ADOLESCENT AND CAREGIVER EMOTIONAL FUNCTIONING, PERCEIVED BARRIERS, AND ADHERENCE IN SOLID ORGAN TRANSPLANT RECIPIENTS

by

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(Under the Direction of Ronald L. Blount)

ABSTRACT

The current study aimed to examine the influence of caregiver and adolescent emotional functioning (i.e., symptoms of depression and anxiety) on medication adherence and the mediational role of adherence barriers with 39 dyads of adolescent transplant recipients and their caregivers. Caregiver emotional functioning accounted for significant additional variance beyond the effects of adolescent emotional functioning in the prediction of adherence barriers and adherence. There was evidence of an indirect effect between caregiver emotional functioning and medication adherence through the Disease Frustration/Adolescent Issues subscale of the Adolescent Medication Barriers Scale. Results suggested that caregiver emotional functioning contributed to having more adherence barriers and subsequently lower adherence in adolescent transplant recipients. Intervention to reduce caregiver depression and anxiety symptoms may reduce adolescents' adherence barriers and increase medication adherence.

INDEX WORDS: Solid Organ Transplant, Adolescent, Caregiver, Emotional Functioning, Barriers, Medication, Adherence

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CHAPTER 1

INTRODUCTION

Medical advances in surgical and pharmacological methods have led to improved organ graft survival rates for pediatric solid organ transplant recipients (Organ Procurement and Transplantation Network [OPTN] and Scientific Registry of Transplant Recipients [SRTR], 2012). More pediatric transplant recipients are surviving into adolescence and young adulthood, and often with significantly enhanced health-related quality of life (HRQOL; LaRosa, Baluarte, & Meyers, 2011; Sundaram, Landgraf, Neighbors, Cohn, & Alonso, 2007). Despite the benefits to successful transplantation, the recipient's wellbeing is largely dependent on the continued health of the organ graft. Thus, for pediatric transplant recipients, both the patient and their family members are tasked with the critical, and often demanding, responsibility of caring for the organ graft to maintain post-transplant improvements.

To support optimal transplant functioning, patients must maintain a high degree of adherence to a specific treatment regimen prescribed by healthcare providers. *Adherence* is defined as "the extent to which a person's behavior—taking medications, following a diet, and/or executing lifestyle changes, corresponds with agreed recommendations from a healthcare provider" (Sabaté & World Health Organization, 2003). For pediatric transplant recipients, optimal adherence primarily includes taking immunosuppressant and other medications as prescribed, in addition to attending regular clinic and laboratory appointments. Failure to follow these recommendations can have severe consequences, including organ rejection, hospitalization, decreased HRQOL, and even death (Fredericks, Lopez, Magee, Shieck, & Opipari-Arrigan,

2007). Costs incurred as a result of adverse medical events related to treatment nonadherence (e.g., rejection, hospitalization, infection) also pose significant financial burdens to the healthcare system (United States Government Accountability Office, 2007).

Even though proper adherence is vitally important to maintaining patients' health, approximately 43% of pediatric transplant recipients are nonadherent to their medication regimens (Dobbels et al., 2010). Adolescence, in particular, is considered an especially problematic developmental period for maintaining adequate adherence across disease populations (DiMatteo, 2004). Adolescent transplant recipients, specifically, have been shown to have significantly poorer medication adherence and experience more allograft loss due to nonadherence when compared to younger children (Dobbels et al.). For adolescents with kidney transplants, up to 12% of kidney transplant failures have been attributed to nonadherence, which is approximately four times the rate of adult patients (Rianthavorn & Ettenger, 2005).

To understand why adolescent transplant recipients tend to have more difficulty with treatment adherence, previous investigations have examined patient and caregiver emotional functioning (e.g., depression, anxiety), perceived barriers to medication adherence, and the interaction of these factors as contributing to and predicting treatment nonadherence (McCormick King et al., 2014; Rodrigue & Zelikovsky, 2009). The role of barriers to adherence is of particular interest in these relationships since, according to the Health Belief Model (HBM), barriers are considered the most powerful predictors of the extent to which a patient will engage in various health-related behaviors, including adherence (Janz & Becker, 1984). Research in these areas examining pediatric transplant recipients, as well as similar research conducted with pediatric patients with other chronic health conditions, will be reviewed.

Child emotional functioning as it relates to treatment adherence emerges as a particularly promising domain for further study in adolescent transplant recipients. Poorer adherence in adolescent transplant recipients has been linked to various aspects of patient emotional functioning, including greater levels of depression, anxiety, posttraumatic stress symptoms, and anger (Maikranz, Steele, Dreyer, Stratman, & Bovaird, 2007; McCormick King et al., 2014; Penkower et al., 2003). Pediatric transplant recipients with comorbid psychiatric illness have also been shown to have greater risk for future graft loss (Shaw, Palmer, Blasey, & Sarwal, 2003), which often occurs as a result of medication nonadherence (Falkenstein, Flynn, Kirkpatrick, Casa-Melley, & Dunn, 2004).

Contrary to the majority of the literature, Wu, Aylward, & Steele (2010) initially found support for a positive association between anxiety symptoms and medication adherence in children and adolescents with solid organ transplants. However, participants' adherence rates declined over time. The authors attributed the initially positive correlation between anxiety and adherence to "reactivity effects" associated with the ongoing use of electronic monitoring. Thus, the results of this study (Wu et al., 2010) emerge as an outlier within the area of adherence and patient emotional functioning research in pediatric transplant recipients.

In adolescent and mixed-age samples of pediatric patients with different health conditions (e.g., inflammatory bowel disorder [IBD], asthma, type 1 diabetes, human immunodeficiency virus [HIV]), poorer treatment adherence has also been consistently associated with greater levels of anxiety (Gray, Denson, Baldassano, & Hommel, 2012; Williams et al., 2006), depression (Armstrong, Mackey, & Streisand, 2011; Gonzalez et al., 2008; Murphy et al., 2005), and psychological distress (Naar-King et al., 2006). Across transplant and other pediatric populations, the evidence continually suggests an association between more symptomatic patient

emotional functioning and worse treatment adherence. This is particularly problematic because the prevalence of psychological disorders (e.g., anxiety, mood, behavior, substance use) tends to increase as children age (Merikangas et al., 2010), placing adolescents at increased risk for adherence-related difficulties relative to younger children.

Less research has addressed the association between caregivers' emotional functioning and treatment adherence in adolescent transplant recipients. In a study by Fredericks et al. (2007), parents of adolescent transplant recipients who were classified as "nonadherent" based on immunosuppressant blood levels and clinic attendance rates reported significantly poorer emotional functioning in response to their child's health status and greater illness-related parenting stress than parents of adolescents classified as "adherent." An investigation of a mixed age sample of children, adolescents, and young adults (range 2-20 years) with solid organ transplants reported an association between higher general parent stress and poorer medication adherence (Gerson, Furth, Neu, & Fivush, 2004).

In related research with caregivers of children with other chronic health conditions (e.g., asthma, type 1 diabetes, HIV), greater levels of maternal depression have been associated with more pediatric treatment nonadherence (Bartlett et al., 2004; Wiebe et al., 2011) and poorer disease management (Kub et al., 2006). Greater parental psychological distress (Marhefka, Tepper, Brown, & Farley, 2006) and general caregiver stress (Mellins, Brackis-Cott, Dolezal, & Abrams, 2004) has also been linked to poorer pediatric medication adherence. Although caregiver and child emotional functioning appear to both play important roles in predicting pediatric treatment nonadherence, caregiver and child factors thus far have primarily been examined separately, as independent predictors of adherence.

Some previous researchers have collected both caregiver- and child-reports of psychosocial variables but have not focused on emotional functioning, explicitly, or treated the family as a unit in predicting pediatric treatment adherence. In a study of pediatric transplant recipients, Maikranz et al. (2007) found support for a mediation model in which relationships between parent- and child-reported hope, illness-related uncertainty, and treatment adherence were mediated by child depressive symptoms. The models were not supported when child anxiety was entered as the mediating variable. Although the researchers attempted to examine the contributions of parent-child psychosocial factors in the prediction of treatment adherence, they created latent variables, which were comprised of both parent- and child-reported hope and illness-related uncertainty, rather than examining each reporter's contribution to the prediction of treatment adherence. Additionally, the study only contained measures of child depression and anxiety and did not examine parental symptoms. Fredericks et al. (2007) also obtained parent self-report and proxy-reports of the child on several emotional functioning domains (i.e., parent depression and anxiety symptoms and child internalizing and externalizing symptoms) in families of pediatric liver transplant recipients, but only compared the measures to normative data. The researchers did not examine parent or child emotional functioning variables in the prediction of treatment adherence, which was measured via immunosuppressant blood levels and clinic attendance.

In other pediatric populations, caregiver- and child-reports of emotional functioning and other variables have been obtained but examined separately in the prediction of treatment adherence (Cameron, Young, & Wiebe, 2007; Mackner & Crandall, 2005; Williams et al., 2006). Other studies collected parent and child self-reports of emotional functioning and information on treatment adherence but did not report whether a relationship between the variables existed or

not (Lim, Wood, & Miller, 2008; Mellins, et al., 2004). A study examining children with type 1 diabetes and their parents reported longitudinal relationships over the course of 5 years in which parental diabetes-specific stress predicted increased child depression and improved glycemic control (Helgeson, Becker, Escobar, & Siminerio, 2012). Parental general stress also predicted a decrease in the frequency of blood glucose monitoring and glycemic control (Helgeson et al., 2012), indicating probable treatment nonadherence. However, the study did not obtain parental depression measures until the second data collection time point and did not examine potential relationships between parental depression and child depression or diabetes adherence behaviors at later time points (Helgeson et al., 2012). Rather, the authors reported that parents' general stress predicted increased parental depressive symptoms and decreased life satisfaction (Helgeson et al., 2012). There remains much to learn about how caregiver and child emotional functioning operate together to predict treatment adherence in adolescent transplant recipients and other pediatric populations.

Although there is evidence that adolescent and caregiver emotional functioning are associated with pediatric treatment adherence, less is known about the processes by which these variables may influence adherence. Recently, perceived barriers to medication adherence have emerged as promising mediators to help explain the influence of adolescent emotional functioning and other psychosocial factors on treatment adherence. The HBM (Janz & Becker, 1984) defines barriers to adherence as perceived obstacles that impede a patient's ability to follow prescribed medical regimens (e.g., "I am forgetful and I don't remember to take the medicine every time; Simons & Blount, 2007). Greater numbers of barriers have consistently been associated with poorer treatment adherence in adolescents with solid organ transplants (Simons, McCormick, Devine, & Blount, 2010; Zelikovsky, Schast, Palmer, & Meyers, 2008)

and other pediatric populations (Hommel & Baldassano, 2010; Ingerski, Baldassano, Denson, & Hommel, 2010; Logan, Zelikovsky, Labay, & Spergel, 2003). Barriers are considered modifiable constructs that, if successfully addressed through clinical intervention, could help support better treatment adherence (Rapoff, 2010).

