2020

Cognitive Factors And Treatment Adherence In Individuals With Cystic Fibrosis

Benjamin Edwin Burgess
University of Alabama at Birmingham

COGNITIVE FACTORS AND TREATMENT ADHERENCE IN INDIVIDUALS WITH CYSTIC FIBROSIS

by

BENJAMIN EDWIN BURGESS

SYLVIE MRUG, COMMITTEE CHAIR
EDWIN W. COOK
SIGRID LADORES
KEVIN J. LEON
ZINA TROST

A DISSERTATION

Submitted to the graduate faculty of The University of Alabama at Birmingham
in partial fulfillment of the requirements of the degree of
Doctor of Philosophy

BIRMINGHAM, ALABAMA

2020

COGNITIVE FACTORS AND TREATMENT ADHERENCE IN INDIVIDUALS WITH CYSTIC FIBROSIS

BENJAMIN EDWIN BURGESS
LIFESPAN DEVELOPMENTAL PSYCHOLOGY PROGRAM

ABSTRACT

Cystic fibrosis (CF) is a life-threatening chronic illness which requires adherence to a many complex and time-consuming treatments. Adherence is suboptimal in this population. Thus, it is important to consider predictors of treatment adherence. Research has evaluated a number of cognitive factors that are related to adherence in groups with chronic illnesses, including those with CF. The present study considers three factors (health locus of control (HLC), perceived social support, and perceived disease severity) in order to address important gaps in the literature evaluating their relationships with treatment adherence. For each of these factors, the current research is limited by the use of mostly cross-sectional designs. The current study extended these literatures by using a longitudinal design to evaluate the relationships between these factors and treatment adherence both concurrently and over time.

The first manuscript evaluated the relationship between HLC dimensions (Internal, Powerful Others, and Chance) and adherence to common treatments for CF both concurrently and over a 3-month period. This manuscript addressed inconsistencies in the literature by evaluating the effects of HLC on adherence with perceived disease severity as a moderator. The results of the first manuscript indicated that perceived severity interacted with Internal and Chance HLC to predict concurrent adherence to some treatments.

The second manuscript evaluated the concurrent and longitudinal relationships between three sources of perceived social support (family, friends, and significant other)

and treatment adherence directly and indirectly with depressive symptoms as a mediator. Previous research in this area has largely evaluated the effect of social support derived from family on adherence in children and adolescents. Contrary to the hypotheses, greater social support from all sources was related to lower adherence in some treatment domains (corticosteroid, diabetes, and nutritional adherence) over time. Further, the results of this study did not support an indirect effect of social support on adherence through depressive symptoms.

The third manuscript evaluated direct linear and quadratic effects of perceived and clinically measured severity on treatment adherence concurrently and over a 3-month period. The direction of linear relationships observed between each severity measure and adherence were not consistent in the present study, nor were the relationships between severity and adherence consistent with the results of other studies. However, perceived severity was quadratically related to adherence to corticosteroids in the present study. Further, percentage predicted forced expiratory volume in one second ($\%FEV_1$; a clinical measure of pulmonary exacerbation) was quadratically related to nutritional recommendations and diabetes treatments. For these associations, greater adherence was observed at low and high levels of severity.

Clinicians who care for individuals with CF should consider different cognitive factors that may be related to treatment adherence when trying to encourage adherence. Specifically, they may benefit from understanding the potential relationships between HLC, perceived disease severity, and adherence. Further, clinicians can work with patients to identify and address potential barriers to adherence (including number of people in the household, social engagement, etc.) using cooperative strategies. Mental

health services should also be made available to individuals receiving care for CF in order to address psychosocial adjustment and depression-related non-adherence.

Future studies should continue to evaluate the relationships between treatment adherence and the cognitive factors addressed in the current study (HLC, depressive symptoms, and perceptions of social support and disease severity) using more robust measures of adherence. Additionally, future studies should evaluate these relationships in larger, more representative samples.

Keywords: cystic fibrosis, treatment adherence, health locus of control, social support, disease severity, depression

ACKNOWLEDGEMENTS

I cannot overemphasize the importance of having great mentors when working on a project of this size. Thankfully, Dr. Sylvie Mrug is one of the greatest mentors out there. With her help at every step of the process, I have been able to produce a document whose length is exceeded only by the appreciation I have for her guidance. Moreover, nearly every success I have had while attending UAB can be traced back to her mentorship. Thank you, Sylvie. Additionally, I can't fail to mention Dr. Kevin Leon, whose passion for taking care of the CF community was apparent from the first day I met with him, nearly five years ago. Thank you, Dr. Leon, for inspiring me to support the efforts of doctors and clinicians like you through this research.

My list of social supports is too long to reproduce here, but there are a few who have provided much needed instrumental and emotional support these last two years. Marguerite Devereux has served as an object lesson in the importance of pursuing a fulfilling vocation, Bria Gresham has acted as a seemingly bottomless well of motivation, Pedram Rastegar has been a deterrent to any doubts which would have hindered my success, and both James Kizziah and Nikki Kocher have put a roof over my head for half of the time I have spent in Birmingham. Thank you all for helping me get to this point.

Praise the sun.

TABLES OF CONTENT

Page

LIST OF TABLES

LIST OF FIGURES

Figure *Page*

INTRODUCTION

Cystic fibrosis (CF) is a life-threatening recessive genetic disorder that affects 1 in every 2500-3500 births among Caucasians in the United States (Walters & Mehta, 2007). The most characteristic complications of the illness include impaired pulmonary and gastrointestinal function, as well as infertility in most males (O'Sullivan & Freeman, 2009; Xu et al., 2007). Bacterial infections result from the production and build-up of abnormally viscous mucus in the airways, pancreatic ducts, and biliary systems (Bilton, 2008; O'Sullivan & Freeman, 2009). Additionally, low body mass index (BMI) often results due to complications in gastrointestinal and pancreas function hindering nutritional absorption in individuals with CF (O'Sullivan & Freeman, 2009).

Common Treatments for CF

To combat these symptoms and slow disease progression, individuals with CF must complete daily regimens of complex and time-consuming treatment. For instance, airway clearance techniques (ACT) are a set of treatments used across most individuals with CF to maintain pulmonary health by slowing pulmonary decline. Daily ACT, such as chest physical therapy (CPT), aim to loosen mucus from airway walls so that it may be expelled through coughing or huffing. This process is often accomplished through the use of a high-frequency chest wall oscillation (i.e., the Vest) which allows for multi-tasking and greater autonomy (Yankaskas, Marshall, Sufian, Simon, & Rodman, 2004). During ACT, bronchodilators are used to relax the muscles lining the airway, allowing the

airway to dilate. Mucolytics, such as dornase alfa, are administered through a nebulizer to help loosen mucus so that it can be expelled. After ACT, and while the airways and lungs are relatively clear of mucus, inhaled antibiotics such as aztreonam and tobramycin are used to treat bacterial infections of the lungs. Antibiotics are also administered intravenously as needed to combat infection during CF exacerbations. In cases of lung failure, bilateral lung transplant is often performed. Short-term anti-inflammatory therapies, such as corticosteroids and inhaled steroids, are also administered when bronchodilators alone do not alleviate chronic airway inflammation.

Nutritional health is supported through the use of pancreatic enzyme replacement therapy (PERT), vitamin supplements, and high calorie and high fat diet, and exercise is recommended to improve muscle mass and pulmonary health. Individuals with CF are advised to have increased energy intake (120% compared to healthy individuals of the same age), with 35-40% of calories coming from fat consumption (Borowitz, Baker, & Stallings, 2002; Sinaasappel et al., 2002). It is standard practice to include a registered dietician on patients' clinical care teams to ensure adequate nutritional guidance and intervention. In childhood and adolescence especially, growth is monitored closely, and therapies are adjusted according to patient growth to ensure optimal health into adulthood (Borowitz et al., 2002). For instance, pancreatic enzyme replacements are taken multiple times a day when patients eat meals and snacks and are adjusted based on care recommendations and their effectiveness from patient to patient (Stallings et al., 2008). These exogenous enzymes are designed to replace those that are produced by the pancreas but cannot reach patients' intestines due to mucus buildup (Kopito, Shwachman, Vawter, & Edlow, 1976; Sturgess, 1984). A majority of individuals with CF are classified

as pancreatic insufficient, with 86.5% reported as taking PERT in 2016 (Couper et al., 1992; Cystic Fibrosis Foundation, 2017). Vitamin supplementation is also recommended due to the risk of malabsorption-related vitamin insufficiency.

Treatments that directly address dysfunction in the cystic fibrosis transmembrane regulator (CFTR) have been developed in the last few years, and currently include ivacaftor (Kalydeco®), lumacaftor/ivacaftor (Orkambi ®), elexacaftor/tezacaftor/ivacaftor and ivacaftor (Trikafta), ivacafter (Symdeko), and tezacaftor/ivacaftor (Accurso et al., 2010; Taylor-Cousar et al., 2017; Van Goor et al., 2011; Wainwright et al., 2015). These drugs are taken orally each day by individuals who have specific gene mutations for which a given drug has been developed.

Before these treatments were developed, individuals with CF would not normally live beyond infancy (Andersen, 1938). However, with new treatments and early diagnosis through newborn screening panels, life expectancy has increased in the CF population. According to the 2017 Cystic Fibrosis Foundation (CFF) patient registry annual report, the median age for patients has increased from 15 years to 19 years between 2001 and 2016. Likewise, the predicted median survival age has increased from 34 years in 2001 to almost 48 years in 2016 (CFF, 2017). However, this improved life expectancy has led to the development of tertiary complications (e.g., low bone mineral density, CF-related diabetes complications, and liver disease) which require additional treatments (Jones & Helm, 2009).

Treatment Efficacy

Clinical studies have evaluated the efficacy of the most common treatments to improve health in individuals with CF. For instance, mucolytics such as dornase alfa have

been shown to improve lung function, decrease rate of exacerbations, improve survival rates in patients with late-stage CF lung disease, and improve pulmonary inflammation (Konstan & Ratjen, 2012). Efficacy for oral antibiotics such as azithromycin has been established for improved forced expiratory volume in one second (FEV_1) (Southern & Barker, 2004). Likewise, research indicates that inhaled antibiotics, such as tobramycin, are effective at improving FEV_1 and decreasing rates of pulmonary exacerbations (Ryan, Singh, & Dwan, 2011). A review of CPT use, a cornerstone of treatment for pulmonary health in individuals with CF, indicates that this treatment is effective in promoting sputum expectoration and slowing decline in FEV_1 when performed in combination with regular exercise (Thomas, Cook, & Brooks, 1995). The specific type of CPT appears to have little or no effect on these benefits. As a method of improving airway clearance, exercise is best used in combination with CPT. However, reviews of the health benefits of exercise in individuals with CF also show evidence for increased cardiovascular fitness, pulmonary function, strength, and quality of life (Bradley & Moran, 2008; Radtke, Nolan, Hebestreit, & Kriemler, 2015). A review of pancreatic enzyme use in individuals with CF suggests that enzyme use leads to improved energy and improved weight gain and maintenance within normal ranges for height and age, which is associated with better health in adults and children (Stallings et al., 2008). Finally, CFTR modulators, such as ivacaftor and lumacaftor/ivacaftor, improve important aspects of health when appropriately used, including less decline in FEV_1, decreased rates of pulmonary exacerbations, and improved weight maintenance (Guimbellot et al., 2019; Wainwright et al., 2015).

