Associations Between Internalizing Symptoms and Trajectories of Medication Adherence Among Pediatric Renal and Liver Transplant Recipients

Yelena P. Wu, MA, Brandon S. Aylward, MA, and Ric G. Steele, PhD, ABPP
University of Kansas

All correspondence concerning this article should be addressed to Ric G. Steele, PhD, Clinical Child Psychology Program, University of Kansas, 2010 Dole Human Development, 1000 Sunnyside Ave; Lawrence, KS, 66047, USA. E-mail: rsteele@ku.edu

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Objectives To examine medication adherence trajectories posttransplantation and the association between adherence trajectories and self-reported internalizing symptoms in a pediatric population.

Methods Multilevel modeling was used to examine internalizing symptoms and longitudinal medication adherence, as assessed by electronic monitoring, among 55 children and adolescents who received liver or kidney transplantation. Results Medication adherence generally declined over the study assessment window, and higher levels of anxiety were associated with higher and more stable patterns of medication adherence. Conclusions Anxiety may be an important factor to consider when assessing and intervening with posttransplantation medication adherence. Future research should consider the potential reactivity effects of adherence monitoring, as well as individual and family behaviors associated with anxiety that may influence adherence.

Key words adherence; organ transplantation; psychosocial functioning.

With medical advances, solid organ transplantation has become a frequently used treatment for end-stage illnesses such as end-stage renal and liver diseases, particularly for children and adolescents (Rianthavorn & Ettinger, 2005; Rodrigue & Zelitkovsky, 2009). Between 1998 and 2007, nearly 18,000 children under the age of 18 received organ transplants, with more than 13,000 of these transplants being liver or kidney transplantations (2008 OPTN/SRTR). Moreover, outcomes and management of pediatric transplant patients have improved over time, and safer and more effective immunosuppressive medications have contributed significantly to increased survival rates (Gummert, Ikonen, & Morris, 1999; Hariharan et al., 2000; Sweet et al., 2006). While medical advances, such as transplantation, have extended the life expectancy of children with end-stage renal and liver diseases, estimates of the prevalence of posttransplantation complications such as opportunistic infections and graft rejections remain high (e.g., 30–36% graft rejections 1 year posttransplantation and 47% graft rejections 5 years posttransplantation; Hariharan et al., 2000; Sieders et al., 2002).

Nonadherence to immunosuppressive medications has been cited as one of the most important contributing factors to graft rejection and graft loss (Dobbs, Van Damme-Lombaert, Vanhaecke, & De Geest, 2005; Rianthavorn & Ettinger, 2005). In the transplant literature, nonadherence to immunosuppressant medication has been defined in various ways: some define nonadherence as missing, forgetting, altering, or delaying a dose of medication a certain number of times (e.g., at least three times per month, Penkower, et al., 2003; at least once per month, Teixeira de Barros & Cabrita, 2000); others define nonadherence as missing some percentage of doses (e.g., 20%, Chisholm et al., 2000); and others define nonadherence as a combination of these examples and other definitions (Fredericks et al., 2008; Simons et al., 2008). Although estimates of nonadherence vary by definition and method of assessment (e.g., self-report, pill count), as
many as 25–70% of pediatric transplant patients are non-adherent at some point posttransplantation (see Dobbels et al., 2005, for a review). For example, using electronic monitoring of medication dosage, Blowey et al. (1994) found that 26% of the pediatric renal transplant recipients in their sample missed three or more consecutive doses of their immunosuppressive medications over a several month monitoring period.

Given the importance of posttransplantation medication adherence, a growing body of literature has focused on assessing adherence and determining factors potentially related to adherence. There are several subjective and objective methods used to assess rates of adherence, including self-report (e.g., questionnaires, daily diaries), measurement of how much medication has been taken, and drug assay levels (e.g., blood or urine samples; Rapoff, 2009). Each assessment method has unique advantages and disadvantages (see Quittner, Espelage, Levers-Landis, & Drotar, 2000; Rapoff, 2009, for reviews). Furthermore, one concern common to all assessment methods is the notion of reactivity and the idea that measurement itself affects what is being assessed (Heisenberg Uncertainty Principle; Heisenberg, 1958; Rapoff, 2009). Although research on reactivity to medication assessment is limited, the existing literature suggests that reactivity biases may not be longlasting (Hawkshead & Krousel-Wood, 2007; Riekert & Rand, 2002; Quittner et al., 2000).