In a recent study examining adolescent transplant recipients, McCormick King and colleagues (2014) demonstrated a mediational role of barriers in the relationship between emotional functioning and medication nonadherence. The Regimen Adaptation/Cognitive Issues (RA/CI) subscale of the Adolescent Medication Barriers Scale (AMBS; Simons & Blount, 2007), which reflects barriers related to executive functioning difficulties (e.g., lack of organization, not planning ahead), fully mediated the relationship between both adolescent depression and posttraumatic stress symptoms and medication nonadherence. The RA/CI barriers subscale partially mediated the relationship between adolescent anxiety symptoms and medication nonadherence. Overall, poorer emotional functioning was significantly related to having more RA/CI barriers, which was significantly related to worse medication adherence. Thus, the RA/CI barriers appear to explain the process by which adolescent emotional functioning is related to medication adherence in adolescents with solid organ transplants.

A similar model was tested in adolescent patients with inflammatory bowel disease (IBD), focusing on adolescents' externalizing behavioral symptoms of attention problems and conduct problems (Reed-Knight, Lewis, & Blount, 2013). In this study, the RA/CI barriers subscale of the Parent Medication Barriers Scale (PMBS; Simons & Blount, 2007) fully mediated the relationship between both attention problems and conduct problems and medication adherence. Greater severity of behavioral problems was significantly related to having more RA/CI barriers and poorer medication adherence. Although this study focused on behavioral

functioning rather than emotional functioning, the results lend further support for a mediational role of adherence barriers in the relationship between adolescent psychosocial factors and medication adherence.

Despite support from the previously reviewed studies, the role of adherence barriers in the relationship between adolescent psychosocial variables and medication adherence is not entirely clear. Reed-Knight and colleagues (2013) demonstrated that a mediational rather than moderational model better explained the relationship between behavioral functioning, barriers, and medication adherence. However, another study examining adolescents with IBD found that adolescent emotional functioning (i.e., anxiety and depression symptoms) moderated the relationship between barriers and medication adherence (Gray et al., 2012). In this study, medication adherence was significantly lower when adolescents had higher numbers of barriers and more anxiety and depression symptoms. Thus, there is a need for additional research to clarify the role of barriers to adherence in the relationship between emotional functioning and medication adherence in adolescent patients.

Based on the current literature review, several areas emerge as needing further research. First, little attention has been given to the role of caregiver emotional functioning in medication adherence in adolescent solid organ transplant literature, though the association has been indicated in studies with other pediatric patients. Second, the role of adherence barriers in the relationship between caregiver emotional functioning variables and adolescent medication adherence has not been addressed. Third, the contributions of both caregiver and adolescent emotional functioning on relationships with adherence barriers and medication adherence have yet to be examined in adolescent transplant recipients. To our knowledge, the last two points have not been addressed in the pediatric adherence literature.

The Current Study

The current study was guided by the HBM and previously reviewed research that has identified significant relationships between emotional functioning, perceived adherence barriers, and medication adherence in adolescent transplant recipients, other pediatric patient populations, and their caregivers. Thus, relationships between caregiver and adolescent emotional functioning (e.g., depression, anxiety), perceived barriers to adolescent adherence, and medication adherence were examined. Each barriers subscale of the AMBS and PMBS was examined in the initial analyses since these subscales have been separately associated with medication adherence in prior research (McCormick King et al., 2014; Reed-Knight et al., 2013; Simons et al., 2010). Consistent with previous studies examining the meditational role of barriers in the relationship between psychosocial functioning and treatment adherence in pediatric patients, each subscale of the AMBS and PMBS was used in multiple mediation analyses to examine potential indirect effects associated with all subscales.

To assess the hypothesized role of caregiver-adolescent emotional functioning (e.g., depression, anxiety) on perceived adherence barriers and treatment adherence, caregivers and adolescents were examined as a family unit in which both members' contributions to the prediction of dependent variables will be assessed. Within the family unit, caregiver and adolescent were each posited to have influential effects on the adolescents' health behaviors and outcomes. A positive association between parental and child psychological adjustment has been demonstrated in children with a variety of chronic health conditions (Drotar, 1997; Lim et al., 2008; Phipps, Long, Hudson, & Rai, 2005), supporting the likelihood that caregiver-child emotional functioning has a mutual influence on one-another's psychosocial outcomes. Additionally, parents are often collaboratively involved with helping their adolescent follow

treatment recommendations (Gilleland, Amaral, Mee, & Blount, 2012; Pai & Ostendorf, 2011). Thus, there are ample opportunities for caregiver-child interactions in completing adherence-related tasks and greater likelihood that the emotional functioning of each family unit member will affect the adolescent's adherence-related behaviors and overall level of treatment adherence. Thus far, caregivers and children have typically been examined independently rather than as a unit in the literature (Driscoll, Schatschneider, McGinnity, & Modi, 2012). To date, there have been no empirical studies testing these theorized relationships.

Based on these overarching goals, the current study aimed to address the following unanswered questions using a sample of adolescents with solid organ transplants and their caregivers: (a) how do levels of caregiver and adolescent emotional functioning compare to normative data?; (b) how does caregiver emotional functioning relate to adolescent emotional functioning, medication adherence, and perceived barriers to medication adherence?; (c) does caregiver emotional functioning predict adolescent medication adherence and perceived barriers to medication adherence above and beyond the contribution of adolescent emotional functioning?; (d) is caregiver emotional functioning indirectly related to adolescent medication adherence through perceived barriers to medication adherence?; and (e) is caregiver emotional functioning indirectly related to adolescent medication adherence through perceived barriers to medication adherence above and beyond adolescent emotional functioning?

It was hypothesized that (a) the emotional functioning of adolescent transplant recipients and their caregivers would be significantly lower than that of healthy norms; (b) adolescent and caregiver emotional functioning and barriers to adherence would be positively correlated, while these variables would be negatively correlated with medication adherence; (c) adolescent emotional functioning would predict adolescent medication adherence and barriers to adherence,

as perceived by caregivers or adolescents; (d) caregiver emotional functioning would account for significant additional variance beyond the effects of adolescent emotional functioning in the prediction of adolescent medication adherence and barriers to adherence, as perceived by caregivers or adolescents; (e) the hypothesized relationship between caregiver emotional functioning and adolescent medication adherence would be mediated by adherence barriers, as perceived by caregivers or adolescents; and (f) perceived barriers would mediate the relationship between caregiver emotional functioning and adherence when controlling for variance accounted for by adolescent emotional functioning.

CHAPTER 2

Method

Participants

All participants were recruited at their scheduled transplant follow-up appointment at Children's Healthcare of Atlanta (CHOA) at Egleston, in Atlanta, Georgia. Inclusion criteria for eligibility to participate in this study included: (a) having received a kidney, liver, or heart transplant no less than 4 months prior to enrollment; (b) being younger than 21 years of age at the time of enrollment; (c) being able to speak and read English; and (d) attending the transplant follow-up appointment with a primary caregiver if under 18 years of age for informed consent purposes. Exclusion criteria for this study included having a significant developmental or cognitive delay as noted in the medical record or per caregiver report.

A total of 54 adolescents and/or caregivers were eligible to participate in the study. Of these eligible individuals, 51 adolescents and/or caregivers consented to participate in the study and three declined to participate. Reasons for declining to participate included lack of interest in completing measures during clinic visits. Of those who consented to participate, four families withdrew from the study or left the clinic before completing the measures. Stated reasons for withdrawing or leaving the clinic before completing measures included not speaking English well enough to complete the measures, feeling overwhelmed by the length of the measures, or finishing meetings with medical providers. Additionally, eight adolescents who were 18 years or older attended their clinic visit independently and participated in the study without their caregiver. The families who withdrew or left before completing measures and the adolescents

who participated without their caregivers were not included in the current study's final sample or analyses. As a result of these omissions, the current study included 39 adolescent-caregiver dyads. A consort diagram describing recruitment is provided in Figure 1. Detailed demographic data for participants in the current study (e.g., gender, ethnicity, family income) are described in Table 1.

The average age of adolescents was 16.41 years (*SD* = 1.79) and 56.4% were male. Approximately 20.5% (*n* = 8) of adolescents received kidney transplants, 30.8% (*n* = 12) received liver transplants, and 48.7% (*n* = 19) received heart transplants. The average time since receiving the transplanted organ was 8.68 years (*SD* = 6.13; range = 5.50 months – 18.31 years). The average number of medications prescribed to the adolescent was 7.56 (SD = 3.77; range = 1 – 16). Approximately 41.0% (*n* = 16) of adolescents had private health insurance, 33.3% (*n* = 13) had Medicare/Medicaid, 23.1% (*n* = 9) had multiple types of health insurance (e.g., private and public health insurance), and 2.6% (*n* = 1) had an "other" form of health insurance.

For caregivers, the average age was 45.87 years (*SD* = 7.99) and 89.7% were female. Regarding the relationship of the caregiver to the adolescent, 87.2% (*n* = 34) were biological parents, 7.7% (*n* = 3) were legal guardians, 2.6% (*n* = 1) were step-parents, and 2.6% (*n* = 1) were grandparents.

Measures

Caregiver participants completed a brief demographic questionnaire to provide basic information about themselves and their child, such as age, gender, ethnicity, education, employment status, income, etc. A review of each adolescent's electronic medical chart was conducted to obtain information about currently prescribed medications (e.g., name, dosage frequency, and dosage amount).

Adolescent symptoms of anxiety and depression. The Behavior Assessment System of Children-2nd Edition Self-Report of Personality, Adolescent Version (BASC-2-SRP-A; Reynolds & Kamphaus, 2004) is a self-report measure of emotional and behavioral functioning for adolescents ages 12 to 21 years. For the purposes of assessing adolescent self-report of their own depression and anxiety symptoms, only items from the Anxiety and Depression subscales from the BASC-2-SRP-A were administered. Adolescents answered whether they agreed or disagreed with a given statement using "true" or "false" responses (e.g., "I worry a lot of the time") or how often they felt a certain way using Likert-style anchors ranging from "Never" to "Almost Always" (e.g., "I get nervous"). *T*-scores were used to compare respondents' answers to norms. *T*-scores ranging from 60 to 69 were considered "at-risk" and *T*-scores greater than or equal to 70 were considered "clinically significant." The current study demonstrated good internal consistency for both the Anxiety (α = .89) and Depression subscales (α = .81).

