), hospitalizations ($r = .44$, $p < .00$), and mortality ($r = .61$, $p < .00$; Simons, Gilleland et al., 2009).

Adherence

Parent and Self-Reported Medication Adherence

The Medication Adherence Measure (MAM; Zelikovsky & Schast, 2008; Zelikovsky et al., 2008), was used to assess adherence to medical regimens. Using structured interviews, parents and adolescents individually reported how many doses of each medication the adolescent missed or took late in the prior seven days. The number of missed/late doses, divided by number prescribed, times 100 yielded a percentage of missed and late doses. Preliminary data on the MAM suggest adequate convergent validity with established measures of adherence. In a sample of patients with renal disease ($n = 25$), the percent of missed doses identified on the MAM was significantly correlated with the missed doses tracked by the Medication Event Monitoring System electronic technology ($r = .40$, $p = .04$). In another study of outcomes among renal transplant recipients ($n = 29$), percent of missed doses identified on the MAM was associated with the number of documented acute rejection episodes by year two post-transplant ($r = .62$, $p < .001$), suggesting good predictive validity of clinical outcomes in this population (Zelikovsky et al., 2008).

Immunosuppressant Drug Assay Levels

Measures of immunosuppressant blood levels were collected from the time of the initial interview to the current follow-up interview. Out-of-therapeutic range blood levels of cyclosporine (e.g., <150 or >400), sirolimus (e.g., <5 or >10), and tacrolimus (e.g., <4 or >18 or *SD* of drug level >3) that have been found to be associated with poor adherence were examined (Chisholm, 2002; Shemesh et al., 2004). We consulted with the transplant coordinator responsible for each patient who could describe potentially influential, atypical medical factors that would necessitate the omission of specific collected drug assays. These factors include recent medication changes or recent aggressive medical treatments due to an acute rejection episode or infection. The final dichotomous categorization of drug levels, as ''adherent'' or ''non-adherent,'' was determined by the presence of one or more out-of-range blood levels or a tacrolimus with $SD > 3$.

Procedure

Recruitment

Following approval from the institutional review board, eligible adolescents and parents who were part of the original study were invited to participate. Patients and parents were contacted at clinic or via telephone. New informed consent, assent, and HIPPA release were obtained at clinic or via postal mail after contact was made with the family.

Interview

The structured interview with each parent and adolescent consisted of verbal administration of all study measures over the phone. Each structured interview was conducted by research assistants or graduate students in psychology. Training involved instruction and observed practice of procedures and skills taught, including comfort level conducting phone interviews, verbally administering the questionnaires in an accurate and comfortable manner, and answering participants' questions in an instructive manner that did not bias the research. Twenty dollar gift cards were provided for participation.

Statistical Analysis

Data were analyzed with parametric tests using SPSS 16.0 for Windows. Pearson product moment correlations and paired *t*-tests were conducted to examine stability of barriers over time. Pearson product moment correlations were conducted to examine associations between barriers and self-reported and parent-reported medication adherence, while point biseral correlations were conducted to examine relations between barriers and drug assay levels and clinical outcomes. Specifically for the variable of death, the full initial sample ($n = 82$) was used, whereas all other analyses

involved the follow-up sample only ($n = 66$). Another aim of this study was to examine potential individual barriers associated with negative medical outcomes (i.e., at the item level). Although this approach does increase the chance of Type I error, exploring these relations was deemed clinically meaningful and the alpha level was set at .05 for all interpretable relations.

Results

Descriptive Information for Adherence and Clinical Outcomes

Adherence (missed doses, dose taken late, and out-of-range drug levels) and clinical outcomes (one or more rejection episodes and one or more hospitalizations for transplant-related issues) were examined for those who participated in follow-up interviews. The clinical outcome of death was calculated from the full initial sample. These values are detailed in Table I. Of the five deceased patients, two had received kidney transplants, two had received heart transplants, and one had received a liver transplant. Causes of death were severe pancreatitis, end-stage renal disease (ESRD), transplant coronary disease, transplant coronary artery disease, and end-stage liver disease/renal insufficiency, respectively. Two of the five patient charts had documented incidences of non-adherence. These five individuals were also examined in a previous study with this group wherein all five were classified as ''genuinely nonadherent'' based on self-reported nonadherence and erratic immunosuppressant drug levels (Simons, Gilleland et al., 2009).