One method of adherence assessment is electronic monitoring. Devices such as the Medication Events Monitoring System (MEMSTM) TrackCap are used as a proxy for daily adherence to pill medications by recording how many times and when a pill bottle is opened. Such devices provide an in-depth and prospective examination of medication adherence patterns and has been considered as a ‘gold standard’ method relative to other methods (Cramer, 1995; Neu, 2006); however, like all adherence assessment techniques, they are not without limitations (see Riekert & Rand, 2002 for further review). For instance, some transplant recipients have noted the burdens associated with MEMS tracking (Shellmer & Zelikovsky, 2007). These limitations notwithstanding, electronic monitoring allows for longitudinal assessment of daily medication adherence in real-time format to track deviations from and to inform recommended medication dosing (Shellmer & Zelikovsky, 2007).

Several studies of pediatric transplant recipients have used electronic monitoring to describe medication adherence. For example, Blowey and colleagues (1994) described patterns of daily medication adherence (e.g., drug holidays, missed doses) among adolescent kidney transplant recipients using the MEMS-4. They found that 21% of their sample took <80% of their prescribed medication over the study monitoring period and that there was a trend towards decreasing medication adherence over time (determined by calculating mean adherence rates for 30-day time intervals). Similarly, Gerson, Furth, Neu, and Fivush (2004) reported that although their sample of pediatric kidney transplant recipients took, on average, 80% of their medications, individuals’ trajectories of medication adherence (displayed in graphical format) varied widely. Unfortunately, Gerson et al.’s methods did not allow a statistical examination of the variability in adherence trajectories.

Although a few studies have examined longitudinal medication adherence in pediatric transplant recipients (Blowey et al., 1994; Gerson et al., 2004) and others have relied on cross-sectional assessments of adherence and risk factors for nonadherence (see Rodrige & Zelikovsky, 2009, for a review), it may also be important to statistically examine the trajectory of medication adherence over time. Examining overall mean adherence (and not taking into account patterns of adherence over time) may lead to inaccurate adherence estimates and ignore acceleration or deterioration in adherence that can have varying effects on health outcomes (Gerson et al., 2004; Rohan et al., 2009). While traditional techniques of analyzing repeated measures data require that certain assumptions be met (e.g., constant variances and covariances), multilevel modeling (MLM) can be used to analyze repeated measures or “clustered” data when these assumptions are violated, which often is the case with longitudinal data.

Beyond questions surrounding best practices for the assessment of medication adherence, a number of studies have examined a variety of predictors or correlates of nonadherence among children who have received solid organ transplantation. Examination of predictors and correlates of nonadherence is consistent with proposed theoretical frameworks for understanding medical outcomes following transplantation and more generally, adherence to chronic illness management regimens. Specifically, these frameworks emphasize the relationship between patient factors (e.g., psychosocial adjustment, sociocultural features) and aspects of the illness and transplant experience (e.g., relationship with healthcare providers; Christensen, 2000; Maloney, Clay, & Robinson, 2005).
A consistent finding in the literature regarding patient factors is the importance of child psychosocial functioning, including depression and anxiety, as a correlate or perhaps a predictor of nonadherence in this population (DiMatteo, Lepper, & Croghan, 2000; Dobbels et al., 2005; Shaw, 2001). Specifically, previous research suggests that children who have had solid organ transplantation are at higher risk for poor psychosocial functioning relative to healthy peers or those with other medical conditions. For example, Gritti et al. (2006) found that pediatric liver transplant recipients had significantly more behavioral problems than age-matched controls with chronic liver disease. Similarly, Wu, Aylward, Steele, Maikranz, and Dreyer (2008) found that children and adolescents who received liver and kidney transplantations had significantly elevated parent-reported internalizing symptoms relative to the BASC normative sample; however, youths themselves reported no such elevations. Fredericks, Lopez, Magee, Shieck, and Opipari-Arrigan (2007) also reported that parents of children who received liver transplantation reported significantly higher rates of internalizing symptoms than parents in the Child Behavior Checklist normative sample. Due to the findings reviewed above, it may be important to continue examining internalizing symptoms on a continuum rather than focusing only on whether diagnosable disorders are related to adherence.

Consistent with existing models of posttransplantation outcomes (Christensen, 2000; Maloney et al., 2005), psychosocial issues may negatively influence posttransplantation medication adherence, thereby placing children at-risk for graft failure and the attendant consequences. However, there have been a relatively small number of studies examining the relationship between internalizing problems and medication adherence among children who received solid organ transplantation and findings have been equivocal (Dobbels et al., 2005; Griffin & Elkin, 2001). Some findings indicate that pediatric transplant recipients with psychosocial difficulties are not at a higher risk for adherence problems (Fredericks et al., 2007; Penkower et al., 2003). For example, adherence as measured by blood assay levels of immunosuppressant medication was not significantly associated with decreased adherence to immunosuppressive medications as measured by self-report and an overall average medication adherence indicated by MEMSTM.