Caregiver symptoms of anxiety and depression. The Brief Symptom Inventory-18 (BSI-18; Derogatis, 2001) is an 18-item self-report measure of adults' psychiatric symptoms. Caregiver participants completed the entire BSI-18 scale (Somatization, Depression, and Anxiety subscales) but, for the purposes of this study, only the Anxiety and Depression subscales were analyzed. Caregivers responded to how often they experienced specific symptoms of distress over the past 7 days (e.g., "Feeling lonely") using a Likert-type scale ranging from "Not at all" to "Extremely often." Higher scores on each subscale indicate greater severity of symptoms. If the Global Severity Index *T*-score (i.e., the total of all three subscales) was 63 or greater, the respondent's score was considered to be in the "clinically significant" range. In the currently study, the BSI-18 demonstrated "good" internal consistency on the Depression (α = .87) and the Anxiety subscales (α = .89). The scale's validity was supported by high correlations (r = 0.91-

0.96) with the Symptom Checklist-90-Revised, on which the BSI-18 was based (Recklitis & Rodriguez, 2007).

Adolescent Medication Barriers Scale. The Adolescent Medication Barriers Scale (AMBS; Simons & Blount, 2007) is a 17-item, factor analytically-derived measure of adolescents' self-reported barriers to taking current medications as prescribed by their physician. The three factors include Disease Frustration/Adolescent Issues (RF/AI; eight items), Ingestion Issues (II; five items), and Regimen Adaptation/Cognitive Issues (RA/CI; four items). Adolescents were instructed to endorse the extent to which they agree or disagree with a particular barrier (e.g., "I am not very organized about when and how to take the medication") using a 5-point Likert scale ranging from 1 ("strongly disagree) to 5 ("strongly agree"). As evidence for the measure's construct validity, higher frequency and intensity of perceived treatment side effects was significantly associated with the AMBS total score, DF/AI score, and RA/CI score and lower parent and adolescent medication knowledge was significantly associated with greater scores on the II subscale (Simons & Blount, 2007). Additionally, nonadherent adolescents with solid organ transplants had significantly higher AMBS scores than adherent patients, supporting the measure's criterion validity (Simons & Blount, 2007).

Previous research using the AMBS demonstrated strong internal consistency for the Total Barriers score (α = .86), RA/CI subscale (α = .76 to .81), and DF/AI subscale (α = .75 to .84; McCormick King et al., 2014; Simons et al., 2010). The II subscale has shown variable internal consistency (α = .55 to .70; McCormick King et al., Simons et al., 2010). Despite lower internal consistency, the II subscale was included in the current study, given its clinical relevance and associations with negative health outcomes, such as rejection and death (Simons et al., 2010), suggesting that the II subscale is capturing important barriers with predictive validity. For the

current study, only the AMBS subscales were analyzed. In the current sample, the AMBS demonstrated good internal consistency on the RA/CI (α = .70), DF/AI (α = .81), and II subscales (α = .83).

Parent Medication Barriers Scale. The Parent Medication Barriers Scale (PMBS; Simons & Blount, 2007) is a 16-item, factor analytically-derived measure of caregivers' perceived barriers to adherence that their adolescent may experience when taking current medications as prescribed by their physician. The four factors include Disease Frustration/Adolescent Issues (DF/AI; seven items), Regimen Adaptation/Cognitive Issues (RA/CI; five items), Ingestion Issues (II; three items), and Parent Reminder (PR; one item). Previous research using the PMBS has shown that parents of nonadherent adolescents with a solid organ transplant had significantly higher scores on the PMBS, reflecting a greater number of barriers to adherence, than adherent adolescents (Simons & Blount, 2007), thus supporting the measure's criterion validity. Previous research using the PMBS has demonstrated adequate to good internal consistency for the Total Barriers score (α = .87), RA/CI subscale (α = .77 to .82), DF/AI subscale (α = .69 to .84), and II subscale (α = .66 to .69; Reed-Knight et al. 2013; Simons et al., 2010). For the current study, only the four PMBS subscales were analyzed. In the current sample, the PMBS demonstrated good internal consistency the RA/CI subscale (α = .75), and DF/AI subscale (α = .80). The II subscale demonstrated poor internal consistency (α = .58).

Medication adherence. The Medication Adherence Measure (MAM; Zelikovsky & Schast, 2008), a semi-structured interview, was used to assess adolescent and caregiver self-reports of each adolescent's level of adherence to prescribed medications (both prescription and over-the-counter) over the previous 7 days. The MAM was administered separately to adolescents and caregivers to obtain each individual's report of how many medications the

adolescent missed in the past week. A total percentage of doses of anti-rejection medications, other prescription medications, and over-the-counter medications that were missed in the past week was calculated by dividing the total number of missed doses by the total number of prescribed doses and multiplying by 100. The percentage of missed medication doses was subtracted from 100 to provide an indicator of adherence (i.e., the percentage of medications taken on time in the past week). Medications taken on an "as needed" basis were not included in calculations. Adherence rates measured with the MAM have been shown to positively correlate with adherence rates measured with electronic monitoring devices in pediatric transplant populations (Dobbels et al., 2010), which indicates good convergent validity.

Procedures

The current study is part of a larger research project. All study procedures were approved by both participating institutions' Institutional Review Boards. Before clinics began, a research assistant identified potentially eligible participants using the hospital's electronic scheduling system. The research assistant then approached families in the waiting room before their regularly scheduled transplant clinic visit to describe the study, answer questions, and invite them to participate. Adolescents and caregivers who agreed to participate in the study signed appropriate consent, assent, and Health Information Portability and Accountability Act release forms before completing any questionnaires.

Participating adolescents and caregivers completed their respective self-report measures independently, with the research assistant available to assist as needed (e.g., explaining items that were unclear). The MAM, a semi-structured interview, was administered to caregivers and adolescents before or after the regular clinic visit by a trained research assistant or staff pharmacist. Before completing the MAM, the patient's medical chart was reviewed to verify the

names, dosages, and schedules of currently prescribed medications. The MAM was completed with adolescents and caregivers separately and in different exam rooms to reduce biased responding. After completing all study materials, participating adolescents and caregivers each received a $10 gift card to a local retail store as compensation for their time.

Statistical Analyses

All statistical analyses were conducted using IBM Statistical Package for the Social Sciences, Version 20 (SPSS). Levels of adolescent and caregiver depression and anxiety symptoms in the current sample were compared to normative data using *t*-tests. Bivariate relationships between levels of adolescent emotional functioning, caregiver emotional functioning, perceived barriers to adherence, and medication adherence were analyzed using two-tailed Pearson product-moment correlations.

To examine the amount of variance accounted for by caregiver or adolescent emotional functioning on medication adherence or the barriers subscales, hierarchical regression analyses were used. If any demographic covariates emerged from bivariate or *t*-test analyses, these variables were entered in the first step of the hierarchical regression model. In the next step, one adolescent emotional functioning variable (i.e., depression or anxiety symptoms) was entered in the prediction of the barriers subscales or medication adherence. In the next step, one corresponding caregiver emotional functioning variable (i.e., depression or anxiety) was entered in the prediction of barriers or medication adherence. Thus, these analyses allowed for examination of the amount of variance accounted for by adolescents' emotional functioning alone in one step and the amount of additional variance accounted for by caregivers' emotional functioning in the next step when predicting adolescent barriers subscales or medication

adherence. If the *p*-values for the previously described hierarchical regression analyses were less than .05, the null hypothesis was rejected and the alternate hypothesis was accepted.

If the hypothesized relationships between predictor and outcome variables were found based on results of correlational and hierarchical regression analyses, parallel multiple mediation analyses were used to examine whether perceived barriers (each subscale of the AMBS or PMBS) mediated the hypothesized relationship between caregiver emotional functioning variables and medication adherence. If this model was supported for any of the caregiver emotional functioning variables of interest (i.e., depression and anxiety), multiple mediation models were run with the corresponding adolescent emotional functioning variables entered as a covariate to determine whether barriers mediated the relationship between caregiver emotional functioning and adherence after accounting for the effects of adolescent emotional functioning.

To examine the direct, indirect, and total effects of these proposed parallel multiple mediation models, the PROCESS procedures for SPSS outlined in Hayes (2013) were used. The SPSS macro for PROCESS is available online at http://www.afhayes.com/introduction-to-mediation-moderation-and-conditional-process-analysis.html. To account for potential normality assumption violations in the current sample, bootstrapping procedures were used, via the PROCESS macro, to examine 95% bias-corrected confidence intervals for the indirect effects of the proposed models based on 10,000 bootstrap samples. Bootstrapping confidence intervals do not make assumptions about the shape of the sampling distribution and thus, are considered more powerful methods for making inferences about indirect effects than normal theory approaches, such as the Sobel test (Hayes, 2013). If zero did not fall within this confidence interval, the null hypothesis was rejected and the specific indirect effect was accepted as being significantly different than zero. In all proposed parallel multiple mediation models, the perceived barriers

subscales on the AMBS or PMBS were entered as the mediating variables between caregiver emotional functioning variables and adolescent medication adherence.

Power

Sample sizes necessary to detect significant statistical effects were determined a priori. G*Power (Faul, Erdfelder, Lang, & Buchner, 2009) was used to calculate the sample size necessary to detect effects with power = .80, α = .05, and effect size = .30 when up to three predictors were entered in hierarchical regression analyses. It was determined that 36-41 participants were required to detect effects for multiple regression analyses.

For multiple mediation analyses, the sample size necessary to detect effects with power = .80, α = .05, and effect size = .30 was determined based on previous research that tested similar models with adolescent transplant recipients (McCormick King et al., 2014) and a published literature review that identified ideal sample sizes necessary for .80 power in tests of mediation (Fritz & MacKinnon, 2007). McCormick King and colleagues found evidence for full mediation with a sample size of 72 adolescents using bias-corrected bootstrap tests. Fritz & MacKinnon indicated that 118 participants are necessary to achieve similar alpha and beta path sizes to those reported in McCormick King and colleagues' study, using bias-corrected bootstrap tests. A sample size of 71 was necessary to detect medium sized alpha and beta paths (i.e., α and β = .39) with power = .80. Based on this information, between 71 and 118 participates were necessary to confidently detect effects in proposed multiple mediation analyses. Due to the actual sample size, the current study was considered underpowered for detecting statistically significant effects in mediation analyses.

CHAPTER 3

Results

Preliminary Analyses

Means, standard deviations, and ranges for all study variables are shown in Table 2. No significant differences were found on study variables based on participants' gender, race, type of transplant, or age. Preliminary bivariate correlations revealed that time since transplantation was significantly correlated with the DF/AI (r = -.33, p = .04) and II (r = -.40, p = .01) subscales of the AMBS. Adolescents with more time that had passed since their solid organ transplantation surgery reported fewer barriers associated with disease frustration or issues ingesting their medications. Therefore, time since transplantation was entered as a medical covariate in the first step of the planned regression analyses that included the DF/AI or II subscales of the AMBS. Time since transplantation was also entered as a covariate in subsequent planned mediation analyses using the AMBS subscales.