Table I. *Frequency of Non-adherence for the Different Methods of Assessment and Clinical Outcomes*

Transplant patients	Percentages
Adolescent self report ($n = 51$)	
Missed >10%	13.6
Late >10%	50.0
Parent report ($n = 62$)	
Missed >10%	11.0
Late >10%	42.5
Out-of-range drug levels ($n = 61$)	53
Clinical outcomes ($n = 66$)	
Rejection episodes	21.2
Hospitalizations	28.8
Deaths (five from initial sample $n = 82$)	6.1

Replication of Concurrent Validity at Follow-Up

Examining the relations between the PMBS and AMBS scores with adherence behaviors concurrently at follow-up resulted in several significant associations. Notably, adolescent reported missed doses was significantly associated with the AMBS-total scale ($r = .33$, $p < .05$), AMBS-regimen adaptation/cognitive issues ($r = .44$, $p < .01$), and AMBS-disease frustration/adolescent issues ($r = .27$, $p < .05$). Parent-reported missed doses was significantly associated with the PMBS-regimen adaptation/cognitive issues ($r = .34$, $p < .01$) while parent reported late doses was significantly associated with PMBS–regimen adaptation/cognitive issues ($r = .39$, $p < .01$). Out-of-range drug levels were significantly associated with several domains including: AMBS-total scale ($r = .35$, $p < .01$), AMBS-disease frustration/adolescent issues ($r = .36$, $p < .01$), PMBS-total scale ($r = .34$, $p < .01$), PMBS-regimen adaptation/cognitive issues ($r = .34$, $p < .01$), and PMBS-disease frustration/adolescent issues ($r = .29$, $p < .05$).

Barrier Scale: Stability over Time

Correlations and paired *t*-tests between PMBS and AMBS scores over time are detailed in Table II. As seen in the table, PMBS and AMBS total scale scores were stable over time with no significant differences from the original interview (Time 1) to 18 months later (Time 2). PMBS-disease frustration/adolescent issues and PMBS-parent reminder had the highest stability with the greatest degree of variability observed for PMBS-ingestion issues and AMBS-regimen adaptation/cognitive issues.

Barriers and Adherence

Correlations between parent-perceived barriers at Time 1 and parent-reported adherence at Time 2 yielded several significant relations (Table III). At the subscale level, regimen adaptation/cognitive issues was associated with more missed doses of medication. At the item level, ''forgetful,'' ''not organized,'' and ''not there to remind my child'' barriers were significantly associated with more missed doses. ''Too many side effects'' was associated with more erratic drug levels and no specific barrier items were significantly associated with taking doses late.

For adolescent-perceived barriers assessed at Time 1 and adolescent-reported adherence obtained at Time 2, significant relations are detailed in Table IV. Unique from parent perceived barriers, the subscale disease frustration/adolescent issues was associated with nonadherence, specifically taking more doses late and erratic immunosuppressant drug levels. At the item level, ''don't realize when

Table II. *Comparing PMBS and AMBS Scale Scores from Time 1 to Time 2*

	Time 1		Time 2			
Scale	*M*	*SD*	*M*	*SD*	*r*	*t*
PMBS						
Total scale	34.5	10.5	34.9	12.4	.68**	−0.35
Disease frustration/ adolescent issues	15.6	5.72	15.5	6.06	.71**	0.06
Regimen adaptation/ cognitive issues	10.8	4.28	11.4	4.76	.50**	−1.18
Ingestion issues	5.58	2.13	5.40	2.80	.43**	0.56
Parent reminder	2.36	1.26	2.60	1.43	.62**	0.32
AMBS						
Total scale score	36.59	10.8	38.8	11.5	.62**	−1.62
Disease frustration/ adolescent issues	15.1	5.93	16.4	6.17	.59**	−1.61
Regimen adaptation/ cognitive issues	10.9	3.91	11.7	3.60	.49**	−1.55
Ingestion issues	10.9	3.70	10.7	3.62	.58**	−.26

*$p < .05$; **$p < .01$ (two-tailed).