Given this evidence for the efficacy of CF treatments, greater adherence would be expected to lead to better health and well-being. Evidence from a meta-analysis suggests that greater treatment adherence is generally associated with better health outcomes, with stronger associations seen in patients with chronic illness (DiMatteo, Giordani, Lepper, & Croghan, 2002). For individuals with CF, specifically, some evidence suggests that treatment adherence is associated with better health or lower disease severity. In one cross-sectional study, medical staff ratings of dietary compliance and parent-reported compliance with antibiotic and enzyme medications were correlated with Shwachman and Brasfield indices (clinical measures of severity which include evaluations of physical fitness, pulmonary healthy, and nutritional status) of illness severity (Eddy et al., 1998). In a longitudinal study of family correlates of pulmonary health in children with CF, baseline parent-reported compliance rates for daily CPT predicted more favorable FEV_1 trends over the following years (Patterson, Goetz, Budd, & Warwick, 1993). Eakin and colleagues (2011) sought to test if adherence to pulmonary medication predicts patient health in individuals with CF by measuring adherence using a medication possession ratio (MPR; calculated as the sum of number of days a medication was received, as reported in pharmacy records, divided by number of days the medication was prescribed for). They found that lower composite MPR scores, retrospectively measured over a 12-month period, predicted whether patients had at least one pulmonary exacerbation, and that higher MPR scores were associated with higher baseline FEV_1. However, MPR scores did not predict the number of pulmonary exacerbations experienced by patients or decline in FEV_1 over the 12-month period. In a study of adherence to tobramycin, an inhaled antibiotic used to fight bacterial infections in patients' lungs, lower adherence to

prescribed tobramycin inhalation solution predicted greater likelihood of hospitalization (Briesacher et al., 2011). In a retrospective study of MPR scores for dornase alfa, adherence was not associated with the number of respiratory exacerbations, but lower MPR scores predicted longer lengths of stay in the hospital (Nasr, Chou, Villa, Chang, & Broder, 2013). In contrast, another study found no association between adherence to dornase alfa and changes in FEV_1 at 3-year follow-up (Burrows, Bunting, Masel, & Bell, 2002). In a study of parental depression and child adherence to enzyme therapy, higher adherence (greater than 50%) to pancreatic enzymes over a three-month period was associated with weight gain at patients' next clinic visit, whereas lower adherence (less than 33%) was associated with weight loss (Barker & Quittner, 2016).

Eakin and colleagues (2011) suggested that the question of treatment efficacy and whether treatment adherence improves health may be best answered by considering the collective influence of multiple treatments on health. They suggest that clinical trials should evaluate the cumulative effects of different treatments on health and that a composite measure of adherence would more comprehensively evaluate the impact of treatment adherence on health (although adherence was highly correlated across medications in their study). It is clear that research on the prediction of health in individuals with CF from treatment adherence is limited at this time. Despite this, trials illustrating the individual efficacy of the various treatments and studies that have tested the effects of adherence on health for individuals with CF underline the importance of maintaining health through adequate engagement in treatment.

Adherence Rates in Individuals with CF

For the past few decades, adherence to physician-recommended guidelines has been a focus of scientific research in individuals with chronic and acute illnesses. For those with a chronic illness, such as CF, the assumption is made that greater treatment adherence will lead to a reduction in symptoms and slowing of disease. Therefore, much of the research on treatment adherence in individuals with CF has been directed toward determining rates of adherence in patients, as well as potential predictors of—and barriers to—adherence that can be utilized to increase adherence in this population.

Adherence differs greatly by treatment for individuals with CF, so many studies in this area forego a measurement of overall adherence in favor of measuring patient adherence to different treatments separately. Overall, adherence is suboptimal despite the effectiveness of various treatments in improving health in individuals with CF. In a cross-sectional study measuring self-reported treatment adherence of a sample of children and adults with CF, only 62% of participants had complete compliance for respiratory medications, 41% were compliant to chest physiotherapy, 59% were compliant to nutritional supplements, and 88% were compliant to digestive medications (Llorente, García, & Martín, 2008). The authors also observed that patients considered compliant were significantly younger (mean age: 10.4, SD = 6.1) than patients who were considered non-compliant (mean age: 20.5, SD = 10.8), with adults and late adolescents being less compliant than children younger than 15 years old. The authors of the study also noted that patients overestimated their overall compliance, considering themselves 85% compliant across their medications.

A study that used MPR scores calculated from pharmacy records for a sample of children and adults with CF found that median MPR scores ranged 49% to 76% across pulmonary medications (azithromycin, dornase alfa, hypertonic saline, and inhaled tobramycin; Eakin et al., 2011). The same method was used in another study to measure and compare MPR scores across different age groups of individuals with CF, reporting mean MPR scores for pulmonary medications (azithromycin, dornase alfa, hypertonic saline, inhaled aztreonam, inhaled colistin, and inhaled tobramycin) of 40% to 57% (Quittner et al., 2014). In this study, children aged 6-10 had higher adherence (mean MPR = 59%) than the other age categories for all medications (mean MPR = 42% to 49%). In another study of children and adults with CF, mean MPR scores for adherence to dornase alfa were 59% (SD = .30; Nasr et al., 2013). In this study, the youngest group also had significantly higher MPR scores than the older age groups. Of note, MPR scores were shown to differ by season in this sample, with higher adherence seen in fall and winter than in spring and summer. The authors suggested that this seasonal difference in adherence may be a result of patients having fewer respiratory infections during the spring and summer months and choosing to forgo some of their treatments.

In a study that utilized an electronic delivery device to measure twice-daily adherence to nebulized antibiotics over a 12-month period, mean adherence among children with CF ranged between 60% and 70% (McNamara, McCormack, McDonald, Heaf, & Southern, 2009). Similar to other studies, adherence was higher in children younger than twelve years old (71% vs. 50%), but novel to this study was the observation of adherence being significantly higher in the evenings (75%) than in the mornings (58%). Another study of children and adolescents using Medication Event Monitoring

System (MEMS) SmartCaps reported mean adherence rates for an oral multivitamin as 71% in children and 57% in adolescents (Zindani, Streetman, Streetman, & Nasr, 2006). For dornase alfa, mean adherence rates were 63% in children and 70% in adolescents.

Some studies identified subgroups of patients based on different levels of treatment adherence. In a study of adherence to tobramycin inhalation solution over a 12-month period in children and adults, 71% of participants fell in the low utilization group, 22% fell in the medium utilization group, and only 7% fell in the high utilization group (Briesacher et al., 2011). In a 12-month retrospective study of adherence to dornase alfa, patients were separated into three groups based on adherence estimated by pharmacy records: good adherence (patient collected 9-12 months' supply of medication; 24%), moderate adherence (patient collected 5-8 months' supply of medication; 48%), and poor adherence (patient collected 1-4 month's supply of medication; 28%; Burrows et al., 2002). In this study, participants—and, to a lesser extent, physicians—over-estimated patient adherence rates compared to pharmacy records. In another study, an interview with adult CF patients indicated that full compliance was highest for enzyme treatment (85%) and exercise (75%), but lower for vitamin therapy (47%) and chest physiotherapy (32%) (Abbott, Dodd, Bilton, & Webb, 1994).

Predictors of Treatment Adherence

In the literature describing treatment adherence for chronic illness, a number of potential predictors and barriers for adherence have been identified. For instance, patients' fear of medication side effects has been suggested as a major contributor to non-adherence, leading to complete non-adherence or lowering of doses to lessen medication side effects (Donovan & Blake, 1992). Specifically, the balance of side effects against

treatment efficacy is assumed to play a major role in patients' decision to perform a given treatment (Chengappa et al., 2003; Donovan & Blake, 1992; Masand, 2003). The dosing and complexity of a given treatment or treatment regimen (i.e., treatment burden) can also factor into patients' decision to adhere to their treatments (Bernard & Cohen, 2004; Claxton, Cramer, & Pierce, 2001; Ingersoll & Cohen, 2008; Richter, Anton, Koch, & Dennett, 2003). For instance, a patient may be more adherent to treatments that involve taking an oral medication once a day than to treatments which require a significant amount of time to complete or treatments which must be completed multiple times a day (e.g., CPT and inhaled bronchodilators therapy). Adherence may also be lower for individuals who have more and varied treatments to complete on a daily basis, and this is particularly relevant for patients with complex treatment regimens. Given the progressive nature of CF, the complexity of patients' treatment regimen generally increases as they age (Sawicki et al., 2013), which may account for some of the age differences in adherence rates. However, there is evidence that greater treatment complexity is associated with greater adherence in individuals with CF (Hilliard, Eakin, Borrelli, Green, & Riekert, 2015; Quittner et al., 2014). Authors suggest that care providers may be hesitant to prescribe additional treatments if patients cannot adhere to current regimens. Therefore, patients who are already more adherent may be selectively given more complex treatments. Alternatively, greater treatment complexity may be an indication of greater disease severity which may facilitate patients' greater adherence in an effort to control symptoms.

The immediacy of a treatment's desired effects (or effects of not taking a given medication) may also influence individuals' adherence behaviors (Bernard & Cohen,

2004). For instance, an individual with CF may experience immediate clearing of his or her airways after CPT and become motivated to perform this treatment regularly. However, CPT may often appear to have no immediate beneficial effects for patients, and this could lead to lower adherence even though adherence to the treatment would benefit the patients' long-term pulmonary health (Desmond, Schwenk, Thomas, Beaudry, & Coates, 1983).

Patients' poor understanding of their treatments or lack of knowledge about their disease and how their treatments affect their health have been suggested as contributing to lower overall adherence (Conway, Pond, Watson, & Hamnett, 1996; Ingersoll & Cohen, 2008; Modi & Quittner, 2006). A possible contributor to this lack of understanding or knowledge is patients' relationship with the medical staff charged with their care. Cystic fibrosis patients' trust in their medical staff is an important determinant of health and well-being because it helps ensure that patients listen to and follow the recommendations of the team, including following instructions related to their treatments and therapies (Ingersoll & Cohen, 2008).

Personal and cognitive factors are also related to treatment adherence. For instance, in reviewing the literature on barriers to treatment across various illness groups, Jack and colleagues (2010) reported that higher levels of depression, anxiety, and helplessness, as well as poor adherence-related social support, consistently predicted lower adherence. By contrast, previous adherence behavior and higher self-efficacy consistently predicted higher treatment adherence. However, one personal factor that may be protective for adherence in patients with CF is anxiety. In one study of children with CF, those with an anxiety disorder were actually more likely to be adherent to treatments

(including adherence to diet, physiotherapy, and pulmonary medications; White, Miller, Smith, & McMahon, 2009). The authors suggested that patients may have been more compliant in reaction to anxiety related to their illness (perhaps as a means of coping) or that patients with anxiety were more likely to over-report adherence as a result of their anxiety.

Theoretical Models for Predicting Adherence

Historically, treatment adherence research has referred to non-adherence as non-compliance, implicitly marking non-adherence as deviant behavior (Donovan & Blake, 1992). Non-adherence was thought to largely be a problem of understanding and applying knowledge about treatments, or forgetfulness in performing treatments and therapies. This type of non-adherence is often referred to as unintentional non-adherence, and properly educating patients about the importance of taking medications was expected to increase adherence and eliminate non-adherence. However, Donovan and Blake (1992) emphasized that patients take an active role in deciding to adhere to their treatments. Intentional adherence or non-adherence was suggested as arising due to "reasoned decision-making", a process in which patients weigh the costs of performing a treatment and the severity of their illness against the benefits of the treatment. For instance, a patient may decide that the benefits of performing a given treatment (e.g., reduction of illness symptoms) are outweighed by the adverse effects that accompany that treatment (e.g., negative side-effects, loss of time for other activities, and stigma) and choose not to perform the treatment. Known as intentional non-adherence or intelligent non-adherence, this reasoned behavior can be viewed as a beneficial (or at least benign) exercise of patient autonomy when paired with sufficient medical literacy in the patient, but may be

detrimental to patient health under different conditions (Nafradi, Nakamoto, & Schulz, 2017; Schulz & Nakamoto, 2013). Indeed, evidence showing that individuals with CF consider the relative need for treatments as well as the potential side-effects when deciding to administer treatments supports the idea that treatment adherence can be an active decision-making process for this population (Bucks et al., 2009).