However, Maikranz et al. (2007) did not examine whether internalizing symptoms affected the trajectory of medication adherence. In fact, no studies could be identified that examine whether internalizing symptoms affect trajectories of medication adherence. This information may have important clinical implications for professionals working with children posttransplantation. For example, having information on expected trajectories of adherence for children with differing levels of internalizing symptoms, professionals might adjust the timing of intervention sessions or total length of the intervention to target expected adherence problems. The aim of the current study was therefore to extend a previous analysis of the relationship between internalizing symptoms and medication adherence (using the same recruited sample as Maikranz et al., 2007). Specifically, rather than examining how internalizing symptoms are related to adherence represented by single mean ratings covering a span of several months, the current study examined how internalizing symptoms as indicated by multiple reporters (child and parent) on multiple measures may be independently related to the trajectory of
posttransplantation medication adherence assessed on a daily basis. Consistent with theoretical frameworks in the transplant literature (Christensen, 2000; Maloney et al., 2005), and prior findings that internalizing symptoms are negatively related to medication adherence (DiMatteo et al., 2000; Gerson et al., 2004), we hypothesized that higher internalizing symptoms would be related to poorer posttransplantation medication adherence. A second exploratory aim of this study was to examine the potential role of reactivity to adherence assessment within a sample of children who received solid organ transplantation.

Methods
Participants
The participants included in the current study were part of a larger project examining a model of medication adherence (Maikranz et al., 2007). Participants for the larger study \( (n = 70) \) were recruited from five children’s hospitals between May 1, 2002 and November 30, 2004. Eligibility criteria included that the child (a) was a renal or liver organ transplant recipient, (b) was between the ages of 7 and 18, (c) was at least 6 months posttransplantation, (d) spoke English as the primary language, (e) did not have a developmental delay (defined as an IQ less than 65 based on parent report) and (f) had a primary caregiver who provided informed consent. The participation rate across the five hospitals was 79.8% (100% at three hospitals, 72% and 27% at the other two hospitals). The two hospitals with lower rates of participation recruited participants via mailed letters rather than face-to-face.

The current analysis focused on a subset of participants in the larger study. That is, the current study included children who completed electronic monitoring of medication adherence \( (n = 55) \); mean age = 13.3 years, \( SD = 3.7 \) years; 32 liver transplantations, 23 kidney transplantation; 35 cadaveric and 18 living donor transplants; mean years since transplantation = 6.2, \( SD = 4.1 \) years; mean annual income = $36,000–$48,000, \( SD \) annual income = $24,000). The current sample was 50.9% female. Parents reported that their children were Caucasian (83.6%), African-American (10.9%), Biracial (1.8%), and Hispanic (1.8%). There were no significant differences between children who completed electronic monitoring and those who did not (on demographic variables and measures of psychosocial functioning).

Measures
Demographics
Demographic data were collected from the caregivers and by chart review. These data included income, age, type of transplant (liver or kidney), age at transplant, time since transplant, whether the transplanted organ came from a living or deceased donor, number of medications in children’s current regimen, and name of transplant medications.

Medication Adherence
Adherence to prescribed immunosuppressant medication regimens was measured using MEMSTM Trackcaps. The MEMSTM Trackcap includes a microchip that records the time and date of each bottle opening (i.e., a presumed dosing event). Data from the microchips are retrieved when the Trackcaps are returned to the investigators. While no specific reliability data on the device has been published within populations of transplantation recipients, device failure is reportedly low (Shellmer & Zelikovsky, 2007; Liu et al., 2001) and this method of assessing medication adherence has been used in numerous prior studies, including those of pediatric transplant recipients (Blowey et al., 1994; Gerson et al., 2004; see Riekert & Rand, 2002, for a review). Recent studies including patients with individuals taking HIV medication provide preliminary evidence that the MEMSTM method of assessing adherence is valid and reliable (Lu et al., 2008; Müller, Bode, Myer, Roux, & von Steinbüchel, 2008).

The mean length of MEMSTM Trackcap monitoring was 89.71 days \( (SD = 25.09) \). For each day of monitoring, a continuous measure of medication adherence was calculated by dividing the number of bottle openings by the number of prescribed dosages per day. This method of adherence calculation allows quantitative examination of over-dosage of medication (i.e., adherence values >100%) as well as the perhaps more typical under-dosage of medication (i.e., adherence values <100%). Particularly in the case of medication over-dosage, daily adherence measurements are more accurate than weekly or monthly measurements (Riekert & Rand, 2002).