Table III. *Relations Between Parent-Perceived Barriers at Time 1 to Parent-Reported Adherence and Clinical Outcomes at Time 2*

	Adherence			Clinical outcome		
	Missed	Late	Drug level	Rejection	Hospital	Death
Total scale	.19	.05	.21	.07	−.06	.10
Disease frustration/adolescent issues	.07	.04	.14	.02	−.08	.04
My child feels that it gets in the way of his/her activities.	−.04	−.04	.14	.01	−.15	−.05
My child does not want other people to notice him/her taking the medication.	.07	.08	.00	−.12	−.20	**.23***
My child sometimes feels sick and can't take the medication.	.13	.05	.02	.05	.11	−.03
My child doesn't like what the medication does to his/her appearance.	−.08	−.08	.14	−.02	.02	−.02
My child is tired of taking medicine.	.10	−.01	.17	.11	.01	.04
My child is tired of living with a medical condition.	.14	.05	.18	−.09	−.17	.09
My child believes the medicine has too many side effects.	.05	.16	**.32***	−.01	−.17	−.02
Regimen adaptation/cognitive issues	**.33***	.02	.19	−.01	−.10	.05
My child is forgetful and doesn't remember to take his/her medication every time.	**.37****	.05	.13	−.02	.09	.04
My child is not very organized about when and how he/she takes his/her medication.	**.25***	−.12	.18	.11	−.01	.09
My child is very busy with other things that get in the way of taking the medication.	.18	.08	.06	.04	−.18	.11
My child finds it hard to stick to a fixed medication schedule.	.15	−.18	.19	.01	.04	−.07
I am not always there to remind my child to take his/her medication.	**.26***	.20	.00	−.06	**−.25***	−.03
Ingestion issues	.06	.09	.16	**.25***	.02	**.26***
My child has a hard time swallowing the medicine.	.15	.15	.05	**.23***	.03	**.27***
My child has too many pills to take.	.09	.03	.16	−.09	−.17	.12
My child does not like how the medicine tastes.	−.08	.04	.12	**.42***	.18	**.26***
Parent reminder	.07	.01	.15	.13	.14	−.01
My child relies on me to remind him when to take his medication						

Note: Descriptions and values in bold denote statistical significant relations.
*$p < .05$; **$p < .01$ (two-tailed).

I run out pills'' was associated with more missed doses of medication. ''Don't feel like taking the medicine,'' ''don't like what the medication does to appearance,'' and ''tired of taking medicine'' were all associated with taking more doses late. With regard to drug levels, ''don't want to take the medicine at school,'' ''tired of taking medicine,'' and ''tired of living with a medical condition'' barriers were significantly associated erratic immunosuppressant drug levels.

Barriers and Clinical Outcomes

Correlations between parent-perceived barriers at Time 1 and clinical outcomes at Time 2 yielded several significant

Table IV. *Relations Between Adolescent-Perceived Barriers at Time 1 to Adolescent-Reported Adherence and Clinical Outcomes at Time 2*

	Adherence			Clinical outcome		
	Missed	Late	Drug level	Rejection	Hospital	Death
Total scale	.23	.19	.19	.14	.20	.10
Disease Frustration/Adolescent Issues	.25	**.32***	**.29***	**.27***	.15	.10
I don't want to take the medicine at school.	.23	−.01	**.28***	.25	.19	.11
I feel that it gets in the way of my activities.	.20	.13	−.09	.07	.25	.05
I am forgetful and I don't remember to take the medicine every time.	.10	.21	.05	−.10	.07	.06
I do not want other people to notice me taking the medicine.	.23	.24	.21	**.32***	.12	.19
I sometimes just don't feel like taking the medicine.	.23	**.39****	.20	**.26***	.09	−.08
I don't like what the medication does to my appearance.	.01	**.33***	.10	.09	−.01	.07
I am tired of taking medicine.	.26	**.37****	**.37****	.22	.05	.05
I am tired of living with a medical condition.	.10	.26	**.34***	.22	.07	.08
Regimen adaptation/cognitive issues	.27	.11	−.13	−.18	.05	−.01
I am not very organized about when and how to take the medication.	.22	−.03	−.11	−.21	.14	−16
I find it hard to stick to a fixed medication schedule.	.13	.02	−.06	−.15	−.09	.08
Sometimes I don't realize when I run out of pills.	**.38***	.26	−.16	−.07	.02	.04
Sometimes it's hard to make it to the pharmacy to pick up the prescription before the medicine runs out.	.04	−.16	−.23	−.17	.05	−.10
Ingestion issues	−.01	−.11	.23	.16	**.26***	.13
I believe that the medicine is hard to swallow.	−.13	−.23	.11	.01	.09	**.24***
I believe that I have too many pills to take.	.03	−.09	.22	.09	**.31***	.15
I don't like how the medicine tastes.	.07	−.05	.08	.25	.12	−.01
I believe the medicine has too many side effects.	.07	−.01	.20	.06	**.29***	−.03
I get confused about how the medicine should be taken (with or without food, with or without water, etc.).	−.10	.05	.14	.10	.02	.10