A number of theoretical models and perspectives have been used to explain the influence of personal and environmental factors on patients' adherence to medications and treatments. For instance, the Health Beliefs Model (HBM) is used to explain individuals' decisions to perform health behaviors. Originally developed for predicting behaviors aimed at preventing illness in generally healthy individuals (e.g., healthy diet and exercise, and regular health screening), the HBM has been later used to explain behaviors aimed at lessening the effects of an existing illness (e.g., adherence to physician-prescribed treatments; Rosenstock, 1974). Much like Donovan and Blake's (1992) concept of reasoned decision-making for determining treatment adherence, the HBM proposes that individuals assess the benefits and disadvantages of a given treatment before choosing whether to perform the treatment. Individuals' perceptions of illness severity and personal susceptibility to symptoms of their illness factor into this decision-making process, with greater perceived severity and susceptibility assumed to lead to performance of health behaviors. This model has been applied to patients with CF, with some support for its use in predicting treatment adherence (Abbott, Dodd, & Webb, 1996). However, the relationship between disease severity perceptions and performance of health behaviors might be non-linear. For instance, some patients with the greatest perceived severity may neglect treatment, possibly as a means of avoidance coping. This

is supported by the rates of avoidance coping seen in CF patients with lower adherence (Abbott, Gee,Webb, 2001).

The Health Promotion Model (HPM; Pender, 1996) can be thought of as a theoretical extension of the HBM, with both theories having roots in Bandura's Social Cognitive Theory. This model has been used to help nurses guide patients toward performing positive health behaviors (Jackson, Tucker, & Herman, 2007). Individuals' beliefs about their competency to perform health behaviors along with other cognitive and environmental factors (e.g., self-efficacy, emotion states, and social support) are considered determinates of health behaviors under this model, with adherence behavior enacted through a reasoned decision-making process. The model asserts that health behaviors are determined by three components: 1) Individual characteristics and experiences, 2) Behavior-specific cognitions and affect, and 3) Interpersonal and behavioral influences (Pender, 1996). Empowerment models emphasize the role of health locus of control (HLC) and self-efficacy in determining treatment adherence. In general, greater adherence is expected to result from higher internal HLC and greater self-efficacy (Nafradi et al., 2017). Self-efficacy is central to determining health behavior under the HPM. According to the model, when making decisions regarding a given health behavior, the individual might only perform the behavior if the benefits outweigh the risks *and* if the patient has sufficient confidence in his or her ability to perform the behavior (i.e., self-efficacy).

The Current Study

The current study evaluates the relationships between cognitive factors (HLC, social support, perceived disease severity, and depressive symptoms) and treatment adherence in adults with CF.

The first manuscript examines HLC dimensions (Internal, Powerful Others, and Chance HLC) as predictors of treatment adherence and whether these relationships vary by perceived disease severity. Previous studies on adherence in individuals with CF have addressed adherence to a variety of treatments. However, most studies have focused on a limited number of treatment types in the same study, so this investigation will examine adherence to a broader range of treatments (e.g., adherence to inhaled antibiotics, airway clearance therapy, vitamins and enzymes, disease modifying medication, and exercise). Further, evidence for the relationship between different dimensions of HLC and adherence is present in samples of children and adolescents with CF, but little research has addressed this relationship in adults with CF. This study seeks to fill these gaps in the literature.

The second manuscript evaluates the role of social support (from family, friends, and significant others) in treatment adherence and whether these effects are explained by depressive symptoms. Previous research indicated the importance of family support in treatment adherence in children with CF. However, few studies have examined the role of social support from family and other sources in predicting adherence among adults with CF. Further, no studies have evaluated the role of psychosocial factors (e.g., depression) in explaining the relationship between social support and adherence in individuals with CF. The current study will address these gaps in the literature.

The final manuscript evaluates the potential quadratic effects of disease severity (perceived as well as clinically measured) on adherence to different treatments. Current research evaluating this relationship is inconsistent, with some studies suggesting that disease severity is related to greater adherence and others indicating it is related to lower adherence. However, one explanation for these inconsistencies may be a nonlinear relationship between disease severity and adherence. Specifically, it has been suggested that adherence is highest when severity is moderate but lower at upper and lower extremes of severity. The current study evaluates this hypothesis.

REFERENCES

Abbott, J., Dodd, M., Bilton, D., & Webb, A. (1994). Treatment compliance in adults with cystic fibrosis. *Thorax, 49*(2), 115-120.

Abbott, J., Dodd, M., & Webb, A. K. (1996). Health perceptions and treatment adherence in adults with cystic fibrosis. *Thorax, 51*(12), 1233-1238.

Abbott, M. D., Louise Gee, Kevin Webb, Janice. (2001). Ways of coping with cystic fibrosis: implications for treatment adherence. *Disability and Rehabilitation, 23*(8), 315-324.

Accurso, F. J., Rowe, S. M., Clancy, J., Boyle, M. P., Dunitz, J. M., Durie, P. R., . . . Donaldson, S. H. (2010). Effect of VX-770 in persons with cystic fibrosis and the G551D-CFTR mutation. *New England Journal of Medicine, 363*(21), 1991-2003.

Andersen, D. H. (1938). Cystic fibrosis of the pancreas and its relation to celiac disease: a clinical and pathologic study. *American Journal of Diseases of Children, 56*(2), 344-399.

Barker, D. H., & Quittner, A. L. (2016). Parental depression and pancreatic enzymes adherence in children with cystic fibrosis. *Pediatrics, 137*(2), e20152296.

Bernard, R. S., & Cohen, L. L. (2004). Increasing adherence to cystic fibrosis treatment: a systematic review of behavioral techniques. *Pediatric Pulmonology, 37*(1), 8-16.

Bilton, D. (2008). Cystic fibrosis. *Medicine, 36*(5), 273-278.

Borowitz, D., Baker, R. D., & Stallings, V. (2002). Consensus report on nutrition for pediatric patients with cystic fibrosis. *Journal of Pediatric Gastroenterology and Nutrition, 35*(3), 246-259.

Bradley, J. M., & Moran, F. (2008). Physical training for cystic fibrosis. *Cochrane Database of Systematic Reviews*(1).

Briesacher, B. A., Quittner, A. L., Saiman, L., Sacco, P., Fouayzi, H., & Quittell, L. M. (2011). Adherence with tobramycin inhaled solution and health care utilization. *BMC Pulmonary Medicine, 11*(1), 5.

Bucks, R. S., Hawkins, K., Skinner, T., Horn, S., Seddon, P., & Horne, R. (2009). Adherence to treatment in adolescents with cystic fibrosis: the role of illness perceptions and treatment beliefs. *Journal of Pediatric Psychology, 34*(8), 893-902.

Burrows, J. A., Bunting, J. P., Masel, P. J., & Bell, S. C. (2002). Nebulised dornase alpha: adherence in adults with cystic fibrosis. *Journal of Cystic Fibrosis, 1*(4), 255-259.

Chengappa, K. R., Parepally, H., Brar, J. S., Mullen, J., Shilling, A., & Goldstein, J. M. (2003). A random-assignment, double-blind, clinical trial of once-vs twice-daily administration of quetiapine fumarate in patients with schizophrenia or schizoaffective disorder: a pilot study. *The Canadian Journal of Psychiatry, 48*(3), 187-194.

Claxton, A. J., Cramer, J., & Pierce, C. (2001). A systematic review of the associations between dose regimens and medication compliance. *Clinical Therapeutics, 23*(8), 1296-1310.

Conway, S., Pond, M., Watson, A., & Hamnett, T. (1996). Knowledge of adult patients with cystic fibrosis about their illness. *Thorax, 51*(1), 34-38.

Couper, R., Corey, M., Moore, D., Fisher, L., Forstner, G., & Durie, P. (1992). Decline of exocrine pancreatic function in cystic fibrosis patients with pancreatic sufficiency. *Pediatric Research, 32*(2), 179-182.

Desmond, K. J., Schwenk, W. F., Thomas, E., Beaudry, P. H., & Coates, A. L. (1983). Immediate and long-term effects of chest physiotherapy in patients with cystic fibrosis. *The journal of Pediatrics, 103*(4), 538-542.

DiMatteo, M. R., Giordani, P. J., Lepper, H. S., & Croghan, T. W. (2002). Patient adherence and medical treatment outcomes a meta-analysis. *Medical Care,* 794-811.

Donovan, J. L., & Blake, D. R. (1992). Patient non-compliance: deviance or reasoned decision-making? *Social Science & Medicine, 34*(5), 507-513.

Eakin, M. N., Bilderback, A., Boyle, M. P., Mogayzel, P. J., & Riekert, K. A. (2011). Longitudinal association between medication adherence and lung health in people with cystic fibrosis. *Journal of Cystic Fibrosis, 10*(4), 258-264.

Eddy, M. E., Carter, B. D., Kronenberger, W. G., Conradsen, S., Eid, N. S., Bourland, S. L., & Adams, G. (1998). Parent relationships and compliance in cystic fibrosis. *Journal of Pediatric Health Care, 12*(4), 196-202.

Foundation, C. F. (2017). Cystic Fibrosis Foundation patient registry: 2016 annual data report.

Guimbellot, J., Solomon, G. M., Baines, A., Heltshe, S. L., VanDalfsen, J., Joseloff, E., . . . Investigators, G. (2019). Effectiveness of ivacaftor in cystic fibrosis patients with non-G551D gating mutations. *Journal of Cystic Fibrosis, 18*(1), 102-109.

Hilliard, M. E., Eakin, M. N., Borrelli, B., Green, A., & Riekert, K. A. (2015). Medication beliefs mediate between depressive symptoms and medication adherence in cystic fibrosis. *Health Psychology, 34*(5), 496.

Ingersoll, K. S., & Cohen, J. (2008). The impact of medication regimen factors on adherence to chronic treatment: a review of literature. *Journal of Behavioral Medicine, 31*(3), 213-224.

Jack, K., McLean, S. M., Moffett, J. K., & Gardiner, E. (2010). Barriers to treatment adherence in physiotherapy outpatient clinics: a systematic review. *Manual Therapy, 15*(3), 220-228.

Jackson, E. S., Tucker, C. M., & Herman, K. C. (2007). Health value, perceived social support, and health self-efficacy as factors in a health-promoting lifestyle. *Journal of American College Health, 56*(1), 69-74.

Jones, A. M., & Helm, J. M. (2009). Emerging treatments in cystic fibrosis. *Drugs, 69*(14), 1903-1910.

Konstan, M. W., & Ratjen, F. (2012). Effect of dornase alfa on inflammation and lung function: potential role in the early treatment of cystic fibrosis. *Journal of Cystic Fibrosis, 11*(2), 78-83.

Kopito, L., Shwachman, H., Vawter, G., & Edlow, J. (1976). The pancreas in cystic fibrosis: chemical composition and comparative morphology. *Pediatric Research, 10*(8), 742-749.