Parent-reported Youth Psychosocial Functioning
The Behavioral Assessment System for Children, Parent Report Form (BASC-PRF, Reynolds & Kamphaus, 1992) is a comprehensive measure of a child’s overall psychosocial functioning. Parents completed the parent-report form (PRF) and children completed the self-report form (SRP). This measure has demonstrated good internal consistency.
and test-retest reliability (Reynolds & Kamphaus, 1992). The BASC provides composite t-scores ($M = 50, SD = 10$) for specific problem and adaptive areas (e.g., externalizing, internalizing, adaptive functioning). Both parent- and child-reported anxiety and depressive scale t-scores were used in the current analyses.

**Youth Depressive Symptoms**
The Children’s Depression Inventory (CDI; Kovacs, 1992) is a 27-item self-report measure that examines depressive symptoms and has several subscales including mood disturbance, self-perceptions, and relationships with others. The total CDI score was used in the present analyses. T-scores of greater than 65 indicate clinically significant symptoms. The CDI has well-established internal consistency ($\alpha = .86$) and validity (Kovacs, 1992). Internal consistency in the present sample was good ($\alpha = .83$).

**Youth Anxiety**
The State-Trait Anxiety Inventory for Children (STAIC; Spielberger, Edwards, Montuori, Lushene, & Platzek, 1970) is comprised of self-report scales measuring state anxiety (worry or tension that varies over time) and trait anxiety (worry or tension that is relatively stable over time). Scores on the two anxiety scales are raw scores. Published Trait-anxiety $\alpha$-coefficients are .79 or greater with a median $\alpha = .88$ for the normative sample (Spielberger et al., 1970). Similarly, reported State-anxiety alpha coefficients range from .71 and .76 (Spielberger et al., 1970). The $\alpha$-coefficients in the current sample were .90 and .83 for Trait- and State-anxiety, respectively.

**Procedure**
As mentioned earlier, data for the present investigation were collected as part of a larger investigation of a model of medication adherence to posttransplant regimens (Maikranz et al., 2007); however, the analyses in this report have not been previously published. Children and their families who met eligibility criteria were informed of the study by clinic personnel. Those who expressed interest in the study were asked to participate. Informed consent and youth assent were obtained from the primary caregiver and child, respectively. Children and primary caregivers completed pencil and paper measures (BASC, CDI, STAIC) at the baseline study visit. Questions were read to the children if they could not complete the measures independently. Families who completed the pencil and paper measures were provided with the MEMSTM Trackcap and instructions on proper usage. All measures and procedures were approved by the Institutional Review Board of the authors’ institution, as well as by the Institutional Review Boards of each of the participating hospitals.

**Analytic Plan**
In contrast to Maikranz et al. (2007), who examined latent constructs of depression, anxiety, uncertainty, and hope to predict a static mean level of adherence, the present investigation used MLM (using the same recruited sample as Maikranz et al., 2007) to examine the degree to which internalizing symptoms (depression and anxiety) were related to linear change in medication adherence. As mentioned earlier, MLM can be used to analyze “clustered” data, including repeated measures, and provides less biased effect size estimates than traditional statistical methods (Snijders & Bosker, 1999). Moreover, MLM has several advantages over more traditional methods of longitudinal data analysis (e.g., accommodation of missing data, allowing for inferences about individual change over time; see Snijders & Bosker, 1999, for further review).

In order to determine how “time” should be modeled for the current study, intraclass correlation coefficients (ICCs) were calculated for a null model (no predictors, random intercepts) with “day” as a level-1 effect and “participant” as a level-2 effect. ICCs are a measure of the proportion of variance in the outcome variable (percent adherence) accounted for by each level or grouping variable (Snijders & Bosker, 1999). In the current study, “day” was nested within “participant.” Internalizing symptoms were then added as level-2 predictor variables using the build-up strategy, and the likelihood ratio deviance test, with a criteria of $p < .05$, was used to determine whether predictors were retained and the final, best-fitting model. When the likelihood ratio deviance test is used to determine whether predictors should be retained, predictors which are non-significant by the Wald test may still be retained. This is because the likelihood ratio deviance test takes into account the sum of all the effects (random, fixed, and conditional main effects), some of which, individually, may not be significant by the Wald test. All models included random intercepts and slopes at all levels. After including “day” as a level-1 predictor, parent- and child-reported internalizing symptoms as well as the interaction between the internalizing symptoms and “day” were added successively as level-2 predictors. All predictors were centered so that intercept estimates were interpretable and significant interactions were probed and plotted (Preacher, Curran, & Bauer, 2006).
Table I. Descriptive Statistics