Note: Descriptions and values in bold denote statistical significant relations.
*$p < .05$; **$p < .01$ (two-tailed).

relations (Table III). At the subscale level, Ingestion Issues was associated with a higher likelihood of subsequent rejection episodes and death. At the item level, ''hard time swallowing the medicine'' and ''does not like the way the medicine tastes'' barriers were associated with the occurrence of one or more rejection episodes. Lastly, ''not wanting other people to notice him/her taking the medication,'' ''hard time swallowing medicine,'' and ''not liking how the medicine tastes'' were all associated with a greater likelihood of patient death. Contrary to expectations, lower scores on the ''not always there to remind my child to take his/her medication'' was associated with a lower probability of subsequent hospitalization.

Associations between adolescent-perceived barriers to medication taking at Time 1 and clinical outcomes over the course of the subsequent 18 months yielded several findings (Table IV). At the subscale level, disease frustration/adolescent issues were associated with the occurrence of a rejection episode, while ingestion issues were associated with the occurrence of one or more subsequent hospitalizations. When examining specific barrier items, ''do not want other people to notice me taking the medicine'' and ''don't feel like taking the medicine'' were both associated the occurrence of one or more subsequent rejection episodes. Hospitalization was associated with ''I have too many pills to take'' and ''too many side effects.'' Lastly, ''the medicine is hard to swallow'' was associated with patient death.

Discussion

The aim of this study was to provide further validation for the PMBS and AMBS for assessing perceived barriers to medication adherence among adolescent transplant recipients. The findings in this investigation support the temporal stability of parent proxy and adolescent self-reported barriers, and also demonstrate links between stated barriers and both adherence and medical outcomes at 18 months follow-up.

In the current sample, the rate of nonadherence ranged from 8 to 53% based on method of measurement,

with parent and adolescent reports of missed doses yielding the lowest rates, compared to higher levels of nonadherence for late doses and erratic serum drug levels. These results are consistent with the pediatric transplant literature where adherence rates range from 5 to 50%, based on method of assessment (Dew et al., 2009; Rianthavorn, Ettenger, Malekzadeh, Marik, & Struber, 2004). The rate of medical complications ranged from 6% for the gravest of outcomes, death, to 21 and 29% for rejections and hospitalizations, respectively. These are comparable to the initial rates of rejection episodes (26%) and hospitalizations (27%) that occurred 6 months prior to interviews at Time 1 with the full initial sample (Simons, Gilleland et al., 2009).

The temporal stability of the PMBS and AMBS total scale scores was above .60, which is slightly below the desired range (≥.70; DeVellis, 2003). However, the magnitudes of the correlations are impressive given the year and a half window of time across measurements. Across specific subscales, stability ranged from .43 to .71, with the highest stability noted for PMBS-disease frustration/adolescent issues, whereas AMBS-disease frustration/adolescent issues (.59) was less stable. It may be that parents as external observers perceive a consistent impact of disease frustration/adolescent issues, which often encompass emotional facets of dealing with transplantation (e.g., My child is tired of living with a medical condition), whereas adolescents serve as better reporters of their current internal experience, which may fluctuate more over time, and perhaps even within short time periods. Additionally, for purposes of psychometric evaluation, high temporal stability is considered an asset for an inventory and an indication that the underlying factor being assessed, barriers to adherence in this case, are stable over time. However, from a clinical standpoint, this also suggests that those patients who have high barriers to medication adherence at Time 1 are the ones who are likely to continue to have high barriers at Time 2, 18 months later. This highlights the necessity of assisting those patients in overcoming barriers to adherence and resultant medical complications. Barriers to medication adherence do not seem to go away unaided.