Llorente, R. P. A., García, C. B., & Martín, J. J. D. (2008). Treatment compliance in children and adults with cystic fibrosis. *Journal of Cystic Fibrosis, 7*(5), 359-367.

Masand, P. S. (2003). Tolerability and adherence issues in antidepressant therapy. *Clinical Therapeutics, 25*(8), 2289-2304.

McNamara, P. S., McCormack, P., McDonald, A. J., Heaf, L., & Southern, K. W. (2009). Open adherence monitoring using routine data download from an adaptive aerosol delivery nebuliser in children with cystic fibrosis. *Journal of Cystic Fibrosis, 8*(4), 258-263.

Modi, A. C., & Quittner, A. L. (2006). Barriers to treatment adherence for children with cystic fibrosis and asthma: what gets in the way? *Journal of Pediatric Psychology, 31*(8), 846-858.

Nafradi, L., Nakamoto, K., & Schulz, P. J. (2017). Is patient empowerment the key to promote adherence? A systematic review of the relationship between self-efficacy, health locus of control and medication adherence. *PLOS one, 12*(10).

Nasr, S. Z., Chou, W., Villa, K. F., Chang, E., & Broder, M. S. (2013). Adherence to dornase alfa treatment among commercially insured patients with cystic fibrosis. *Journal of Medical Economics, 16*(6), 801-808.

O'Sullivan, B. P., & Freeman, S. D. (2009). Cystic fibrosis. *The Lancet, 373*(9678), 1891-1904.

Patterson, J. M., Goetz, D., Budd, J., & Warwick, W. J. (1993). Family correlates of a 10-year pulmonary health trend in cystic fibrosis. *Pediatrics, 91*(2), 383-389.

Pender, N. (1996). Health promotion in nursing Practice. 3rd. *Stamford: Appleton & Lange, 251*.

Quittner, A. L., Zhang, J., Marynchenko, M., Chopra, P. A., Signorovitch, J., Yushkina, Y., & Riekert, K. A. (2014). Pulmonary medication adherence and health-care use in cystic fibrosis. *Chest, 146*(1), 142-151.

Radtke, T., Nolan, S. J., Hebestreit, H., & Kriemler, S. (2015). Physical exercise training for cystic fibrosis. *Cochrane Database of Systematic Reviews*(6).

Richter, A., Anton, S. E., Koch, P., & Dennett, S. L. (2003). The impact of reducing dose frequency on health outcomes. *Clinical Therapeutics, 25*(8), 2307-2335.

Rosenstock, I. M. (1974). Historical origins of the health belief model. *Health Education Monographs, 2*(4), 328-335.

Ryan, G., Singh, M., & Dwan, K. (2011). Inhaled antibiotics for long-term therapy in cystic fibrosis. *Cochrane Database of Systematic Reviews*(3).

Sawicki, G. S., Ren, C. L., Konstan, M. W., Millar, S. J., Pasta, D. J., Quittner, A. L., . . . Fibrosis, C. o. t. E. S. o. C. (2013). Treatment complexity in cystic fibrosis: trends over time and associations with site-specific outcomes. *Journal of Cystic Fibrosis, 12*(5), 461-467.

Schulz, P. J., & Nakamoto, K. (2013). Health literacy and patient empowerment in health communication: the importance of separating conjoined twins. *Patient Education and Counseling, 90*(1), 4-11.

Sinaasappel, M., Stern, M., Littlewood, J., Wolfe, S., Steinkamp, G., Heijerman, H. G., . . . Döring, G. (2002). Nutrition in patients with cystic fibrosis: a European Consensus. *Journal of Cystic Fibrosis, 1*(2), 51-75.

Southern, K., & Barker, P. (2004). Azithromycin for cystic fibrosis. *European Respiratory Journal, 24*(5), 834-838.

Stallings, V. A., Stark, L. J., Robinson, K. A., Feranchak, A. P., Quinton, H., on Growth, C. P. G., . . . Group, A. H. W. (2008). Evidence-based practice recommendations for nutrition-related management of children and adults with cystic fibrosis and pancreatic insufficiency: results of a systematic review. *Journal of the American Dietetic Association, 108*(5), 832-839.

Sturgess, J. M. (1984). Structural and developmental abnormalities of the exocrine pancreas in cystic fibrosis. *Journal of Pediatric Gastroenterology and Nutrition, 3*, S55-66.

Taylor-Cousar, J. L., Munck, A., McKone, E. F., Van Der Ent, C. K., Moeller, A., Simard, C., . . . Lu, Y. (2017). Tezacaftor–ivacaftor in patients with cystic fibrosis homozygous for Phe508del. *New England Journal of Medicine, 377*(21), 2013-2023.

Thomas, J., Cook, D., & Brooks, D. (1995). Chest physical therapy management of patients with cystic fibrosis. *Am J Respir Crit Care Med, 151*, 846-850.

Van Goor, F., Hadida, S., Grootenhuis, P. D., Burton, B., Stack, J. H., Straley, K. S., . . . Olson, E. R. (2011). Correction of the F508del-CFTR protein processing defect in vitro by the investigational drug VX-809. *Proceedings of the National Academy of Sciences, 108*(46), 18843-18848.

Wainwright, C. E., Elborn, J. S., Ramsey, B. W., Marigowda, G., Huang, X., Cipolli, M., . . . Flume, P. A. (2015). Lumacaftor–ivacaftor in patients with cystic fibrosis homozygous for Phe508del CFTR. *New England Journal of Medicine, 373*(3), 220-231.

Walters, S., & Mehta, A. (2007). Epidemiology of cystic fibrosis. *Cystic Fibrosis, 3*, 21-45.

White, T., Miller, J., Smith, G. L., & McMahon, W. M. (2009). Adherence and psychopathology in children and adolescents with cystic fibrosis. *European Child & Adolescent Psychiatry, 18*(2), 96-104.

Xu, W. M., Shi, Q. X., Chen, W. Y., Zhou, C. X., Ni, Y., Rowlands, D. K., . . . Wang, X. F. (2007). Cystic fibrosis transmembrane conductance regulator is vital to sperm fertilizing capacity and male fertility. *Proceedings of the National Academy of Sciences, 104*(23), 9816-9821.

Yankaskas, J. R., Marshall, B. C., Sufian, B., Simon, R. H., & Rodman, D. (2004). Cystic fibrosis adult care: consensus conference report. *Chest, 125*(1), 1S-39S.

Zindani, G. N., Streetman, D. D., Streetman, D. S., & Nasr, S. Z. (2006). Adherence to treatment in children and adolescent patients with cystic fibrosis. *Journal of Adolescent Health, 38*(1), 13-17.

HEALTH LOCUS OF CONTROL AND TREATMENT ADHERENCE IN INDIVIDUALS WITH CYSTIC FIBROSIS

by

BENJAMIN EDWIN BURGESS

SYLVIE MRUG

Format adapted for dissertation

Abstract

Objectives: Patients with cystic fibrosis (CF) must complete complex and time-consuming treatment regimens. However, adherence has been documented as suboptimal in this population. Health locus of control (HLC) and disease severity are related to adherence in chronic illness populations, but the findings have been inconsistent. The combined roles of HLC and disease severity in adherence, which may help explain these findings, have not been addressed in individuals with CF. ***Methods:*** Adults with CF (n = 123) completed measures of HLC (Internal, Powerful Others, and Chance), perceived disease severity, and adherence to common treatments for CF. ***Analyses:*** Hierarchical multivariate regression analyses tested the main and interactive effects of HLC and perceived disease severity on treatment adherence concurrently and over a 3-month follow-up. ***Results:*** Perceived severity interacted with Internal and Chance HLC to predict adherence to some treatments. Internal HLC predicted greater adherence to enzyme therapy and exercise only when perceived severity was high, and Chance HLC predicted lower adherence to enzyme therapy only when perceived severity was low. Internal HLC also directly predicted lower nutritional care adherence, and Chance HLC predicted lower airway clearance therapy adherence. ***Conclusions:*** The results suggest that perceptions of disease severity and HLC interact to predict some forms of treatment adherence in adults with CF and targeted interventions should be developed to improve adherence and resultant clinical outcomes.

Keywords: Cystic Fibrosis; Treatment Adherence; Health Locus of Control; Locus of Control; Disease Severity

Health Locus of Control and Treatment Adherence in Individuals with Cystic Fibrosis

Cystic fibrosis (CF) is a life-threatening recessive genetic disorder whose most characteristic complications include impaired pulmonary and gastrointestinal function, as well as infertility in most males (O'Sullivan & Freeman, 2009; Xu et al., 2007). Production and build-up of abnormally viscous mucus in the airways, pancreatic ducts, and biliary systems create blockages that cause complications in pulmonary and gastrointestinal function (Bilton, 2008). These blockages result in bacterial infection in patients' lungs and airways and decline of respiratory function which can lead to pulmonary failure and need for lung transplant (O'Sullivan & Freeman, 2009). Complications in gastrointestinal and pancreas function hinder nutritional absorption, resulting in malnutrition and low body mass index (BMI; O'Sullivan & Freeman, 2009).

Patients with CF have complex and time-consuming treatment regimens, most commonly including antibiotics, nebulized medications, pancreatic enzymes and vitamin replacement, chest physiotherapy techniques, and blood-glucose monitoring (Bilton, 2008). Because there is no cure for CF, these regimens aim to mitigate the progressive CF-related organ dysfunction in order to prolong patients' lives. The CF Foundation has developed a number of clinical care and treatment guidelines to include in patients' treatment routines (Lahiri et al., 2016; Yankaskas, Marshall, Sufian, Simon, & Rodman, 2004). For instance, individuals with CF periodically (generally four times a year) meet with a team of clinical specialists to evaluate disease progression and adjust treatments to

meet their specific needs. During these visits, assessments of health status and disease progression, including BMI, forced expiratory volume in one second (FEV_1), and microbiological assessment of expectorated sputum, are performed. Hospitalization is often necessary to treat pulmonary exacerbations and other complications, such as pneumothorax and massive hemoptysis.

Treatment Adherence

Efficacy has been demonstrated for the most common treatments aimed at improving health in individuals with CF (e.g., dornase alfa, inhaled antibiotics, chest physiotherapy, and pancreatic enzyme replacement) in a number of clinical studies (Bradley & Moran, 2008; Guimbellot et al., 2019; Konstan & Ratjen, 2012; Radtke, Nolan, Hebestreit, & Kriemler, 2015; Ryan, Singh, & Dwan, 2011; Southern & Barker, 2004; Stallings et al., 2008; Thomas, Cook, & Brooks, 1995; Wainwright et al., 2015). Therefore, adherence to these medications is important to improve health outcomes and slow disease progression. In general, greater treatment adherence is associated with better health outcomes in patients with chronic illness (DiMatteo, Giordani, Lepper, & Croghan, 2002). However, the rate of adherence that is required to improve health outcomes is not well-established and differs by illness, with some health conditions requiring nearly absolute adherence to benefit patients' health (Osterberg & Blaschke, 2005). For individuals with CF, specifically, global adherence to various medications predicts better health outcomes (e.g., more favorable FEV_1 trends, better weight management, and fewer exacerbations and hospitalizations) over time (Barker & Quittner, 2016; Briesacher et al., 2011; Eakin, Bilderback, Boyle, Mogayzel, & Riekert, 2011; Eddy et al., 1998; Osterberg & Blaschke, 2005; Patterson, Goetz, Budd, &

Warwick, 1993). Although studies do not always find a relationship between adherence to individual medications and their targeted health outcomes, treatment adherence and the efficacy of patients' treatments may be best addressed by considering the collective influence of multiple treatments on health (Eakin et al., 2011).