Rates of Depression and Anxiety Symptoms

Are caregiver and adolescent levels of depression or anxiety symptoms higher compared to normative data? *T*-test analyses revealed that caregivers' levels of depression were significantly lower compared to normative data (M = 46.82, SD = 8.79; $t(38)$ = -2.26, p = .03). Caregivers' levels of anxiety were also significantly lower compared to normative data (M = 43.87, SD = 9.05; $t(38)$ = -4.23, $p < .001$).

T-test analyses revealed that adolescents' levels of depression were not significantly different compared to normative data (M = 47.37, SD = 8.38; $t(37)$ = -1.94, p = .06).

Adolescents' levels of anxiety were significantly lower compared to normative data (M = 42.63, SD = 9.75; $t(37) = -4.66$, $p < .001$).

Correlational Analyses

Is caregiver emotional functioning correlated with adolescent emotional functioning? Pearson product-moment correlation analyses indicated that caregivers' symptoms of depression were not significantly correlated with adolescents' symptoms of depression (r = .01, p = .97) or anxiety (r = -.01, p = .97). Caregivers' symptoms of anxiety were not significantly correlated with adolescents' symptoms of anxiety (r = .04, p = .80) or depression (r = .11, p = .50).

Are caregiver and adolescent symptoms of depression and anxiety correlated with barriers to adherence? See Table 3 for more details on correlations between family members' emotional functioning, and barriers to adherence. Caregiver symptoms of depression were significantly and positively correlated with the RA/CI and II subscales the AMBS (RA/CI r = .35, p = .03; II r = .37, p = .02) but not with the DF/AI subscale of the AMBS (r = .27, p = .09). Caregiver symptoms of anxiety were significantly and positively correlated with the RA/CI and II subscales (RA/CI r = .35, p = .03; II r = .42, $p < .01$) but not with the DF/AI subscale (r = .25, p = .13) of the ABMS.

Caregiver symptoms of depression were significantly and positively correlated with the DF/AI subscale of the PMBS (r = .35, p = .03). No other subscales of the PMBS were significantly correlated with caregiver symptoms of depression or anxiety.

Adolescent symptoms of depression were significantly and positively correlated with the DF/AI, RA/CI, and II subscales of the AMBS (DF/AI r = .45, p = .005; RA/CI r = .49, p = .002; II r = .46, p = .004). Adolescent symptoms of anxiety were also significantly and positively

correlated with the DF/AI, RA/CI, and II subscales of the AMBS (DF/AI r = .45, p = .004; RA/CI r = .39, p = .02; II r = .54, p < .001). There were no significant correlations between adolescent symptoms of depression and anxiety and any subscales of the PMBS.

Are caregiver and adolescent symptoms of depression and anxiety correlated with medication adherence? See Table 3 for more details on correlations between family members' emotional functioning and medication adherence. Caregiver symptoms of depression were significantly and negatively correlated with caregiver-reported medication adherence (r = -.38, p = .02). Caregiver symptoms of anxiety were also significantly and negatively correlated with caregiver-reported adherence (r = -.38, p = .02). There were no significant correlations between caregiver symptoms of depression or anxiety and adolescent-reported medication adherence.

Adolescent symptoms of depression were significantly and negatively correlated with adolescent-reported medication adherence (r = -.40, p = .01). Adolescent symptoms of anxiety were also significantly and negatively correlated with adolescent-reported medication adherence (r = -.33, p = .04). There were no significant correlations between adolescent symptoms of depression or anxiety and caregiver-reported medication adherence.

Are barriers to adherence correlated with medication adherence? See Table 3 for more details on correlations between the AMBS, PMBS, and medication adherence. The DF/AI, RA/CI, and II subscales of the AMBS were significantly and negatively correlated with both caregiver- and adolescent-reported medication adherence (rs = -.33 to -.51, ps = .001 to .04). Only the RA/CI subscale of the PMBS was correlated with adolescent-reported medication adherence (r = -.36, p = .03). No other subscales of the PMBS were statistically significantly correlated with caregiver- or adolescent-report of medication adherence.

Regression Analyses

Because time since transplantation emerged as a medical covariate in preliminary analyses, it was entered in the first step of the planned hierarchical regression analyses that included the DF/AI or II subscales of the AMBS. These analyses contained three steps, with time since transplantation entered first, adolescent depression or anxiety entered second, and corresponding caregiver depression or anxiety entered third. All other regression analyses contained two steps, with adolescent depression or anxiety entered in the first step and caregiver depression or anxiety entered in the second step. Multicollinearity diagnostic procedures were conducted for all regression models. These procedures did not suggest any issues with multicollinearity for any regression models (tolerance values $\geq .20$ and VIF values ≤ 3).

Predicting Barriers to Adherence

Do caregiver and adolescent symptoms of depression predict barriers to adherence as measured with the AMBS? See Table 5 for more details on the regression models conducted for caregiver and adolescent symptoms of depression as predictors of the AMBS subscales. For the model predicting the DF/AI subscale, time since transplantation and adolescent depression accounted for 29.4% of the variance ($p < .01$). Caregiver depression added additional significant variance when entered in the final step of the model ($\Delta R^2 = .08$, $p < .05$). Time since transplantation, adolescent depression, and caregiver depression were all significant predictors of the DF/AI subscale in the overall model, which accounted for 37.5% of the variance.

For the model predicting the RA/CI subscale, adolescent depression accounted for 23.6% ($p < .001$) of the variance in the first step. In the second step, caregiver depression added significant additional variance to the model ($\Delta R^2 = .12$, $p < .05$). Caregiver and adolescent

symptoms of depression were each significant predictors and accounted for 35.8% of the variance in the overall model.

For the model predicting the II subscale, time since transplantation and adolescent depression accounted for 33.7% (p <.01) of the variance. In the final step, caregiver depression added significant additional variance to the model ($\Delta R^2 = .15$, $p < .01$). Time since transplantation, adolescent depression, and caregiver depression were each significant predictors and accounted for 48.8% of the variance in the overall model.

Do caregiver and adolescent symptoms of depression predict barriers to adherence as measured with the PMBS? For the model predicting the DF/AI subscale of the PMBS, adolescent depression did not account for any of the variance in the first step. In the second step, caregiver depression added significant additional variance to the model ($\Delta R^2 = .12$, $p < .05$). Caregiver depression was the only significant predictor in the second step of the model, ($\beta = .35$, $p < .05$), though the overall model was not statistically significant when adolescent depression was included. None of the models tested with the other three subscales of the PMBS were significant.

Do caregiver and adolescent symptoms of anxiety predict barriers to adherence as measured with the AMBS? See Table 5 for more details on the regression models conducted for caregiver and adolescent symptoms of anxiety as predictors of the AMBS subscales. For the model predicting the DF/AI subscale, time since transplantation and adolescent anxiety accounted for 26.0% (p <.01) of the variance. In the final step, caregiver anxiety did not add significant additional variance to the model. Adolescent anxiety was the only significant predictor of the DF/AI subscale in the final model, which accounted for 33.0% of the variance.

For the model predicting the RA/CI subscale, adolescent anxiety accounted for 16.0% ($p < .05$) of the variance in the first step. In the second step, caregiver symptoms of anxiety added significant additional variance to the model ($\Delta R^2 = .11$, $p < .05$). Caregiver and adolescent symptoms of anxiety were each significant predictors and accounted for 26.6% of the variance in the overall model.

For the model predicting the II subscale, time since transplantation and adolescent anxiety accounted for 36.7% ($p < .001$) of the variance. In the final step, caregiver symptoms of anxiety added significant additional variance to the model ($\Delta R^2 = .20$, $p < .001$). Time since transplantation, adolescent anxiety, and caregiver anxiety were each significant predictors and accounted for 57.2% of the variance in the overall model.

Do caregiver and adolescent symptoms of anxiety predict barriers to adherence as measured with the PMBS? Adolescent anxiety did not account for any statistically significant variance in the first step for any of the models for the three subscales of the PMBS. Caregiver anxiety did not add any significant additional variance in the second step of the PMBS models.

Predicting Medication Adherence

Do caregiver and adolescent symptoms of depression predict adolescent adherence? See Table 6 for more details on the regression models conducted for caregiver and adolescent symptoms of depression as predictors of medication adherence. For the model predicting caregiver-reported medication adherence, adolescent depression accounted for a non-statistically significant amount of the variance in the first step ($p = .51$). In the second step, caregiver depression added significant additional variance to the model ($\Delta R^2 = .14$, $p < .01$). Caregiver depression was the only significant predictor of caregiver-reported medication adherence in the

overall model ($\beta = -.37$, $p < .05$), though the overall model was not statistically significant when adolescent depression was included.

For the model predicting adolescent-reported medication adherence, adolescent depression accounted for 15.8% ($p < .05$) of the variance in the first step. In the second step, caregiver depression did not add statistically significant additional variance to the model. Adolescent depression was the only significant predictor of adolescent-reported medication adherence in the overall model, which accounted for 18.9% of the variance.

Do caregiver and adolescent symptoms of anxiety predict adolescent adherence?

See Table 6 for more details on the regression models conducted for family members' symptoms of anxiety as predictors of medication adherence. For the model predicting caregiver-reported medication adherence, adolescent anxiety accounted for a non-statistically significant amount of the variance in the first step ($p = .21$). In the second step, caregiver anxiety added significant additional variance to the model ($\Delta R^2 = .14$, $p < .01$). Caregiver anxiety was the only significant predictor of caregiver-reported medication adherence in the overall model, which accounted for 18.5% of the variance.

For the model predicting adolescent-reported medication adherence, adolescent anxiety accounted for 10.9% ($p < .05$) of the variance in the first step. In the second step, caregiver anxiety did not add statistically significant additional variance to the model. Adolescent depression was the only significant predictor of adolescent-reported medication adherence in the overall model, which accounted for 13.2% of the variance, though the overall model was not statistically significant.