Of clinical interest is the degree to which perceived barriers can be linked to future adherence and medical outcomes. Adolescents' reports of disease frustration/adolescent issues barriers were associated with poorer adherence to medication taking. Many of these items reflect the adolescents' internal emotional reactions and concerns regarding peers (e.g., not wanting to take medication at school, seeming different from peers). Peer support resources (e.g., *Transplant Experience Journal*, http://www.experiencejournal.com/transplant/index.shtml), support groups, or enlisting peer support may be an appropriate intervention to assist children for whom these barriers predominate (e.g., Pendley et al., 2002). Other examples of specific barriers in this subscale (e.g., tired of taking the medication, tired of living with condition) may be responsive to cognitive behavioral therapy to assist them in overcoming any despondency associated with having an organ transplant and the requirements for caring for that transplant (Stark, Nelson, & Kendall, 2004). In contrast to adolescents, parents primarily endorsed barriers that were less emotion laden but were instead within the regimen adaptation/cognitive issues subscale (e.g., forgetfulness, lack of organization) as being associated with nonadherence. Strategies for overcoming these barriers might include parents assisting their adolescent in establishing a good cueing procedure to facilitate adherence. The parent could be more or less actively involved, depending on the adolescent's competence in responding independently to the established cues (Kahana, Drotar, & Frazier, 2008). In sum, these findings underscore the importance of collecting perceptions from both parents and adolescents as each provide unique data.

Both parent- and adolescent-reported ingestion issues were the type of barriers most strongly associated with medical complications, including death. The specific barriers included hard time swallowing medication and too many side effects. We have previously indicated that the five patients who died in this cohort were classified as Genuinely nonadherent in our article describing the four group multidimensional adherence classification systems (MACS; Simons, Gilleland et al., 2009). Thus, even though ingestion issues may not be a very prevalent problem (Simons, McCormick, Mee, & Blount, 2009), when they do exist, they may serve as salient risk factors for profound adverse outcomes. Endorsement of these particular items or an elevated ingestion issues subscale score may point to the need for quick identification and intervention. There are empirically supported interventions for problems such as pill swallowing training (Blount, Dahlquist, Baer, & Wuori, 1984) and physicians may be able to modify administration of medications (e.g., liquid form, smaller pills; Chisholm, 2004). Parents can also provide rewards or incentives for quickly taking medication (Penza-Clyve, Mansell, & McQuaid, 2004). Our various recommendations for overcoming barriers, regardless of type, are conceptually consistent with the results of a recent meta-analysis of psychological interventions

for promoting adherence in pediatric chronic health conditions. Those results indicated that behavioral and multi-component interventions, consisting of behavioral plus educational components, were most effective (Kahana et al., 2008).

This study has clear limitations. For example, there is no one gold standard for assessing adherence. For this reason, we chose multiple assessment methods to provide a more comprehensive representation of adherence. Second, the magnitude of some of the correlations was small. Given the extended duration of time between baseline assessment and follow-up (18 months), these correlations appear to be clinically meaningful as well as robust. Third, a number of correlational analyses were performed, and thus some of the results could be due to chance. However, virtually all significant results (except one) were in the expected direction. Chance correlations would have been in expected and unexpected directions. Moreover, we believe the consequences for this vulnerable population of making a Type II error, missing significant but real associations between barriers and long-term adherence and medical outcomes, are greater than the consequences of making a Type I error, in which an insignificant association is incorrectly accepted. With this acknowledgement, we trust that the readership will be sophisticated and wise in their interpretation of the results. Fourth, over half of the patients were kidney transplant recipients; however, this sample distribution is representative of pediatric transplant patients in general, as adolescent kidney recipients are the largest group of adolescent transplant patients nationwide. Fifth, this sample was recruited from one major transplant center in the southeastern USA. Replication of this research at other major medical institutions and at other geographic locations is needed. Sixth, the use of phone interviews to complete all measures may have elicited more favorable responses than if paper-and-pencil methods were used (McHorney, Kosinski, & Ware, 1994). However, every effort was made for participants to complete the interview in private and phone interviews have been shown to be comparable to in-person interviews for emotional symptoms (Rohde, Lewinsohn, & Seeley, 1997). Finally, we suspect there are barriers beyond those assessed in this study that influenced adherence and medical outcomes. To help overcome this limitation, the AMBS and PMBS includes one open-ended question that in part addresses this issue (Simons, McCormick et al., 2009).

This investigation provides several suggested directions for future research. This study provides support for targeting barriers to medication adherence in treatment interventions. Using the face valid PMBS and AMBS as assessment tools before, during, and at the conclusion of a treatment intervention study would enable interventionists to generate individually tailored treatment plans, monitor progress, and evaluate success in overcoming stated barriers. In addition, certain barriers (e.g., I am tired of living with a transplanted organ) suggest the need to explore the role of emotional distress in maintaining nonadherent behaviors that potentially lead to detrimental health outcomes. Ongoing assessment of barriers and informed individualized interventions are crucial for pediatric transplant patients, given the life and death issues involved. The AMBS and PMBS provide an empirically promising means of doing so.

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