Because differences in the measurement of treatment adherence can affect the validity of research in this area, the advantages and disadvantages of different measurement methods must be considered. For instance, self-report measures (e.g., treatment diary, questionnaire recall, interview, and report from a third-party such as a family member) can be problematic because they are often subject to reporter bias (overestimating adherence) or inaccuracy due to problems with recall (Kettler, Sawyer, Winefield, & Greville, 2002; Quittner, Espelage, & Drotar, 2000). However, self-report measures of adherence are widely used in adherence research due to their convenience and low cost. Other more objective methods (e.g., electronic monitoring systems, prescription records, and internal monitoring and blood assays) accurately measure adherence, but they are often more costly and time-consuming and cannot be applied to all methods of treatment administration (DiCarlo et al., 2016; McNamara, McCormack, McDonald, Heaf, & Southern, 2009; Urquhart, 1997; Yeung, O'Connor, Parry, & Cochrane, 1994). Despite differences in adherence measurement in studies with CF patients, it is evident that adherence varies by treatment but overall is suboptimal in this population (Eakin et al., 2011; Llorente, García, & Martín, 2008; Nasr, Chou, Villa, Chang, & Broder, 2013; Quittner et al., 2014). For instance, one study found that median medication possession ratios (a value calculated by dividing the number of days' worth of a medication that an individual possesses by the length of time observed) ranged from

49% to 76% across pulmonary medications for children and adults with CF (Eakin et al., 2011). In another study, only 62% of participants were compliant to their respiratory medications, and only 41% were compliant to their chest physiotherapy (Llorente et al., 2008). By contrast, 59% were adherent to their nutritional supplements, and 88% were adherent to their digestive medications during meals (although only 23% took their digestive medications when eating snacks; Llorente et al., 2008).

Health Locus of Control

Various personal and treatment factors have been examined as predictors of treatment adherence in patients with chronic illness. For instance, health locus of control (HLC) is a multidimensional construct that indicates the degree to which individuals believe that they or outside influences can control their health. In health research, HLC is generally conceptualized as having three to four primary dimensions: Internal (belief that one's actions affect one's health), Powerful Others (belief that powerful others like medical professionals affect one's health; sometimes HLC beliefs related to Doctors are distinguished from general Powerful Others HLC beliefs), and Chance (belief that one's health is influenced by chance; Wallston, Strudler Wallston, & DeVellis, 1978). Each of these dimensions is expected to interact with other individual factors (e.g., disease severity, social support, and demographics) to impact health and health behaviors (Wallston et al., 1978). In general, higher Internal HLC is expected to lead to an increase in health-promoting behaviors, while higher Chance HLC is expected to lead to a decrease in these behaviors. For chronic illness populations (e.g., individuals with CF), higher Internal HLC is expected to lead to an increase in disease-specific health behaviors (e.g., adherence to therapies and medications), while higher Chance HLC is

expected to lead to a decrease in these behaviors. Higher Powerful Others HLC may also lead to an increase in disease-specific health behaviors if the perceived outside influences promote or support the patient's health behaviors. In turn, increases in normative and disease specific health behaviors would be expected to improve health outcomes, and decreases in these behaviors would be expected to worsen health outcomes.

As expected, in nationally representative samples, greater Chance HLC is often associated with performing fewer general health behaviors (e.g., less exercise, fewer health check-ups, and less seeking of health information; Grotz, Hapke, Lampert, & Baumeister, 2011). In contrast, greater Internal HLC beliefs are often associated with higher rates of health-promoting behaviors such as exercise and healthy diet (Cheng, Cheung, & Lo, 2016; Cobb-Clark, Kassenboehmer, & Schurer, 2014; Hosseini, Aghamolaei, & Ghanbarnejad, 2017; Janowski, Kurpas, Kusz, Mroczek, & Jedynak, 2013; Tripahi, Asthana, & Asthana, 2016; Zou, Tian, Chen, Cheng, & Fan, 2017). According to the literature on various patient populations, Chance HLC is associated with lower rates of nutrition and physical activities in lung cancer patients (Tripahi et al., 2016), lower adherence to prophylactic treatment for chronic physical health problems (Craig & Wright, 2012), and lower adherence to illness-specific medications in patients with asthma, cardiovascular conditions, and diabetes (West, Theuma, & Cordina, 2018). Further, Internal HLC has been linked with greater treatment adherence to hypertension medication for patients with hypertension (Omeje & Nebo, 2011). In a study of older adults with various illnesses, greater Internal HLC was associated with better self-rated health, while greater Powerful Others and Chance HLC were associated with poorer self-rated health (Berglund, Lytsy, & Westerling, 2014). Similarly, in a study of hemodialysis

and peritoneal dialysis patients, higher Internal HLC was related to better quality of life and general health, but Powerful Others HLC (excluding doctors) was linked with greater depression (Theofilou, 2012).

However, little research has focused on the prediction of treatment adherence from HLC beliefs in individuals with CF. One older study with CF patients showed that greater adherence to chest physiotherapy, pancreatic enzyme replacement, and vitamin therapies was related to higher Powerful Others HLC, whereas greater adherence to exercise regimen was linked with greater Internal HLC (Abbott, Dodd, & Webb, 1996). This suggests that patients' perception of their care team's control over their health may affect adherence to illness-specific treatments, whereas more general health behaviors (such as exercise) may be more related to beliefs of personal control. Another study reported positive correlations between overall treatment adherence (combined across nine key treatment areas) and Doctors HLC as well as general Powerful Others HLC in individuals with CF (Myers & Myers, 1999). However, in another study, no relationships were observed between HLC and transplant-specific adherence for individuals with CF who received lung transplants (Lindgren et al., 2002).

Despite this evidence for a relationship between HLC and health behaviors in chronic illness patients, the results for the prediction of treatment adherence from HLC are mixed. According to a systematic review of the links between empowerment variables and adherence, when significant relationships between Internal HLC and adherence are reported in the literature, higher Internal HLC scores generally predict greater adherence (Nafradi, Nakamoto, & Schulz, 2017). However, null findings made up a majority (58%) of the studies that evaluated this relationship. For external measures of

HLC, the significant relationships reported were less consistent (with the exception of Doctors HLC, which appeared to promote adherence). Some studies indicated positive associations between external measures of HLC and adherence, and a similar number indicated negative associations. Further, a majority of studies found no relationship between external HLC and adherence (50-67% of studies had null findings across different external measures of HLC).

In order to address the inconsistencies in previous studies addressing the relationship between HLC and treatment adherence, the current study is following recommendations to consider other variables that may impact the proposed relationship (e.g., disease severity). Perceived disease severity (i.e., an individual's evaluation of their current health) has been studied as a predictor of treatment adherence and might serve as a motivation for patients to complete their treatments. Indeed, higher perceived severity is generally associated with increased adherence to medications and other treatments in various illness groups (Kardas, Lewek, & Matyjaszczyk, 2013). However, in individuals with CF, there is conflicting evidence, with some studies finding a positive association between disease severity and adherence (DeLambo, Ievers-Landis, Drotar, & Quittner, 2004; Oermann, Swank, & Sockrider, 2000) and others finding an inverse association (Llorente et al., 2008). However, the cross-sectional design of these studies makes it difficult to understand the causal relationships between disease severity and treatment adherence.

In the context of the Health Promotion Model (Pender, 1996), an individual would be expected to perform a given health behavior (e.g., complete a treatment) if they believe they are capable of doing so *and* if they are sufficiently motivated by perceptions

of their disease severity. That is, Internal HLC may predict greater adherence, but only when perceived disease severity is high enough to prompt patients to respond by performing the treatment or health behavior. When patients perceive their current condition to be healthy, they may be less motivated to adhere to treatments even if they feel they are in control of their health.

One final concern in the literature exploring the relationships between treatment adherence, perceived disease severity, and HLC is the lack of longitudinal designs. This is especially true for the studies conducted with CF patients, which were all cross-sectional.

Aims and Hypotheses

The present study aims to examine HLC dimensions as predictors of adherence to illness-specific treatments in adults CF and whether these relationships vary by disease severity perceptions. Previous studies on adherence in individuals with CF have addressed adherence to a variety of treatments. However, most studies have focused on a limited number of treatment types in the same study, so this investigation will examine adherence to a broader range of treatments (e.g., adherence to inhaled antibiotics, airway clearance therapy, vitamins and pancreatic enzymes, disease modifying medication, and exercise). Given the impact that patients' care providers have had on adherence to treatment-specific medications in CF samples and other chronic illness groups, Powerful Others HLC is expected to be associated with increased adherence to CF-specific treatments (e.g., CPT and enzyme treatment). Additionally, Internal and Chance HLC are expected be directly related to treatment adherence behaviors, including those not specific to CF (e.g., exercise). Specifically, Internal HLC is expected to relate to

increased adherence, whereas Chance HLC is expected to relate to decreased adherence. Finally, HLC is expected to interact with perceived disease severity such that Powerful Others and Internal HLC will be more strongly associated with adherence when perceived severity is high.

METHODS

Participants and Procedures

Between 2016 and 2017, 123 patients with cystic fibrosis were recruited from outpatient pulmonary clinics and inpatient units at the University of Alabama Hospital and Children's Hospital of Alabama, which collectively serve about 230 adults with CF. Eligibility criteria included a diagnosis of CF and age of 18 years or older. Participants were asked to complete two surveys administered approximately three months apart. Of 176 patients approached, 158 (90%) agreed to participate and 123 (70%) completed the baseline survey. Of the 123 who completed the baseline survey, 111 (90%) completed the second survey. Participants had a mean age of 31.8 years (SD = 11.4 years; age range: 19-67 years), 47% were male, 93% were White, and 7% were African American.

The Institutional Review Board approved all study procedures. Participants provided written informed consent during recruitment and later completed online or paper questionnaires. They were compensated for their time with a $30 Visa gift card for each questionnaire completed.

Measures

Treatment Adherence. Adherence to various illness-specific treatments was measured using a 16-item self-report questionnaire modified from the Treatment Adherence Questionnaire-CF (Quittner et al., 2000). Each item addresses adherence to a particular treatment or component of patients' treatment routines (e.g., adherence to

various aerosols, airway clearance, meal and exercise recommendations, and pancreatic enzymes). For each item, participants indicated how often they missed the given treatment on a 7-point scale (*Not at All* to *3 or more times per day*), with higher scores indicating higher non-adherence. Where available, patient records were used to determine what treatments were prescribed to each participant. For participants who were not prescribed a given treatment but who responded to the adherence question for that treatment, responses were coded as missing because adherence was not applicable for that item. Information for how frequently and over what period patients were prescribed to take oral and inhaled antibiotics was not available, so these adherence items were not included in the study.