Mediation Analyses

Is there an indirect relationship between caregiver symptoms of depression and adolescent medication adherence through barriers to medication adherence? Given evidence of correlational relationships between caregiver symptoms of depression, the AMBS subscales, and caregiver-reported adherence, the hypothesized indirect relationship between caregiver depression and medication adherence as mediated by barriers to adherence was tested via multiple mediation analyses. Caregiver depression was entered as the independent variable, the three subscales of the AMBS were entered as mediators, time since transplantation was entered as a covariate due to significant correlations with the DF/AI and II subscales of the AMBS, and caregiver-reported medication adherence was entered as the dependent variable (see Figure 2). The total effect of caregiver depression on medication adherence was statistically significant (B = -.3078, *SE* = .1261, $p < .05$). The effect of caregiver depression on the RA/CI and II subscales were statistically significant (RA/CI subscale B = .1214, *SE* = .0552, $p < .05$; II subscale B = .2145, *SE* = .0767, $p < .01$). The effect of caregiver depression on the DF/AI subscale approached statistical significance (B = .2137, *SE* = .1127, $p = .066$). There were no statistically significant effects of barriers subscales on medication adherence. The direct effect of caregiver depression on medication adherence became nonsignificant when barriers were included in the model (B = -.2368, *SE* = .1327, $p = .084$).

Despite the non-significant *a* and *b* paths, an analysis of the bootstrap confidence intervals indicated evidence of a small, statistically significant indirect effect for the DF/AI subscale in the relationship between caregiver depression and medication adherence, with a point estimate of -.0968 (*SE* = .0767; 95% CI -.3376 to -.0021). As discussed in Hayes (2013), it is possible to conclude that an indirect effect is statistically significant using preferable and more

powerful inferential tests, such as the bootstrapped confidence intervals used in these analyses, even in the absence of non-statistically significant *a* and/or *b* paths. See Table 7 for more details on the bootstrap confidence intervals calculated to determine the statistical significance of indirect effects. The total model accounted for 27.29% of the variance in medication adherence, $F(4, 33) = 3.0964$, $p < .05$.

The same model involving caregiver depression, barriers, and medication adherence was re-analyzed when controlling for variance accounted for by adolescent depression, in addition to time since transplantation. When controlling for adolescent depressive symptoms, the total effect of caregiver depression on medication adherence remained significant (B = -.3061, *SE* = .1286, $p < .05$). The effect of caregiver depression on the RA/CI and II subscales also remained statistically significant (RA/CI subscale B = .1234, *SE* = .0489, $p < .05$; II subscale B = .2158, *SE* = .0685, $p < .01$). The effect of caregiver depression on the DF/AI subscale continued to approach statistical significance (B = .2092, *SE* = .1036, $p = .052$). The model failed to demonstrate statistically significant effects of barriers subscales on medication adherence. The direct effect of caregiver depression on medication adherence became nonsignificant when barriers were included in the model (B = -.2375, *SE* = .1358, $p = .090$).

Although the *a* and *b* paths remained non-significant when controlling for adolescent depression, an analysis of the bootstrap confidence intervals continued to indicate evidence of a small, statistically significant indirect effect for the DF/AI subscale in the relationship between caregiver depression and medication adherence, with a point estimate of -.0950 (*SE* = .0721; 95% CI -.3157 to -.0041). The total model accounted for 27.02% of the variance in medication adherence, $F(4, 32) = 2.9617$, $p < .05$.

Because the PMBS was generally uncorrelated with caregiver or adolescent depression and medication adherence, the four PMBS subscales were not examined as mediators in the relationship between caregiver depression and medication adherence.

Is there an indirect relationship between caregiver symptoms of anxiety and adolescent medication adherence through barriers to medication adherence? Given evidence of correlational relationships between caregiver symptoms of anxiety, the AMBS subscales, and caregiver-reported adherence, the hypothesized indirect relationship between caregiver anxiety and medication adherence as mediated by barriers to adherence was tested via multiple mediation analyses. Caregiver anxiety was entered as the independent variable, the three subscales of the AMBS were entered as the mediators, time since transplantation was entered as a covariate due to significant correlations with the DF/AI and II subscales of the AMBS, and caregiver-reported medication adherence was entered as the dependent variable (see Figure 3). The total effect of caregiver anxiety on medication adherence was statistically significant (B = -.3023, *SE* = .1220, $p < .05$). The effects of caregiver anxiety on the RA/CI and II subscales were statistically significant (RA/CI subscale B = .1200, *SE* = .0540, $p < .05$; II subscale B = .2616, *SE* = .0703, $p < .001$). The effect of caregiver anxiety on the DF/AI subscale approached statistical significance (B = .2174, *SE* = .1099, $p = .056$). There were no statistically significant effects of barriers subscales on medication adherence, though the effect of the DF/AI subscale on medication adherence approached statistical significance (B = -.5016, *SE* = .2504, $p = .053$). The direct effect of caregiver anxiety on medication adherence became nonsignificant when barriers were included in the model (B = -.2572, *SE* = .1313, $p = .059$).

Despite the non-significant *a* and *b* paths, an analysis of the bootstrap confidence intervals indicated evidence of a small, statistically significant indirect effect for the DF/AI

subscale in the relationship between caregiver anxiety and medication adherence, with a point estimate of -.1090 (*SE* = .0852; 95% CI -.3749 to -.0002). Similar to evidence for indirect effects found in the depression analyses, it is possible to conclude that an indirect effect is statistically significant using bootstrapped confidence intervals, even with nonsignificant *a* and/or *b* paths (Hayes, 2013). See Table 7 for more details on the bootstrap confidence intervals calculated to determine the statistical significance of indirect effects. The total model accounted for 28.58% of the variance in medication adherence, $F(4, 33) = 3.3011$, $p < .05$.

The same model involving caregiver anxiety, barriers, and medication adherence was re-analyzed when controlling for variance accounted for by adolescent anxiety. When controlling for adolescent anxiety symptoms, the total effect of caregiver anxiety on medication adherence remained significant (B = -.3004, *SE* = .1241, $p < .05$). The effect of caregiver anxiety on the RA/CI and II subscales remained statistically significant (RA/CI subscale B = .1113, *SE* = .0511, $p < .05$; II subscale B = .2465, *SE* = .0611, $p < .001$). The effect of caregiver anxiety on the DF/AI subscale was not statistically significant (B = .1951, *SE* = .1051, $p = .072$). The model failed to demonstrate statistically significant effects of barriers subscales on medication adherence, though the effect of the DF/AI subscale on medication adherence approached statistical significance (B = -.5029, SE = .2564, $p = .059$). The direct effect of caregiver anxiety on medication adherence became nonsignificant when barriers were included in the model (B = -.2578, *SE* = .1342, $p = .06$).

Although the *a* and *b* paths remained non-significant, an analysis of the bootstrap confidence intervals continued to indicate evidence of a small, statistically significant indirect effect for the DF/AI subscale in the relationship between caregiver anxiety and medication adherence when controlling for variance accounted for by adolescent anxiety in addition to time

since transplantation, with a point estimate of -.0981 (*SE* = .0782; 95% CI -.3344 to -.0003). The total model accounted for 28.31% of the variance in medication adherence, $F(4, 32) = 3.1594$, $p < .05$.

Because the PMBS was generally uncorrelated with caregiver or adolescent anxiety and medication adherence, the four PMBS subscales were not examined as mediators in the relationship between caregiver anxiety and medication adherence.

CHAPTER 4

Discussion

The purpose of this study was to describe the emotional functioning (i.e., symptoms of depression or anxiety) of adolescents with solid organ transplants and their caregivers, determine the relationship of caregiver emotional functioning with barriers to adherence and medication adherence, and determine if an indirect relationship existed between caregiver emotional functioning and medication adherence. When examining how caregiver emotional functioning related to barriers to adherence and medication adherence, the contribution of adolescent emotional functioning was also considered. The rationale for this approach was to determine whether caregiver emotional functioning accounted for significance variance beyond the already-established effects of adolescent emotional functioning on adherence barriers and medication adherence in transplant recipients (e.g., Maikranz et al., 2007; McCormick King et al., 2014; Penkower et al., 2003). The examination of how caregiver emotional functioning factors in to these relationships is a novel addition to existing literature.

The hypothesis that caregiver and adolescent emotional functioning would be significantly correlated in expected directions with barriers to adherence and medication adherence was generally supported. Adolescent symptoms of depression and anxiety were strongly and positively correlated with all three subscales of the AMBS, which is consistent with previous research (McCormick King et al., 2014). Caregiver symptoms of depression and anxiety were positively correlated with the RA/CI and II subscales of the AMBS. The lack of

significant correlation between caregiver emotional functioning and the DF/AI subscale of the AMBS was likely due to small sample size as the correlations approached “medium” effect sizes.

With the exception of a positive, significant correlation between caregiver depression and the DF/AI subscale of the PMBS, there were no other significant correlations between caregiver or adolescent emotional functioning and any of the four subscales of the PMBS. Adolescents may be better reporters of their own adherence barriers since they are the individuals who actually take the medications and more likely to be influenced by their caregivers’ levels of emotional functioning. Caregivers may not be as aware of adolescents’ barriers to adherence and their perceptions of their adolescents’ barriers do not appear to be influenced by their own or their adolescents’ emotional functioning. Results suggest that adolescents’ report of their own barriers, rather than caregiver proxy-reports, should be more closely monitored during clinic visits. Additional assessment of both caregiver and adolescent symptoms of depression and anxiety is warranted as these symptoms appear to be related to the severity of adherence barriers.

Caregiver and adolescent emotional functioning were significantly and negatively correlated with their own respective reports of adherence, indicating that lower levels of depression and anxiety were associated with better medication adherence. These findings were consistent with previous research identifying a relationship between poorer emotional functioning of pediatric transplant recipients and lower self-reported or electronically monitored medication adherence (e.g., Maikranz et al., 2007; McCormick King et al., 2014; Penkower et al., 2003). The current study contributed to existing literature because it was the first to explicitly show a relationship between caregiver symptoms of depression or anxiety and adherence, rather than examining general stress (Gerson et al., 2004) or emotional responses to their child’s illness (Fredericks et al., 2007). Additionally, the current study’s findings suggested that members of

the family unit have differing reports of adolescents' adherence depending on their own levels of depression or anxiety. The relationship between caregiver or adolescent emotional functioning and their report of the adolescent's medication adherence does not necessarily generalize to the other family members' perception of adherence. These findings suggest the importance of obtaining both caregiver and adolescent reports of their own respective levels of emotional functioning and the adolescent's level of medication adherence.

As hypothesized, caregiver symptoms of depression and anxiety accounted for additional variance beyond the significant effects of adolescent emotional functioning in the prediction of barriers to adherence and medication adherence. Caregiver symptoms of depression accounted for significant additional variance in the prediction of the DF/AI, RA/CI, and II subscales of the AMBS, even after controlling for time since transplantation. Caregiver and adolescent symptoms of depression were each independent predictors of the AMBS subscales in all models, suggesting that both family members' levels of depression significantly influenced the number of barriers endorsed by adolescents. The same relationships were demonstrated when examining caregiver symptoms of anxiety as predictors of the AMBS subscales except in the prediction of the DF/AI subscale. Adolescent symptoms of anxiety may have a greater influence on potentially anxiety-provoking barriers on this subscale, such as how others perceive them (e.g., "I don't like what the medication does to my appearance," "I do not want other people to notice me taking the medication"). The only significant predictor of any of the PMBS subscales was caregiver depression, suggesting that, in general, neither adolescent nor caregiver emotional functioning influenced how caregivers perceived adolescents' barriers to adherence. Clinical assessment of both adolescent and caregiver symptoms of depression or anxiety may help identify patients at risk for experiencing more barriers to adherence.