<table>
<thead>
<tr>
<th>Measure</th>
<th>Mean</th>
<th>SD</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>BASC Depression (parent-report)</td>
<td>50.97</td>
<td>13.76</td>
<td>34–100</td>
</tr>
<tr>
<td>Anxiety (parent-report)</td>
<td>53.76</td>
<td>13.03</td>
<td>29–84</td>
</tr>
<tr>
<td>Depression (child-report)</td>
<td>46.88</td>
<td>7.80</td>
<td>41–80</td>
</tr>
<tr>
<td>Anxiety (child-report)</td>
<td>44.83</td>
<td>7.73</td>
<td>34–63</td>
</tr>
<tr>
<td>CDI (total score)</td>
<td>44.32</td>
<td>7.67</td>
<td>34–65</td>
</tr>
<tr>
<td>STAIC Trait-anxiety</td>
<td>32.07</td>
<td>8.07</td>
<td>20–50</td>
</tr>
<tr>
<td>STAIC State-anxiety</td>
<td>28.34</td>
<td>4.81</td>
<td>20–43</td>
</tr>
</tbody>
</table>

BASC, Behavioral Assessment System for Children (t-scores); CDI, Children’s Depression Inventory (t-scores); STAIC, State-Trait Anxiety Inventory for Children (raw scores).

Table II. Fixed Effects of Final Model

<table>
<thead>
<tr>
<th>Coefficient</th>
<th>β</th>
<th>SE</th>
<th>Z</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intercept</td>
<td>79.03</td>
<td>3.44</td>
<td>22.99</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>DAY</td>
<td>-0.25</td>
<td>0.04</td>
<td>-6.33</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>CANX</td>
<td>-0.35</td>
<td>0.52</td>
<td>-0.67</td>
<td>0.501</td>
</tr>
<tr>
<td>DCANX</td>
<td>0.02</td>
<td>0.01</td>
<td>2.69</td>
<td>0.007</td>
</tr>
<tr>
<td>CDEP</td>
<td>-0.81</td>
<td>0.53</td>
<td>-1.52</td>
<td>0.128</td>
</tr>
<tr>
<td>DCDEP</td>
<td>-0.01</td>
<td>0.01</td>
<td>-2.29</td>
<td>0.022</td>
</tr>
<tr>
<td>STANX</td>
<td>2.93</td>
<td>0.94</td>
<td>3.14</td>
<td>0.001</td>
</tr>
<tr>
<td>DSTDANX</td>
<td>-0.01</td>
<td>0.01</td>
<td>-1.08</td>
<td>0.282</td>
</tr>
</tbody>
</table>

CANX, BASC, child-reported anxiety; DCANX, DAY × CANX interaction; CDEP, BASC, child-reported depressive symptoms; DCDEP, DAY × CDEP interaction; STANX, child-reported state-anxiety; DSTDANX, DAY × STANX interaction.

Results

On average, children were prescribed four medications (SD = 3, range = 1 to 13), including their anti-organ rejection medication (assessed by the MEMS™ TrackCap). The majority (66%) of participants were prescribed tacrolimus. Other anti-organ rejection medications included mycophenolate mofetil (11%), cyclosporine (11%), sirolimus (5%), and medications such as prednisone, sulfamethoxazole and trimethoprim (7%). Most children (n = 50, 91%) were instructed to take their anti-rejection medication twice per day, and the number of bottle openings recorded ranged from 0 to 5. The average rate of adherence across all monitoring days was 69.7% (range from 0% to 400%). One child was instructed to take the medication four times per day, and four children were instructed to take the medication once per day. There were no significant correlations between adherence at baseline and demographic variables such as type of transplant, age at transplant, time since transplant, and income.