In order to reduce the number of adherence variables, principal components analysis (PCA) was attempted to calculate fewer components (from the original 16 items) for analysis. However, PCA could not be conducted due to high missingness (i.e., only 4 cases had responses to all treatment items). Therefore, mean adherence scores were calculated for clusters of theoretically related items that showed moderate to strong bivariate correlations ($r \geq .50$). See *Table 1.1* for bivariate correlations among the individual adherence items. Seven treatment domains (five considered CF-specific and two considered broad health behaviors) were identified using this method. These domains included: 1) respiratory care to open and clear airways (airway clearance therapy and aerosols to thin mucus, clear mucus, and open airways; 4 items, $\alpha = .94$ and .93); 2) respiratory care to address inflammation (inhaled corticosteroids; single item); 3) nutritional care (nutritional supplements, snacks, and meals; 3 items, $\alpha = .71$ and .81); 4) diabetes care (insulin and blood glucose monitoring; 2 items, $r = .71$ and .35); 5) enzyme

therapy (e.g., vitamins and enzymes; 2 items, r = .74 and .71); 6) disease modifying medications (single item); and 7) exercise (single item). These composite treatment domain scores comprised all adherence items except for inhaled and oral antibiotics. The mean adherence measures were reverse-coded so that higher scores indicated greater adherence.

Health Locus of Control. Health locus of control was measured using Form B of the Multidimensional Health Locus of Control (MHLC) scales (Wallston et al., 1978). This 18-item questionnaire measures three key dimensions of HLC: Internal (e.g., *If I become sick, I have the power to make myself well again*), Powerful Others (e.g., *Other people play a big part in whether I stay healthy or become sick*), and Chance (e.g., *Often I feel that no matter what I do, if I am going to get sick, I will get sick*). Participants indicated their agreement with each item using a 6-point scale (*Strongly Disagree* to *Strongly Agree*). Scores were computed for each 6-item subscale by summing the items (scores range from 6 to 36). Reliability of the three subscales was low (Internal α = .65, Powerful Others α = .54 and Chance α = .64), but consistent with other studies using this measure (Mautner et al., 2017; Pereira, Araújo, Sampaio, & Haddad, 2011; Wallston et al., 1978; Williams, Lynch, Voronca, & Egede, 2016). For additional secondary analyses the Powerful Others HLC scale was split into a Doctors HLC (4 items; α = .54) and a general measure of Powerful Others HLC (2 items; r = .33, p < .001).

Disease Severity. Disease severity was measured using two clinical measures from patients' medical records, percentage predicted scores for forced expiratory volume during the first second of exhalation (FEV_1) and a body mass index (BMI) at baseline. FEV_1 scores are recorded by clinicians during patients' regular clinic visits and indicate

the volume exhaled during the first second of a forced expiratory maneuver. FEV_1 scores are used to calculate percentage predicted FEV_1 ($\%FEV_1$) scores for each patient based on age, height, and sex, with higher percentages indicating less pulmonary obstruction (normal/mild: ≥70%; moderate: 40%-69%; severe: <40%; CFF, 2016). BMI scores are also recorded at regular clinic visits as a marker of healthy weight and to screen for issues of nutritional absorption. These scores are calculated using patients' weight and height measured at each clinic appointment, with participants falling into one of four categories based on their BMI score (<18.5: underweight; 18.5-25: normal healthy weight; 25-30: overweight; >30: obese). Both of these measures of disease severity are widely used as indicators of disease progression in individuals with CF. Additionally, patients' perception of their overall health was measured in the current study with a single question (*How do you think your health is now?*) using a 4-point scale (*Excellent* to *Poor*) (Henry, Aussage, Grosskopf, & Goehrs, 2003).

Demographics. Demographic information (i.e., gender, income level, marital status, education, and age) was collected from participants after informed consent was obtained. Additional information included type of recruitment setting (inpatient vs. outpatient) and clinic type (adult, child, or pediatric-to-adult transition clinic).

Statistical Analyses

Preliminary Analyses. Descriptive statistics were computed for demographics and variables of interest, including screening for sufficient variability. Sample representativeness was addressed by comparing participants to individuals who were approached but did not participate on age using an independent samples t-test and gender using a chi-square test of independence. Participants recruited from inpatient units and

outpatient clinics were compared to determine if they differed on demographics and any variables of interest. Attrition analyses compared those who did vs. did not participate in the follow-up on all demographic and baseline variables. Differences between the three HLC dimensions and change in treatment adherence from baseline to follow-up were evaluated using paired samples t-tests. Bivariate correlations were computed for all demographic and key variables, evaluating bivariate relationships between these variables as well as stability of adherence measures over time. Finally, assumptions of the main analyses (normality, homoscedasticity, and multicollinearity) were tested.

Primary Analyses. Multivariate hierarchical multiple linear regressions conducted in Mplus version 7.11 were used to evaluate the cross-sectional and prospective relationships between HLC, perceived severity, and treatment adherence. In the first, cross-sectional model, baseline measures of each HLC domain (Internal, Chance, and Powerful Others) and perceived disease severity were included as predictors of the five adherence composite scores at baseline. Inhaled corticosteroids and disease modifying medications were not included in any of the models in this study due to their small sample size, which prevented model convergence (n = 58 and 28-30, respectively). The interactions between each HLC subscale and perceived disease severity were added to the model at a second step. Covariates were entered in Step 1 and included demographic variables (age, household income, $\%FEV_1$, and BMI) that were related to adherence, perceived disease severity, and HLC as determined by bivariate correlations. The use of a single multivariate model reduced Type I error and accounted for interrelationships among the adherence domains.

The second multivariate model evaluated the longitudinal relationship of HLC and perceived disease severity with treatment adherence. In this model, each HLC subscale and patients' perceived disease severity were included as predictors of the five adherence composite scores at 3-month follow-up. As in the first model, the interactions of each HLC subscale with perceived disease severity were included in a second step. Covariates included baseline adherence for each treatment domain, number of days between baseline and follow-up survey completion, and demographic variables (age, household income, $\%FEV_1$, and BMI) that were related to adherence, perceived disease severity, and HLC as determined by bivariate correlations. In both models, missing data were handled with full information maximum likelihood (FIML), a method that uses all available data and produces less bias than other methods of addressing missingness (e.g., listwise and pairwise deletion; Enders & Bandalos, 2001; Wang & Wang, 2012). Significant interactions were probed with simple slope analyses using low and high levels of perceived disease severity (1 SD below and above the mean).

Secondary Analyses. To address the potential distinction between Doctors and non-doctor Powerful Others HLC, two additional multivariate models tested the cross-sectional and longitudinal relationships between these two dimensions of the overall Powerful Others HLC scale and treatment adherence. In the first model, baseline measures of each HLC domain (Internal, Chance, and Doctors and non-doctor Powerful Others) predicted five adherence composite scores at baseline. In the second model, baseline measures of each HLC domain predicted the adherence composite scores at follow-up. For both models, covariates included demographic variables that were related to adherence, perceived disease severity, and HLC as determined by bivariate

correlations. For the longitudinal model, covariates included baseline adherence for each treatment domain and number of days between baseline and follow-up survey completion.

RESULTS

Preliminary Analyses

Descriptive statistics for demographics and model variables can be found in *Table 2*. The average for perceived disease severity (M = 2.37) indicated that participants felt their health was *good* to *fair*. Average adherence scores varied by treatment (baseline M = 4.96 to 6.45, follow-up M = 5.50 to 6.64), though most fell between 5 and 7, indicating that participants missed their treatments *1-2 times per week* to *not at all* on average. All adherence outcomes were (except exercise) were negatively skewed. Of participants prescribed each treatment, 17% to 70% reported some non-adherence at baseline, and 21% to 60% reported some non-adherence at the 3-month follow-up.

Comparisons of participants and non-participants indicated that individuals who completed the baseline survey were significantly older (M_{age} = 32.0 vs 27.7 years, $t(148.340) = 2.85$, $p = .005$) and more likely to be females (53% vs 36%, χ^2 (1) = 4.14, $p = .042$). Participants who were recruited from inpatient units exercised less at baseline than those recruited from outpatient clinics, $t(111) = -2.65$, $p = .009$. Attrition analyses indicated that participants were more likely to drop out before the follow-up assessment if they had lower level of education, $t(67.04) = -4.82$, $p < .001$, and lower adherence to diabetes treatments at baseline, $t(57) = -2.06$, $p = .044$. Other demographic factors, HLC measures, perceived severity, and other adherence domains were not related to attrition. Participants reported higher levels of Internal HLC than Chance HLC, $t(120) = 13.98$, $p <$

.001, and Powerful Others HLC, $t(118) = 5.35$, $p < .001$. Participants also reported higher levels of Powerful Others HLC than Chance HLC, $t(118) = 8.31$, $p < .001$. Paired samples t-tests indicated that only exercise adherence differed from baseline to follow-up, $t(101) = -2.372$, $p = .020$. Specifically, exercise adherence was higher at follow-up (M = 5.0 vs 5.5).

Bivariate correlations between HLC measures, perceived disease severity, and treatment adherence domain scores are presented in Table 1.3. Greater perceived severity was related to lower $\%FEV_1$ ($r = -.18$, $p = .047$) and less adherence in the nutritional care ($r = -.26$, $p = .006$) and exercise domains ($r = -.36$, $p < .001$) at baseline as well as less adherence in the nutritional care domain at follow-up ($r = -.28$, $p = .003$), but it was unrelated to BMI ($r = -.07$, $p = .484$). Internal HLC was related to greater adherence to exercise ($r = .20$, $p = .038$) at follow-up, and Powerful Others HLC was related to lower airway clearance ($r = -.21$, $p = .025$) and disease modifying medication ($r = -.40$, $p = .035$) adherence at baseline. No other significant relationships between HLC measures and adherence measures were revealed through bivariate correlations. Most of the final adherence domain measures were moderately correlated over time (r range = .35 to .63, $p < .01$).

For all treatment adherence variables, normality was violated. Therefore, maximum likelihood estimation with robust standard errors (MLR), which is robust to violations of normality, was used in all models. No other major assumptions were violated.

Primary Analyses

Covariates in the main models included %FEV_1, BMI, income, and age because they were correlated with multiple predictor and outcome variables. See *Table 1.4* for standardized regression coefficients from the cross-sectional multivariate regression model. In this model, older age predicted lower nutritional care adherence (β = -.25, *p* = .009), greater enzyme therapy adherence (β = .20, *p* = .009), and lower exercise adherence (β = -.21, *p* = .024). Higher income predicted greater nutritional care adherence (β = .22, *p* = .043), BMI predicted greater enzyme therapy adherence (β = .21, *p* = .003), and perceived disease severity predicted lower exercise adherence (β = -.23, *p* = .009). While none of the main effects of HLC were significant for any of the treatment domains, three significant interactions were observed. One was for Chance HLC and perceived severity predicting enzyme therapy treatment adherence (β = .25, *p* = .013). Simple slopes analyses indicated that Chance HLC predicted lower adherence when perceived severity was low (β = -.34, *p* = .005), but was unrelated to adherence when perceived severity was high (β = .14, *p* = .307; see Figure 1.1). Internal HLC and perceived severity also interacted to predict adherence to exercise (β = .18, *p* = .028) and enzyme (β = .22, *p* = .021) therapies. Simple slopes analyses indicated that Internal HLC was related to higher exercise adherence when perceived severity was high (β = .31, *p* = .030), but not when perceived severity was low (β = -.05, *p* = .605; Figure 1.1). Simple slopes analyses did not find a significant relationship between Internal HLC and enzyme therapy adherence for either low (β = -.09, *p* = .341) or high perceived severity (β = .35, *p* = .061; Figure 1.1) using 1 SD below and above the mean for perceived severity. However, when 1.5 SD below and above the mean were used, Internal HLC was related

to higher enzyme therapy adherence when perceived severity was high (β = .46, *p* = .047), but not when perceived severity was low (β = -.20, *p* = .101; Figure 1.1)

See *Table 1.5* for the standardized regression coefficients from the longitudinal multivariate model. For this model, higher baseline BMI predicted lower airway clearance adherence at follow-up (β = -.22, *p* = .031), and higher baseline %FEV_1 predicted greater diabetes care adherence (β = .26, *p* = .010) and lower enzyme therapy adherence (β = .22, *p* = .031) at follow-up. Older age predicted lower exercise adherence at follow-up (β = -.31, *p* = .017). Higher Internal HLC predicted lower nutritional care adherence (β = -.16, *p* = .039), whereas Chance HLC predicted lower airway clearance adherence (β = -.18, *p* = .032) at follow-up. Higher perceived severity predicted greater enzyme therapy adherence (β = .26, *p* = .003). Perceived severity did not significantly interact with the HLC domains in predicting adherence at follow-up.