Caregiver emotional functioning only predicted caregiver-reported medication adherence and adolescent emotional functioning only predicted adolescent-reported medication adherence. Although levels of caregiver- and adolescent-reported symptoms of depression and anxiety and medication adherence were similar in this sample, it is possible that there was lower agreement between raters on medication adherence. A review of adherence measures demonstrated that self-reported adherence measures had "good" caregiver-child agreement but the authors did not review the MAM, which was used in the current study (Quittner, Modi, Lemanek, Ievers-Landis, & Rapoff, 2008). To date, it does not appear that the MAM's interrater agreement has been investigated and agreement was not explicitly examined in the current study. Additionally, the presence of depressive or anxiety symptoms may have influenced raters' perceptions of adherence. The use of concurrent objective adherence measures, such as serum immunosuppressant levels or electronic monitoring, would provide less opportunity for reporter bias in adherence measurement. Further examination of caregiver-adolescent agreement on self-reported medication adherence and the use of objective adherence measures may inform the lack of predictive relationship between caregiver emotional functioning and adolescent-reported medication adherence. Based on current results, higher levels of caregiver depression and anxiety symptoms appear to predict lower medication adherence, but only when reported by caregivers.

McCormick King et al. (2014) recently found that barriers mediated the effects of adolescent depression and anxiety on medication adherence for pediatric transplant recipients. The current study extends these findings by providing tentative support for the hypothesis that the relationship between caregiver symptoms of depression or anxiety and medication adherence would be mediated by barriers to adherence. Although the *a* and *b* paths in both models were not statistically significant, the *c* paths were significantly different from zero, thus meeting the initial

criterion to suggest that the relationship between caregiver emotional functioning and medication adherence was mediated (Preacher & Hayes, 2004). An interpretation of both models' indirect effects (i.e., the product of *a* and *b*) via bootstrapped CIs further suggested full mediation through the DF/AI subscale of the AMBS (Preacher & Hayes, 2004; Hayes, 2013). Evidence for the indirect effect of the DF/AI subscale of the AMBS remained statistically significant, even when controlling for adolescent symptoms of depression or anxiety. Thus, caregiver emotional functioning appeared to have an indirect relationship with adherence through barriers, beyond the effects of adolescent emotional functioning (McCormick King et al., 2014). The lack of statistically significant *a* and *b* paths likely resulted from low power due to the current study's small sample size, which emphasizes the need to interpret results cautiously with the potential for Type 1 error to occur. With these warning in mind, however, the indirect effects were examined with bootstrap CIs, which are considered appropriate for smaller sample sizes and do not require a normally distributed data set (Hayes, 2013). The selected method of analysis should enhance relative confidence in the interpretation of the current study's results.

Results of the bootstrapped CIs were in the predicted directions (Preacher & Hayes, 2004), indicating that higher levels of caregiver depression or anxiety may lead adolescents to experience more barriers related to this subscale, which in turn, may result in lower medication adherence. It is possible that caregiver symptoms of anxiety and depression led to similar symptoms of negative affect (i.e., sadness, hopelessness, nervousness, fear of social evaluation) in adolescents that manifested as barriers to adherence on the DF/AI subscale of the AMBS. The DF/AI subscale of the AMBS contains barriers related to adolescents' feelings of hopelessness (e.g., "I am tired of living with a medical condition;" "I am tired of taking medications") and anxiety about their medication regimen (e.g., "I do not want other people to notice me taking the

medicine;" "I don't like what the medication does to my appearance"). Barriers related to negative affect may be exacerbated if caregivers are experiencing increased levels of depression or anxiety. Although these analyses require replication with larger samples, results suggest that intervention to reduce caregiver symptoms of depression or anxiety may help reduce adolescent barriers to adherence and, in turn, improve overall medication adherence.

The hypothesis that caregivers and adolescents would have significantly more symptoms of depression and anxiety compared to normative samples was not supported. Both caregivers and adolescent participants endorsed significantly fewer symptoms of depression and anxiety compared to norms. Adolescent findings were in contrast to a previous study of adolescent kidney transplant recipients who demonstrated significantly higher levels of behavioral and emotional problems than healthy controls (Berney-Martinet et al., 2009) but were generally consistent with findings from other studies of adolescent solid organ transplant recipients (Maikranz et al., 2007; McCormick King et al., 2014). Adolescents in the current sample were, on average, older, and had longer times since transplantation than in previous studies, which may have resulted in a sample with better emotional adjustment compared to younger and more recently transplanted patients (Berney-Martinet et al., 2009) Caregiver findings are consistent with a previous study, which found that parents of solid organ transplant recipients reported elevated levels of posttraumatic stress symptoms but no elevations for depression or anxiety symptoms (Young et al., 2003). Given the equivocal findings for adolescents and limited data for caregivers, further research is needed to determine the psychological profile of adolescent solid organ transplant recipients and their caregivers.

Contrary to our hypothesis, there was no significant correlation between caregiver and adolescent symptoms of depression and anxiety. This hypothesized relationship between

caregiver and adolescent emotional functioning was based on prior literature in other disease groups that suggested mutual influences or caregiver-child emotional functioning on one-another's psychosocial outcomes (e.g., Drotar, 1997; Lim et al., 2008; Phipps et al., 2005). The current study was the first to examine the potentially mutual relationship between caregiver and adolescent emotional functioning in solid organ transplant recipients and, as such, previous findings from other disease groups may not have generalized to the current sample. The relationship between caregiver and adolescent symptoms of depression or anxiety may be moderated by other variables. The caregiver-adolescent correlation between symptoms of depression and anxiety may be stronger, for example, when there is conflict within the family (Drotar, 1997). Given evidence of the mutual contributions of caregiver and adolescent emotional functioning to having increased adherence barriers and poorer medication adherence, adolescents may be at risk for poorer outcomes when the moderating variable between caregiver-adolescent emotional functioning is present. Future research should examine potential moderators in the relationship between caregiver-adolescent emotional functioning.

Despite being the first study to demonstrate that caregiver emotional functioning contributed significant variance beyond adolescent emotional functioning in the prediction of medication adherence as well as evidence for an indirect effect of adherence barriers within this relationship, the current study was not without limitations. First, the current study's sample size was smaller than expected and, therefore, was considered under-powered for conducting multiple mediation analyses. Second, the current sample had an overrepresentation of heart transplant recipients, older adolescents, and female caregivers. Although none of these variables emerged as significant covariates in preliminary analyses, findings may not generalize to other samples with more variety of transplant type, patient age, or caregiver gender. Future studies should

attempt to recruit more family units to adequately power all analyses and conduct multisite data collection to recruit a larger sample size and diversify the sample's demographic composition.

Although this study demonstrated that caregiver emotional functioning related to adolescent adherence, analyses were conducted at a "family unit" rather than dyadic level. It was not possible to conduct true dyadic analyses (Kenny, Kashy, & Cook, 2006) since only perceptions of the adolescents' barriers and medication adherence were obtained. Future research should examine caregivers' own barriers to helping their adolescent adhere as well as their own adherence to the regimen if they are still involved in helping their child take medications. Obtaining these data would allow for analysis of how each dyad member's emotional functioning potentially affects the other dyad members' adherence barriers or medication adherence. Lastly, adherence measures were only obtained via self-report with no objective measures, such as serum immunosuppressant levels. Because self-reported adherence has been shown to overestimate adherence compared to electronic monitoring methods (Quittner et al., 2008), future studies should obtain serum immunosuppressant or electronic monitoring data to use as concurrent measures of medication adherence.

Despite these limitations, results of the current study contributed new information that had not previously been reported in pediatric solid organ transplant literature. Caregiver symptoms of depression and anxiety appeared to play a role in predicting adolescents' barriers to adherence and actual medication adherence in hypothesized directions (i.e., more caregiver symptoms of depression and anxiety predicted more adolescent barriers to adherence and lower medication adherence). Preliminary evidence suggested that barriers on the DF/AI subscale of the AMBS, which related to feelings of hopelessness and anxiety about taking medications and having a chronic health condition, mediated the relationship between caregiver emotional

functioning and medication adherence. Results suggested that caregiver emotional functioning is an important variable to consider when assessing adolescent transplant recipients' barriers to adherence and level of medication adherence. Cognitive behavioral intervention to reduce caregivers' symptoms of depression and anxiety may, by proxy, help reduce adolescents' barriers to adherence and improve their overall medication adherence and related health outcomes. Addressing factors related to medication nonadherence on a family level may prove to be a more effective method to enhance adherence and health outcomes for adolescent patients with solid organ transplants.