Table I contains descriptive statistics for the study measures. On average, children and their parents reported levels of anxiety and depression comparable to the normative samples of each measure. ICCs for the null model (Model 1) indicated that a large amount of variance in medication adherence was due to both day (ICC = .54) and participant (ICC = .46). In Model 2, “day” was added as a level-1 predictor of medication adherence. The likelihood ratio test comparing Model 2 to the null model was significant, indicating that “day” should be retained in the model (χ²-deviance = 371.96, df = 3, p < .001). Internalizing symptom predictors were then added, in succession, to the participant level. Including parent-reported anxiety and depression on the BASC yielded nonsignificant likelihood ratio tests when these successive models were compared to Model 2 and thus these predictors were excluded (χ²-deviance = 2.19, df = 2, p > .05; χ²-deviance = 4.87, df = 2, p > .05, respectively). Adding child-reported anxiety and depression on the BASC yielded significant likelihood ratio tests, and thus these predictors and their interactions with “day” were retained (χ²-deviance = 4557.96, df = 2, p < .001; χ²-deviance = 8.00, df = 2, p = .018, respectively). Adding CDI scores yielded a nonsignificant likelihood ratio test (χ²-deviance = .871, df = 2, p > .05). However, state-anxiety yielded a significant likelihood ratio test and was therefore included in the model (χ²-deviance = 10.61, df = 2, p = .004). Finally, trait-anxiety was excluded from the model (χ²-deviance = 1.00, df = 2, p > .05).

The predictors in the final model therefore included “day,” three internalizing symptoms predictors (child-reported depressive symptoms, state-anxiety, and anxiety symptoms), and all interactions between “day” and the three internalizing symptoms predictors (Table II). The significant predictors of adherence were “day,” child-reported state-anxiety, the day X BASC child-reported anxiety symptoms interaction, and the day X BASC child-reported depressive symptoms interaction. The results indicate that on the first day of adherence assessment, children were taking, on average, 79.0% of their medications and that the variance (SD²) in medication adherence (percentage) due to “participant” was 537.23. This variance suggests that there was a sizeable variation in participants’ adherence at the beginning of the monitoring period (1 SD ≈ 23%, mean adherence = 79.0%, 1 SD range in adherence = 56–102%). In addition, when all other predictors were held constant, for each increase in one point on state-anxiety, adherence increased by 2.9%.
Further analysis of the significant interaction between “day” and child-reported anxiety symptoms on the BASC indicated that children with the lowest (t = 34) or typical (t = 44.8) levels of anxiety had a significant decline in medication adherence over time (z = 5.51, p < .001; z = 6.33, p < .001, respectively). Specifically, holding all other predictors constant, for children with the lowest level of anxiety, adherence decreased by .43% each day. This finding suggests that by the end of the second month of monitoring, these children would, on average, be missing approximately half of their prescribed medication (e.g., missing one out of the two prescribed doses per day; .79.0% – [2 months × (.43% × 30 days)] = 53.2%). For children with a typical level of anxiety, adherence decreased by .25% each day. This finding suggests that these children would be missing approximately half of their prescribed medication by the end of their third month of monitoring (79.0% – [3 months × (.25% × 30)] = 56.5%). In contrast, children with the highest levels of anxiety (t = 63) did not have a significant decline in adherence over time (z = .43, p > .05). Figure 1 contains a graph of children’s adherence trajectories depending on their level of anxiety.

In addition, further analysis of the significant interaction between “day” and child-reported depressive symptoms on the BASC indicated that regardless of level of depressive symptoms, adherence is stable at the onset of the monitoring period (z = 1.52, p = .128) but decreases by the middle (z = 2.33, p = .02) and end (z = 2.62, p = .009) of the monitoring period. Specifically, holding all other predictors constant, at the middle of the monitoring period (day 50) adherence was, on average, decreasing by 1.5%, and at the end of the monitoring period (day 151) adherence was, on average, decreasing by 2.8%.

Discussion

The present study was designed to examine the associations between self- and parent-reported internalizing symptoms and trajectories of objectively assessed medication adherence in a relatively large sample of children and adolescents who were approximately 6 years post solid organ (i.e., liver, kidney) transplantation. Associations between adherence and clinical outcomes have typically relied on a summary adherence score, thereby ignoring potentially important individual trajectories; however, recent research has highlighted the utility of examining treatment trajectories (DeLucia & Pitts, 2006; Rohan et al., 2009). Previous investigations have suggested that patterns, or trajectories, of adherence exist in pediatric transplant populations (Gerson et al., 2004). However, the present study is the first to quantitatively examine the associations among these trajectories and indices of child psychosocial functioning. Consistent with previous studies, our results indicate that post-transplantation medication adherence varies widely, and that internalizing symptoms, particularly child-reported anxiety, are significantly associated with trajectories of adherence. However, contrary to our hypothesis, higher internalizing symptoms were not related to poorer adherence. Our results also raise important questions about whether individual differences in symptomatology may differentially impact reactivity to adherence assessment.