Secondary Analyses

Doctors HLC did not predict adherence in either of the additional multivariate models. However, baseline non-doctor Powerful Others HLC predicted higher adherence to nutritional care at baseline (β = .23, p = .015).

DISCUSSION

This study examined the relationships between health locus of control and adherence to routine treatments, both concurrent and over a 3-month period, in patients with CF. Different dimensions of HLC (Internal, Powerful Others, and Chance) were measured, and each dimension was expected to uniquely relate to adherence. Internal HLC was expected to relate to higher overall adherence, Powerful Others HLC was expected to relate to higher adherence for CF-specific treatments, and Chance HLC was expected to relate to lower adherence. In investigating these relationships, the potential moderating role of perceived disease severity was also evaluated. Internal HLC was expected to be more strongly related to adherence behavior at higher perceived severity, but the current study also tested perceived severity as a moderator for Chance and Powerful Others HLC. The results partially supported a moderation effect of perceived severity for cross-sectional, but not prospective relationship between HLC and adherence. Specifically, Internal HLC was related to greater adherence to exercise and enzyme therapy concurrently, but only when patients perceived greater disease severity. Chance HLC was related to lower adherence to enzyme therapy concurrently, but only when patients perceived lower disease severity. Further, Chance HLC was directly related to lower adherence to airway clearance therapies, and Internal HLC was directly related to lower nutritional care adherence over time. Finally, perceived disease severity was related to greater adherence to enzyme therapy over time.

Internal HLC and Adherence

Of the five treatment domains tested in this model, Internal HLC was only directly related to lower enzyme therapy adherence over time, and this relationship was in the opposite direction than expected. Previous studies suggest that Internal HLC is related to higher rates of health and treatment behaviors, while Chance HLC is related to lower rates and Powerful Others HLC is related to higher rates in patient populations like CF. Results supporting these conclusions have been observed in cross-sectional studies of individuals with CF (Abbott et al., 1996; Myers & Myers, 1999) and other patient populations (Craig & Wright, 2012; Omeje & Nebo, 2011; Tripahi et al., 2016; West et al., 2018). Further, results from cross-sectional and longitudinal studies of healthy adults also support these relationships (Cheng et al., 2016; Cobb-Clark et al., 2014; Grotz et al., 2011; Hosseini et al., 2017; Janowski et al., 2013; Tripahi et al., 2016; Zou et al., 2017). Given that all of the studies reporting this relationship for chronic illness patients were cross-sectional, perhaps greater adherence predicts higher internal HLC or some third variable predicts both of these variables in this population. However, while this may help explain why the longitudinal association between Internal HLC and treatment adherence in the present study differs from associations seen in previous studies, it does not explain why no concurrent relationships were found between Internal HLC and treatment adherence in the present study.

Another possible explanation for these inconsistent results comes from a recent systematic review of the direct relationship between HLC and treatment adherence in adults with chronic health conditions. While a number of studies have shown an association between Internal HLC and treatment adherence, an equal number of studies

found no significant relationships (Nafradi et al., 2017). Therefore, the relationship between HLC beliefs and treatment adherence may vary depending on other factors, such as patients' perceptions of disease severity or self-efficacy. In the context of the Health Promotion and Health Beliefs Model, participants' beliefs regarding their own competency to achieve desired health outcomes are most effective when they experience sufficiently motivating health perceptions (e.g., higher perceived disease severity). Consistent with this notion, in the present study Internal HLC was related to higher concurrent adherence to exercise and enzyme therapies when patients perceived their severity as high but not when they perceived it as low. Other studies have investigated the joint and interactive effects of HLC and disease severity on health-related outcomes. For instance, studies have shown internal HLC measures predicting better psychosocial adjustment outcomes (e.g., fewer mood disturbances) when disease severity is high (e.g., more daily symptoms) in patients with end-stage renal disease (Affleck, Tennen, Pfeiffer, & Fifield, 1987). Given that worse psychosocial adjustment (depression and anxiety) are related to lower treatment adherence in chronic illness populations (DiMatteo, Lepper, & Croghan, 2000; Jack, McLean, Moffett, & Gardiner, 2010), the results of this study appear consistent with our moderation results predicting treatment adherence. However, no prior studies of individuals with CF have addressed perceived or clinical disease severity as a moderator of the relationship between Internal HLC and treatment adherence, and few, if any, have done so in other patient populations.

Chance HLC and Adherence

Prospectively over three months, Chance HLC predicted lower adherence to airway clearance treatments as expected, but it did not predict any of the other treatment

domains. As with Internal HLC, perhaps the relationship between Chance HLC and treatment adherence is dependent on other patient factors. In the present study, Chance HLC was related to lower concurrent enzyme therapy adherence only when patients perceived lower disease severity. While our hypotheses did not address the interaction of Chance HLC and perceived severity, these results may indicate that Chance HLC is only detrimental to adherence behaviors when individuals with CF view their current health status favorably. Perhaps an increase in perceived severity causes patients to better adhere to treatments despite their beliefs about their ability to affect their health. Alternatively, other external (Powerful Others or Doctors and medical staff) or internal HLC factors may more strongly drive health behavior when patients perceive their condition as worse. Future research should continue to evaluate the effect of Chance HLC on treatment adherence as well as its interaction with perceived severity and other factors (e.g., other HLC dimensions and self-efficacy).

Powerful Others HLC and Adherence

Previous studies have found that adult CF patients with higher Powerful Other HLC are more adherent to chest physiotherapy, pancreatic enzyme replacement, and vitamin therapies (Abbott et al., 1996) and that Doctors HLC and Powerful Others HLC are related to greater overall treatment adherence (including treatments specific to CF and general measures of health behavior; Myers & Myers, 1999). Because of the findings in these studies, Powerful Others HLC was expected to predict higher adherence to CF-specific treatments (i.e., respiratory, enzyme, and diabetic care adherence domains). However, overall Powerful Others HLC was not related to adherence in the present study, and perceived disease severity did not interact with Powerful Others HLC to affect

adherence concurrently or over time. General Others HLC did predict greater concurrent adherence to nutritional care, but only when it was separated from Doctors HLC. Doctors HLC was not related to any measure of treatment adherence. However, the measure of Powerful Others HLC used in the present study was not intended to distinguish Doctors HLC from non-medical Powerful Others. This separation of the measurement may not be optimal, especially given that the Others HLC subdimension that resulted from dividing the Powerful Others dimension into Doctors and Others HLC contained only two items. Further, these measurement concerns may partially explain why our measure of Doctors HLC was not related to adherence in this study, while other studies that used validated measures of Doctors HLC have found that Doctors HLC is related to higher adherence in individuals with CF (Abbott et al., 1996; Myers & Myers, 1999). However, it is also important to note that these two previous studies are over two decades old. Many factors that may affect the roles of Doctors and Powerful Others in treatment adherence have changed (e.g., changes in standard care practices, development of more effective treatments, and increases life expectancy) and this may alter how Powerful Others and other dimensions of HLC affect adherence behaviors. Future research should evaluate the prediction of treatment adherence (ideally, separated by treatment type) from Doctors and Powerful Others HLC separately while controlling for other relevant factors.

Disease Severity and Adherence

Greater perceived disease severity was related to less exercise concurrently and increased adherence to enzyme therapy over time. A previous meta-analysis suggested that patients' perceptions of higher disease severity are related to greater treatment adherence across multiple disease groups and treatments (DiMatteo, Haskard, &

Williams, 2007). The relatively simple administration of enzyme therapy (i.e., taking pills orally before meals) and the immediacy of its therapeutic effects (as well as the immediacy of symptoms when patients are nonadherent) may explain why perceived disease severity was only related to adherence for enzyme therapies. By comparison, other adherence domains contained treatments which either had longer administration periods or delayed therapeutic effects. These treatment factors may have attenuated the effects of perceived disease severity on these treatments. Further, sufficiently severe symptoms may prohibit patients from completing some activities (e.g., those that are physically exerting) which may explain why perceived severity was related to less exercise in the present study.

While greater perceived severity predicted increased adherence to enzyme therapy in the present study, greater clinically measured severity was related to decreased adherence to nutritional supplements and digestive medications in a previous study (Llorente et al., 2008). In the previous study, the sample was primarily composed of participants under the age of 20 (62% were under the age of 20 and 29% of were under the age of 10) whereas the current study only recruited participants over the age of 18 (Llorente et al., 2008). The difference in age between the present study and the previous study may partially account for the different associations observed between disease severity and adherence. Overall severity was low in the previous study (Llorente et al., 2008), so the child and adolescent patients may not have had as much experience with CF-related normative disease progression and may have responded to increases in disease severity differently than adults. For instance, children and adolescents may take their medications less often in response to worsening health, believing that normative

decreases in lung function indicate that their treatments are ineffective. This may also help explain why adolescence is a period when adherence is particularly low in individuals with CF (McNamara et al., 2009; Zindani, Streetman, Streetman, & Nasr, 2006). Therefore, the differences between the present study and the previous study which included children and adolescents may reflect age-related differences in treatment behavior and responses to normative changes in health. Future research may benefit from comparing the relationship between disease severity and treatment adherence across different age groups (children, adolescents, and adults) to determine if developmental factors affect how disease severity relates to adherence behaviors.

In measuring the effects of HLC on treatment adherence, participants' perceptions of disease severity were distinguished from clinical measures of disease severity and illness progression (FEV_1 and BMI). This was done because these measures of disease severity were not necessarily expected to be congruent (Abbott, Dodd, & Webb, 1995). Indeed, patients' perception of disease severity were unrelated to BMI and only weakly correlated with $\%FEV_1$. Further, patients' perceptions about the severity of their illness were expected to more strongly predict their health behaviors. However, while FEV_1 and perceived disease severity were included as direct predictors of adherence in each of our models, only perceived severity was tested as a moderator. Therefore, it is unclear which measure of disease severity is a better predictor of adherence behavior in this population. Future research should compare direct and indirect effects of clinically measured and self-reported disease severity on adherence in individuals with CF to determine which has the greater influence.

Other Factors and Adherence

Among the covariates, older age consistently predicted lower exercise adherence concurrently and over time. This may reflect normal age-related differences in physical fitness or normative declines in pulmonary function and their influence on patients' capacity to exercise (Shei, Mackintosh, Peabody Lever, McNarry, & Krick, 2019). Patients recruited from inpatient units were also less adherent to exercise recommendations. This may be due to the fact that inpatients have a reduced capacity to exercise because of their health condition or that inpatients have limited opportunities to exercise or perform other physical activities during hospitalization. Higher BMI was related to greater enzyme therapy adherence. Because this relationship was not observed in the longitudinal model, it is likely that these results are a result of the positive influence of enzyme therapy on BMI.