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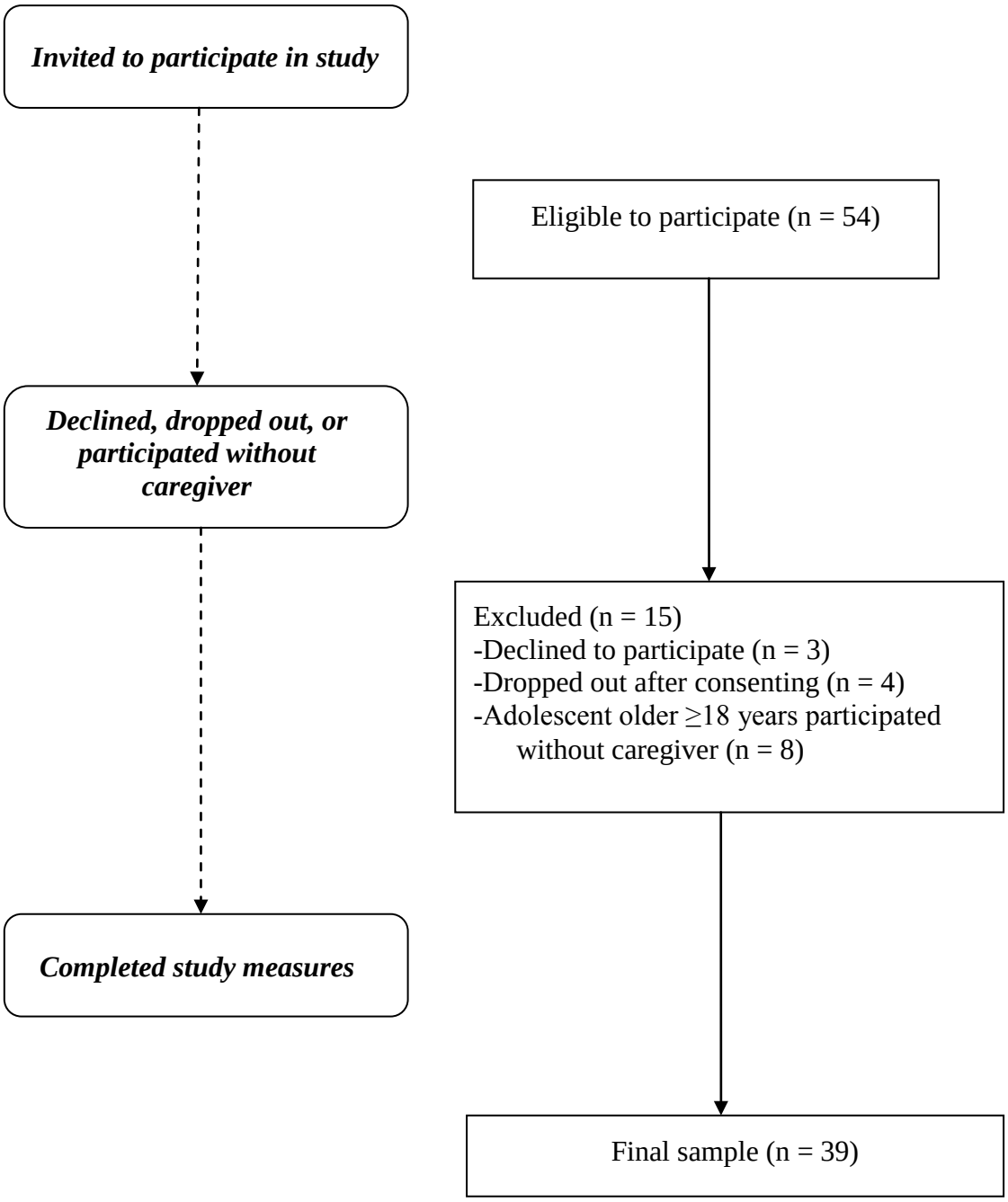

Figure 1. Enrollment and flow of participation for adolescents and caregivers approached for the current study.

Table 1. *Demographic Information*

	Adolescents		Caregivers	
	N = 39		*N* = 39	
Factor	*M*	*SD*	*M*	*SD*
Age (years)	16.41	1.79	45.87	7.99
	Frequency	%	Frequency	%
Sex				
Male	22	56.4	4	10.3
Female	17	43.6	35	89.7
Ethnicity				
Caucasian	23	59.0	23	59.0
African American	11	28.2	10	25.6
Asian-East Indian	3	7.7	3	7.7
Hispanic	0	0	1	2.6
Multiracial	2	5.1	2	5.1
Family income				
Less than $10,000	--	--	2	5.1
$10,000-24,999	--	--	3	7.7
$25,000-49,999	--	--	12	30.8
$50,000-74,999	--	--	5	12.8
$75,000-99,999	--	--	6	15.4
$100,000+	--	--	9	23.1
Prefer not to report	--	--	2	5.1
Caregiver marital status	--	--		
Married	--	--	25	64.1
Single	--	--	6	15.4
Divorced	--	--	7	17.9
Partnered	--	--	1	2.6

Note. Discrepancies in the frequency and percentage of identified ethnicity for adolescents and caregivers resulted from two adolescent-caregiver dyads that identified as different ethnicities.

Table 2. *Descriptive information for study variables*

Measure	*M*	*SD*	Range
Barriers to adherence			
AMBS[a]			
Disease frustration/adolescent issues	19.41	6.57	8 – 35
Regimen adaptation/cognitive issues	8.15	3.05	4 – 16
Ingestion issues	10.69	4.79	5 – 22
PMBS[b]			
Disease frustration/adolescent issues	13.31	5.16	7 – 24
Regimen adaptation/cognitive issues	8.92	3.69	5 – 17
Ingestion issues	4.77	2.19	3 – 11
Parent reminder	2.08	1.18	1 – 5
Emotional functioning[c]			
Caregiver depression (*T*-score)	46.82	8.79	41 – 70
Caregiver anxiety (*T*-score)	43.87	9.05	39 - 72
Adolescent depression (*T*-score)	47.37	8.38	40 – 66
Adolescent anxiety (*T*-score)	42.63	9.75	30 – 64
Medication adherence[d]			
Caregiver-reported adherence	97.33%	7.23	70 – 100%
Adolescent-reported adherence	96.55%	9.19	56.19 – 100%

[a]AMBS = Adolescent Medication Barriers Scale; [b]PMBS = Parent Medication Barriers Scale; [c]Caregiver depression and anxiety = Brief Symptom Inventory-18, Adolescent depression and anxiety = Behavior Assessment System for Children-2nd Edition-Adolescent version; [d]Medication adherence = Medication Adherence Measure.

Table 3. *Correlations between caregiver and adolescent depression and anxiety symptoms and barriers to adherence*

Variables	5	6	7	8	9	10	11
Caregiver emotional functioning[a]							
1. Depression	.27	.35*	.37*	.35*	.10	.29	.01
2. Anxiety	.25	.35*	.42**	.11	.10	.00	.20
Adolescent emotional functioning[b]							
3. Depression	.45**	.49***	.46**	-.01	-.03	.04	.08
4. Anxiety	.45**	.39**	.54***	.24	.12	.30	.21
Adolescent-reported barriers[c]							
5. Disease frustration/adolescent issues	--	.64***	.71***	.26	.12	.15	.13
6. Regimen adaptation/cognitive issues	--	--	.60***	.15	.33*	.05	.14
7. Ingestion issues	--	--	--	.22	-.03	.21	.06
Caregiver-reported barriers[d]							
8. Disease frustration/adolescent issues	--	--	--	--	.38*	.48**	.17
9. Regimen adaptation/cognitive issues	--	--	--	--	--	-.06	.43**
10. Ingestion issues	--	--	--	--	--	--	-.05
11. Parent reminder	--	--	--	--	--	--	--

[a]Brief Symptom Inventory-18; [b]Behavior Assessment Scale for Children-2nd Edition-Self-Report of Personality; [c]Adolescent Medication Barriers Scale; [d]Parent Medication Barriers Scale.

*p < .05; ** p < .01; ***p < .001

Table 4. *Correlations between caregiver and adolescent emotional functioning, barriers to adherence, and medication adherence*

Variables	12	13
Caregiver emotional functioning[a]		
1. Depression	-.38*	-.20
2. Anxiety	-.38*	-.16
Adolescent emotional functioning[b]		
3. Depression	-.12	-.40*
4. Anxiety	-.21	-.33*
Adolescent-reported barriers[c]		
5. Disease frustration/adolescent issues	-.45**	-.43**
6. Regimen adaptation/cognitive issues	-.32*	-.51**
7. Ingestion issues	-.34*	-.38*
Caregiver-reported barriers[d]		
8. Disease frustration/adolescent issues	-.27	-.17
9. Regimen adaptation/cognitive issues	-.28	-.36*
10. Ingestion issues	-.15	-.09
11. Parent reminder	-.11	-.04
Caregiver-reported adherence[e]		
12. Missed medications	--	.78***
Adolescent-reported adherence[e]		
13. Missed medications	--	--

[a] Brief Symptom Inventory-18; [b] Behavior Assessment System for Children-Self Report of Personality; [c]Adolescent Medication Barriers Scale; [d]Parent Medication Barriers Scale; [e] Medication Adherence Measure.

*p < .05; ** p < .01; ***p < .001

Table 5. *Caregiver and adolescent depression and anxiety symptoms as predictors of the AMBS subscales*

		Independent variables	B[d]	SEB[e]	β[f]	R^2	$R^2\Delta$	*F*
Disease frustration/ adolescent issues (DF/AI)	Depression	Step 1:						
		Time since transplantation	-.001	< .001	-.33*	.114		4.63*
		Step 2:						
		Time since transplantation	-.001	< .001	-.30*			
		Adolescent depression	.37	.12	.45**	.294	.18**	7.29**
		Step 3:						
		Time since transplantation	-.001	< .001	-.32*			
		Adolescent depression	.33	.11	.42**			
		Caregiver depression	.21	.10	.29*	.375	.08*	6.80**
	Anxiety	Step 1:						
		Time since transplantation	-.001	< .001	-.34*	.114		4.63*
		Step 2:						
		Time since transplantation	-.001	< .001	-.24			
		Adolescent anxiety	.27	.10	.39*	.260	.15*	6.13**
		Step 3:						
		Time since transplantation	-.001	< .001	-.29			
		Adolescent anxiety	.25	.10	.37*			
		Caregiver anxiety	.20	.10	.27	.330	.07	5.59**
Regimen adaptation/cognitive issues (RA/CI)	Depression	Step 1:						
		Adolescent depression	.18	.05	.49**	.236		11.14**
		Step 2:						
		Adolescent depression	.18	.05	.48**			
		Caregiver depression	.12	.05	.35*	.358	.12*	9.78***
	Anxiety	Step 1:						
		Adolescent anxiety	.13	.05	.39*	.16		6.59*
		Step 2:						
		Adolescent anxiety	.12	.05	.38*			
		Caregiver anxiety	.11	.05	.33*	.266	.11*	6.35**
Ingestion issues (II)	Depression	Step 1:						
		Time since transplantation	-.001	< .001	-.40*	.158		6.74*
		Step 2:						
		Time since transplantation	-.001	< .001	-.36*			
		Adolescent depression	.25	.08	.43**	.337	.18**	8.89**
		Step 3:						
		Time since transplantation	-.001	< .001	-.39**			
		Adolescent depression	.24	.07	.42**			
		Caregiver depression	.21	.07	.39**	.488	.15**	10.82***
	Anxiety	Step 1:						
		Time since transplantation	-.001	< .001	-.40*	.158		6.74*
		Step 2:						
		Time since transplantation	-.001	< .001	-.28			
		Adolescent anxiety	.24	.07	.47**	.367	.21**	10.15***
		Step 3:						
		Time since transplantation	-.001	< .001	-.36**			
		Adolescent anxiety	.22	.06	.43**			
		Caregiver anxiety[c]	.24	.06	.46***	.572	.20***	15.12***

*p < .05; **p <.01; ***p <.001

Table 6. *Caregiver and adolescent depression and anxiety symptoms as predictors of medication adherence*

		B[d]	SEB[e]	β[f]	R^2	$R^2\Delta$	*F*
	Caregiver-reported adherence[a]						
Depression	Step 1:						
	Adolescent depression[b]	-.10	.15	-.11	.013		.45
	Step 2:						
	Adolescent depression[b]	-.10	.14	-.12			
	Caregiver depression[c]	-.31	.13	-.37*	.153	.14*	3.07
Anxiety	Step 1:						
	Adolescent anxiety[b]	-.16	.13	-.21	.05		1.66
	Step 2:						
	Adolescent anxiety[b]	-.16	.12	-.20			
	Caregiver anxiety[c]	-.30	.12	.37*	.185	.14*	3.86*
	Adolescent-reported adherence[a]						
Depression	Step 1:						
	Adolescent depression[b]	-.45	.18	-.40*	.158		6.55*
	Step 2:						
	Adolescent depression[b]	-.45	.18	-.39*			
	Caregiver depression[c]	-.19	.16	-.18	.189	.03	3.97*
Anxiety	Step 1:						
	Adolescent anxiety[b]	-.31	.15	-.33*	.109		4.29*
	Step 2:						
	Adolescent anxiety[b]	-.31	.15	-.33*			
	Caregiver anxiety[c]	-.15	.16	-.15	.132	.02	2.58

[a] Medication Adherence Measure; [b] Behavior Assessment System for Children-Self Report of Personality; [c] Brief Symptom Inventory-18; [d] B = unstandardized coefficients. [e] SEB = standard error of unstandardized coefficients. [f] β = standardized coefficients.