Consistent with previous investigations (see Dobbel et al., 2005, for a review), the current findings document imperfect medication adherence following transplantation. Because deviations from medication prescriptions may negatively impact child health outcomes, the current study defined nonadherence as any deviation (above or below) recommended dosing. In the context of the current study, the wide variance in adherence at the first assessment was in large part due to some children opening their medication bottles more times per day than was recommended by their physicians. Because a greater number of daily openings of medication bottles does not necessarily correspond with overadherence or ingesting more medication than recommended, future studies may wish to
examine whether some children, are, in fact, overadherent to their medication regimens. Children, for example, may open their pill bottles and not ingest medication (Shellmer & Zelikovsky, 2007). Medication overadherence has been examined in adult populations; however, few studies have examined overadherence as a risk for negative outcomes in children (Partridge, Avon, Wang, & Winer, 2002). Future studies should more fully examine whether this type of non-adherence in children affects graft maintenance.

Most previous studies of internalizing symptoms in pediatric transplantation samples have investigated the associations between depressive symptoms and adherence (DiMatteo et al., 2000; Maikranz et al., 2007), with results suggesting an inverse association (i.e., higher depressive symptoms are associated with lower adherence rates). Studies of general “psychosocial adjustment” and adherence in this population suggest a similar pattern (e.g., greater adjustment problems are associated with poorer adherence; Fredericks et al., 2007; Penkower et al., 2003). In light of these previous findings, our results of a positive association between state anxiety and adherence warrant special comment. Perhaps in contrast to previous studies, it is important to note that even the “highest” levels of anxiety obtained in the current sample did not reach BASC or STAIC levels of clinical significance. Thus, participants in our sample with “high anxiety” were generally functioning within the normal range. With that noted, children who reported higher levels of state-anxiety demonstrated trajectories of better medication adherence during the assessment window. Specifically, they demonstrated no decline in adherence over the assessment window. In contrast, children with the lowest and typical levels of anxiety on the BASC demonstrated declining medication adherence over time.

In the absence of a specific literature to contextualize these findings, we offer some speculation about the relationship between mild symptoms of anxiety and medication adherence. Perhaps children who tend to worry about the future may be more likely to take preventative actions such as taking immunosuppressant medications. Or, it may be that children who worry are more likely to be planful in their general habits, including medication-taking behaviors. Another possibility is that children with higher anxiety have parents who have higher levels of anxiety and/or parents who are more involved in their children’s activities, including medication-taking. Future research might therefore explore what behaviors or family characteristics associated with children’s anxiety affect medication adherence. If such behaviors or characteristics are identified, clinicians may be able to teach certain skills or strategies to families to improve their medication adherence. Furthermore, future research on the impact of anxiety symptoms on adherence behaviors for a range of pediatric chronic illness groups might be warranted given recent findings that in a sample of children with diabetes, there was an association between varying levels of anxiety (i.e., low, moderate, high) and adherence and clinical outcomes (Herzer & Hood, 2009); however, there was no clear “optimal” level of anxiety.

As noted above, the current results raise important questions about the role of reactivity in adherence assessment. Although we are not able to comment on our participants’ adherence prior to their participation in our study, it seems unlikely that the trajectories observed during the assessment window are continuous reflections of their adherence trajectory over the (on average) six years prior to the study. Such an assumption would require that the participants’ adherence rates reach asymptote (at 100%) just weeks or months prior to the study’s initiation. Thus, another (and we believe, more likely) scenario is that study entry and the initiation of adherence monitoring amounted to a de facto adherence intervention that improved adherence to the observed 79% at the initial assessment, and that the declining adherence over the course of the study amounted to a return to typical (pre-assessment) conditions. Further supporting the idea that reactivity affected the measured level of adherence is the finding that adherence was stable at the onset of the monitoring period, but was decreasing by the mid- and end-points of the monitoring period. That is, a “return to baseline” may have occurred within several weeks for most participants in our sample. In contrast to some previously published reports (DiMatteo et al., 2000; Penkower et al., 2003), our results therefore raise questions about the significance of the effects of reactivity in study results.

What is of particular interest in this study is the dramatic interaction between the declining adherence rates and our measures of anxiety. Children in our sample with higher levels of anxiety evidenced better medication adherence over the course of our study, perhaps as a result of a stronger and more sustained reaction to being monitored. In contrast, children with lower levels of anxiety may have evidenced steeper declines in adherence as a result of lower sensitivity (or quicker habituation) to observation. We believe our study is the first to show an interaction between self-reported anxiety and such habituation in a pediatric sample. Supporting our findings is a previous study demonstrating that children with cystic fibrosis
with anxiety disorders or internalizing symptoms reported greater adherence (White, Miller, Smith, & McMahon, 2009).

Our results have important methodological implications. First, our results demonstrate the viability and benefits of using statistical analyses such as MLM to account for repeated measurements in adherence research. MLM accommodates key challenges to analyzing repeated measure data, such as correlated residuals and missing data. Second, given that any overt measure of adherence may cause reactivity in the sample being observed, longitudinal assessments of medication adherence are likely the best method of accounting for any reactivity effects and obtaining more accurate adherence assessments. That is, researchers may wish to focus more on adherence assessments from later in the monitoring period, after any reactivity in the initial assessment period has subsided. By using statistical techniques such as testing nested multi-level models with decreasing exponential functions, future studies might identify the points in time at which adherence tends to stabilize and determine whether these points are related to psychosocial or medical variables (e.g., time since transplantation). Future investigations should also examine whether medication adherence may have a curvilinear pattern of change over time or whether the trajectory differs when adherence assessment begins immediately post-transplantation. The current results do suggest, however, that researchers who do not assess adherence longitudinally should be particularly vigilant towards possible reactivity effects (Rickert & Rand, 2002).

Reactivity effects may be particularly important to consider within the context of longitudinal assessments of adherence. That is, certain assessment methods may “pull” for reactivity effects more than others. In the current study, for example, the daily electronic monitoring may have, particularly in the beginning of the study, served as a frequent, overt reminder that adherence was being monitored. In contrast, other methods of assessing longitudinal adherence, including conducting interviews in laboratories or doctor’s offices (Murphy et al., 2005), are typically scheduled ahead of time and are quite separate from participants’ daily adherence routines. Thus, they may not pull for reactivity effects in the same ways that daily electronic monitoring does.

There are several limitations to the current study that warrant discussion. First, although the participation rate was reasonably high, it is possible that sampling bias may have affected the results. Second, it was not feasible, in the context of the current study, to rule out the possibility that the decline in adherence over time was not due to natural fluctuations in adherence or “noise” in the data. Third, the current analysis did not include other measures of adherence such as objective measures (e.g., drug assay) or subjective measures (e.g., self-report, prescription refill information). Finally, by using a global measure of anxiety symptoms, such as the BASC, the current study was unable to examine the perhaps subtle differences (e.g., in behavior) between the “high” versus “low” or “typical” anxiety children. As noted above, even the “high” anxiety symptom children were within the normal range of anxiety on the BASC.

Due to the overt nature of electronic monitoring using the MEMSTM Trackcap, the current study was not able to directly test children’s reactivity to monitoring. Future experimental studies comparing overt and covert assessments are needed in order to confirm our findings. Furthermore, future studies might quantify the degree to which reactivity impacts children of different anxiety levels (e.g., nonclinical vs. clinical) and how anxiety levels at various timepoints posttransplantation might affect adherence and/or reactivity. Future studies should also examine the relationship between other psychosocial problems (e.g., externalizing behaviors) and medication adherence (ideally, assessed using multiple methods), reactivity effects, and health outcomes (e.g., graft rejection or loss). Given that developmental differences may affect adherence behaviors (e.g., whether the parent or child is responsible for medication-taking) and the accuracy of reports of psychosocial adjustment, future studies might examine whether adherence trajectories or psychosocial factors differ based on developmental level. Ultimately, obtaining a better understanding of the many factors related to medication adherence, including adherence method and reactivity effects, psychosocial difficulties and barriers to adherence (Simons et al., 2008), will be essential for informing clinical and research efforts to improve medication adherence and health outcomes.

**Clinical Implications**

The results of the current study suggest that internalizing symptoms may affect medication adherence posttransplantation and that children with higher levels of anxiety may be more reactive to adherence assessment or may be more adherent. The interplay between reactivity effects and psychosocial adjustment should be considered when examining or intervening with medication adherence post-transplantation. More generally, it may be important to consider whether the act of assessing adherence may, in
fact, serve as an adherence intervention (Clowes, Peel, & Eastell, 2004; Wagner & Ghosh-Dastidar, 2002). This phenomenon may be particularly important to explore within pediatric populations, given the cost of implementing adherence interventions.

Although methods of assessing adherence may differ between hospitals and clinicians, the current results highlight the importance of assessing adherence longitudinally. If our interpretations of the current findings are correct—specifically, that the act of assessing adherence may impact adherence itself, depending on individual differences—longitudinal assessment of adherence may be an important component of assessments informing clinical care and measurement of adherence outcomes (e.g., in response to an intervention). In particular, clinicians might consider using longitudinal assessments of adherence if patients have higher levels of anxiety.

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