*p < .05; **p <.01; ***p <.001

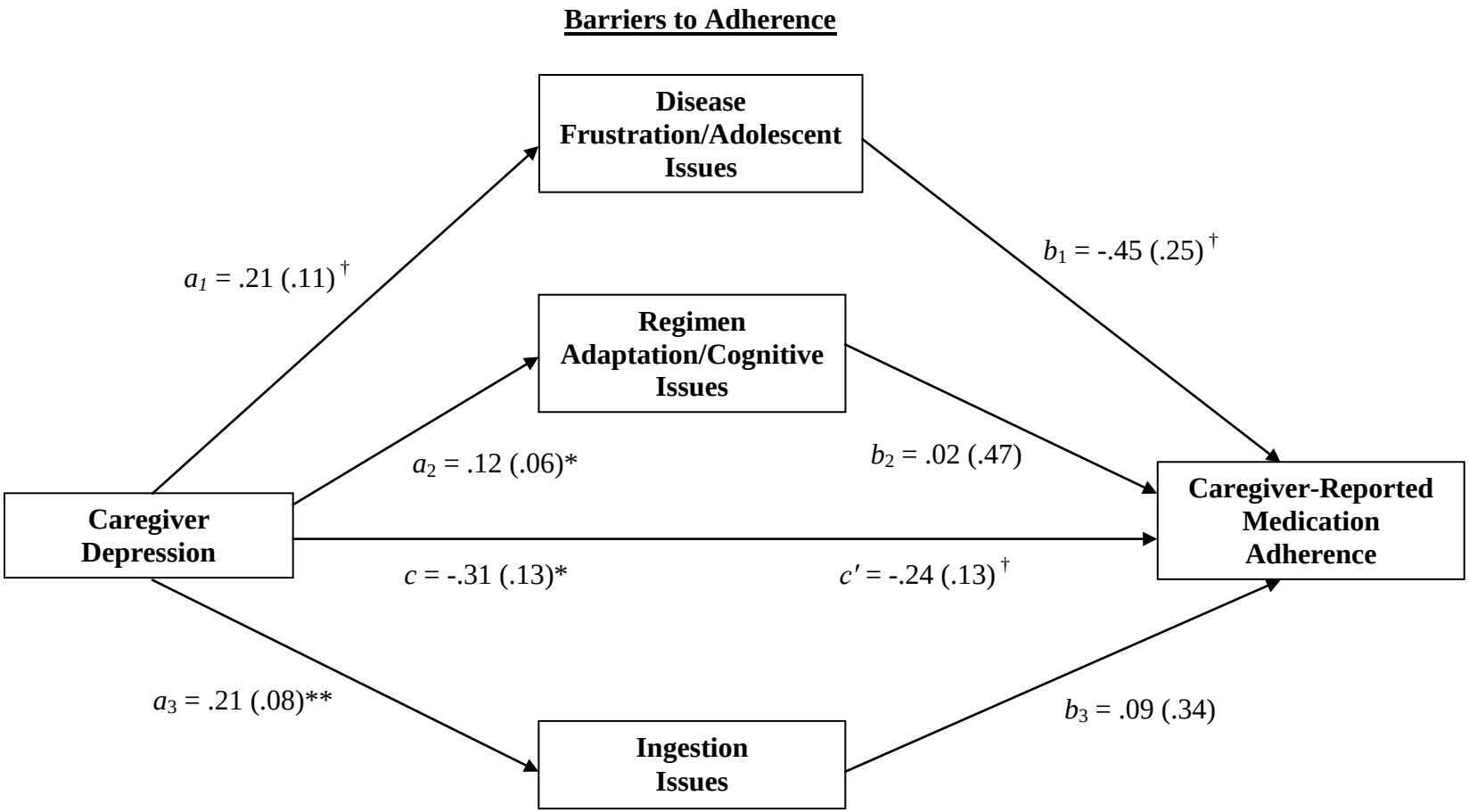

Figure 2. Mediation model of the indirect relationship between caregiver depression symptoms and medication adherence through barriers to adherence.

Note. Unstandardized regression coefficients with standard errors in parentheses are provided for each path. Caregiver depression was measured with the Brief Symptom Inventory-18. Barriers to adherence were measured with the Adolescent Medication Barriers Scale. †$p < .10$, *$p < .05$, **$p < .01$.

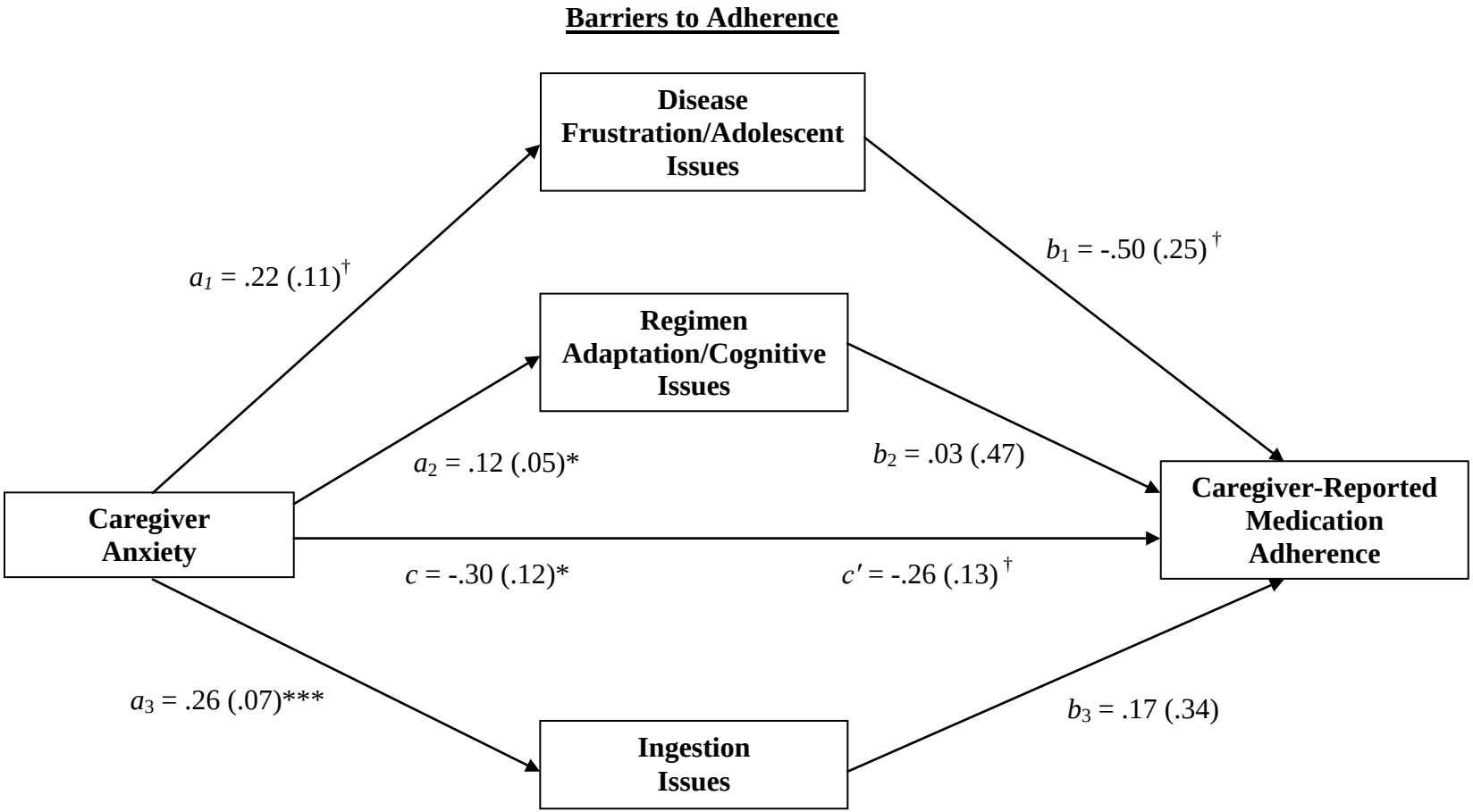

Figure 3. Mediation model of the indirect relationship between caregiver anxiety symptoms and medication adherence through barriers to adherence.

Note. Unstandardized regression coefficients with standard errors in parentheses are provided for each path. Caregiver anxiety was measured with the Brief Symptom Inventory-18. Barriers to adherence were measured with the Adolescent Medication Barriers Scale. †$p < .10$, *$p < .05$, **$p < .01$.

Table 7. *Indirect effects of caregiver symptoms of depression or anxiety on medication adherence*

				Bootstrapping BC 95% CI	
	AMBS subscales	Point estimate	SE	Lower	Upper
		Indirect effects			
Depression	DF/AI subscale	-.0968	.0767	-.3376	-.0021
	RA/CI subscale	.0021	.0735	-.1759	.1293
	II subscale	.0183	.0700	-.1084	.1784
	Total	-.0763	.1138	-.4086	.0755
Anxiety	DF/AI subscale	-.1090	.0852	-.3749	-.0002
	RA/CI subscale	.0034	.0685	-.1495	.1358
	II subscale	.0455	.0815	-.0695	.2913
	Total	-.0601	.1042	-.3225	.0992

Note. AMBS subscales: DF/AI = Disease frustration/adolescent issues, RA/CI = Regimen adaptation/cognitive issues, II = Ingestion issues; BC 95% CI = Bias corrected 95% confidence interval.