Comparison of Treatment Adherence Rates

In this study, adherence was moderate and varied across treatments, which is consistent with previous findings (Eakin et al., 2011; Llorente et al., 2008; Quittner et al., 2014). Although it is difficult to make specific comparisons of adherence rates across studies due to measurement differences, several broader patterns emerged. In general, adherence was highest in disease modifying and enzyme treatment domains and lowest in the exercise and respiratory health (including aerosols and ACT) domains. Enzyme therapy and disease modifying treatments involve taking oral medications 2-3 times per day, whereas the treatments in the exercise and respiratory health domains involve lengthier periods of administration. Therefore, these results may reflect differences in treatment complexity consistent with previous observations that less complex and time-consuming treatments are more likely to be completed by patients with chronic illnesses

(Bernard & Cohen, 2004; Claxton, Cramer, & Pierce, 2001; Ingersoll & Cohen, 2008; Richter, Anton, Koch, & Dennett, 2003). In individuals with CF, however, some studies show that overall complexity in treatment regimen is related to higher adherence (Hilliard, Eakin, Borrelli, Green, & Riekert, 2015; Quittner et al., 2014). It is possible that this relationship may be explained by the confound between complexity and disease severity. That is, patients with greater severity may be given more complex treatments and also may be more likely to adhere to their treatments. Therefore, it is important that studies of treatment adherence account for disease severity. Discrepancies in these CF studies may also be due to the previous studies mostly focusing on inhaled pulmonary medications and measuring adherence with medication possession ratio scores derived from patients' prescription records. In sum, the present results suggest that self-reported adherence in individuals with CF is higher for less complex and time-consuming treatments.

Implications

Healthcare providers who serve patients with CF may benefit from a better understanding of the potential role of patients' HLC beliefs in treatment adherence and the attenuating effect of disease severity on the relationship between HLC and treatment adherence in individuals with CF. Our results suggest that Internal HLC is most prevalent in adults with CF, followed closely by Powerful Others HLC. By contrast, participants reported lower rates of Chance HLC beliefs. Given these rates and the unique relationships seen between different measures of HLC, perceived disease severity, and treatment adherence, patients with CF generally appear primed to take control of their condition through adherence behaviors. However, clinicians may further serve patients by

evaluating their specific HLC beliefs and encouraging positive (yet realistic) beliefs about the influence of their adherence actions on their health. Additionally, clinicians should be aware that patients' perceptions of disease severity are not always congruent with clinical measures of severity and should therefore evaluate patients' own beliefs about their condition and work to correct incongruences when they have the potential to impede health maintenance. Internal HLC beliefs, together with perceptions of poorer health, appear to promote greater adherence to treatments whose effects are more immediate (e.g., enzyme therapy). Chance HLC also appears to deter adherence to enzyme therapy when patients' perceptions of severity are low. Therefore, clinicians should encourage patients to adopt Internal HLC beliefs and perceptions of their disease severity that align with clinical measurement in order to increase adherence and improve health outcomes. Greater Internal HLC beliefs and perceptions of disease severity also appear to promote physical exercise, so encouraging these beliefs may increase these behaviors as well. Based on the results of this study, it is unclear what role HLC perceptions have in promoting adherence to other treatments, including those that are aimed at slowing the decline of pulmonary function (e.g., airway clearance therapy). However, previous research suggests that Internal HLC can promote adherence to pulmonary treatments in CF and other chronic illness populations, so these recommendations may also improve patient adherence to these treatments.

Limitations

Some limitations must be considered when interpreting the results of this study. For instance, self-report measures of adherence may be biased due to social-desirability concerns (Kettler et al., 2002; Quittner et al., 2000). This bias may have led to

participants in the study reporting higher adherence than they actually had. In order to combat this bias, a measure of adherence that asked how many times participants missed their treatments was implemented. This measure was used in an attempt to normalize non-adherence and obtain more accurate reports of adherence. However, the validity of this measure compared to more direct questions about adherence is not available. Another potential limitation of this measure of adherence is the calculation of the mean domain scores. Although this approach helped reduce the number of analyses and was guided by theoretical and empirical similarity of the items, it may have obscured meaningful differences in the links between HLC and adherence for specific treatment behaviors. Additionally, the relatively small sample size, while typical for studies with CF patients, may have contributed to decreased power to detect the hypothesized main and interaction effects in the tested models. Further, few studies address adherence to disease modifying medications (likely due to their recency), and the current study was unable to fill this gap due to small number of participants taking these medications. The 3-month period between baseline and follow-up may not have been optimal to detect prospective relationships of HLC and perceived disease severity with adherence.

Further, single measurements of 2-week retrospective adherence may not accurately reflect trends in treatment adherence over time and are subject to problems with patient recall. Weekly measurements of adherence (through diary or pill count) may allow for a better understanding of how HLC and disease severity perceptions predict adherence behaviors over time. Additionally, for treatments whose effects are more gradual, a longer period of data collection may also allow for patients' initial perceptions of disease severity. Therefore, continuous measurement of adherence (over a period of

six months to one year), while costly and time-intensive, may better answer the proposed research questions. Future research should also address the role of HLC in treatment adherence using larger samples and more robust measures of treatment adherence and more points of data collection (perhaps even continues data collection for treatment adherence).

Another possible limitation is the overall measure of perceived severity used in the moderation analyses. Patients' severity perceptions may also be considered in the context of their different symptoms, and it is possible that illness perceptions for different aspects of their health have a greater impact on adherence to different treatments. For instance, patients' perceptions of their digestive health status may be more relevant to adherence to enzyme therapy and nutrition treatment than an overall severity perception. Likewise, patients' perceptions of their pulmonary health may be more likely to predict their respiratory treatment adherence and physical fitness health behaviors. Future research should address the roles of symptom-specific disease severity measures on treatment adherence.

Conclusions

Because treatment adherence is suboptimal in patients with CF, it is important to study predictors of treatment adherence in this population. This is the first study to address both main effects of HLC and their interactions with perceived disease severity in predicting treatment adherence in individuals with CF. Additionally, this study evaluated these relationships across the range of treatment domains, which is necessary because adherence rates differ by treatment in this population and treatment efficacy is likely reliant on the combined influence of patients' treatments. The results suggest that

different HLC domains are related to patient adherence, but some of these relationships depend on patients' perception of disease severity. Specifically, Internal HLC beliefs may predict treatment adherence for patients with higher perceived disease severity and Chance HLC beliefs may predict lower adherence when perceived severity is low. Clinicians may consider patients' perceptions of disease severity as well as their HLC beliefs to encourage greater treatment adherence. Given the inconsistencies between this and other studies in the relationships between HLC, disease severity, and treatment adherence, future studies should continue to evaluate the direct and moderating relationships between these variables. Further, studies should use more robust and standard measures of treatment adherence in order to more accurately evaluate predictors of adherence and compare results across studies.

REFERENCES

Abbott, J., Dodd, M., & Webb, A. (1995). Different perceptions of disease severity and self care between patients with cystic fibrosis, their close companions, and physician. *Thorax, 50*(7), 794-796.

Abbott, J., Dodd, M., & Webb, A. K. (1996). Health perceptions and treatment adherence in adults with cystic fibrosis. *Thorax, 51*(12), 1233-1238.

Affleck, G., Tennen, H., Pfeiffer, C., & Fifield, J. (1987). Appraisals of control and predictability in adapting to a chronic disease. *Journal of Personality and Social Psychology, 53*(2), 273.

Barker, D. H., & Quittner, A. L. (2016). Parental depression and pancreatic enzymes adherence in children with cystic fibrosis. *Pediatrics, 137*(2), e20152296.

Berglund, E., Lytsy, P., & Westerling, R. (2014). The influence of locus of control on self-rated health in context of chronic disease: a structural equation modeling approach in a cross sectional study. *BMC Public Health, 14*(1), 492.

Bernard, R. S., & Cohen, L. L. (2004). Increasing adherence to cystic fibrosis treatment: a systematic review of behavioral techniques. *Pediatric Pulmonology, 37*(1), 8-16.

Bilton, D. (2008). Cystic fibrosis. *Medicine, 36*(5), 273-278.

Bradley, J. M., & Moran, F. (2008). Physical training for cystic fibrosis. *Cochrane Database of Systematic Reviews*(1).

Briesacher, B. A., Quittner, A. L., Saiman, L., Sacco, P., Fouayzi, H., & Quittell, L. M. (2011). Adherence with tobramycin inhaled solution and health care utilization. *BMC Pulmonary Medicine, 11*(1), 5.

Cheng, C., Cheung, M. W.-L., & Lo, B. C. (2016). Relationship of health locus of control with specific health behaviours and global health appraisal: a meta-analysis and effects of moderators. *Health Psychology Review, 10*(4), 460-477.

Claxton, A. J., Cramer, J., & Pierce, C. (2001). A systematic review of the associations between dose regimens and medication compliance. *Clinical Therapeutics, 23*(8), 1296-1310.

Cobb-Clark, D. A., Kassenboehmer, S. C., & Schurer, S. (2014). Healthy habits: The connection between diet, exercise, and locus of control. *Journal of Economic Behavior & Organization, 98,* 1-28.

Craig, H., & Wright, B. (2012). Nonadherence to prophylactic medication: Negative attitudes toward doctors a strong predictor. *Australian Family Physician, 41*(10), 815.

DeLambo, K. E., Ievers-Landis, C. E., Drotar, D., & Quittner, A. L. (2004). Association of observed family relationship quality and problem-solving skills with treatment adherence in older children and adolescents with cystic fibrosis. *Journal of Pediatric Psychology, 29*(5), 343-353.

DiCarlo, L. A., Weinstein, R. L., Morimoto, C. B., Savage, G. M., Moon, G. L., Au-Yeung, K., & Kim, Y. A. (2016). Patient-centered home care using digital medicine and telemetric data for hypertension: feasibility and acceptability of

objective ambulatory assessment. *The Journal of Clinical Hypertension, 18*(9), 901-906.

DiMatteo, M. R., Giordani, P. J., Lepper, H. S., & Croghan, T. W. (2002). Patient adherence and medical treatment outcomes a meta-analysis. *Medical Care,* 794-811.

DiMatteo, M. R., Haskard, K. B., & Williams, S. L. (2007). Health beliefs, disease severity, and patient adherence: a meta-analysis. *Medical Care*, 521-528.

DiMatteo, M. R., Lepper, H. S., & Croghan, T. W. (2000). Depression is a risk factor for noncompliance with medical treatment: meta-analysis of the effects of anxiety and depression on patient adherence. *Archives of Internal Medicine, 160*(14), 2101-2107.

Eakin, M. N., Bilderback, A., Boyle, M. P., Mogayzel, P. J., & Riekert, K. A. (2011). Longitudinal association between medication adherence and lung health in people with cystic fibrosis. *Journal of Cystic Fibrosis, 10*(4), 258-264.

Eddy, M. E., Carter, B. D., Kronenberger, W. G., Conradsen, S., Eid, N. S., Bourland, S. L., & Adams, G. (1998). Parent relationships and compliance in cystic fibrosis. *Journal of Pediatric Health Care, 12*(4), 196-202.

Enders, C. K., & Bandalos, D. L. (2001). The relative performance of full information maximum likelihood estimation for missing data in structural equation models. *Structural Equation Modeling, 8*(3), 430-457.

Grotz, M., Hapke, U., Lampert, T., & Baumeister, H. (2011). Health locus of control and health behaviour: results from a nationally representative survey. *Psychology, Health & Medicine, 16*(2), 129-140.

Guimbellot, J., Solomon, G. M., Baines, A., Heltshe, S. L., VanDalfsen, J., Joseloff, E., . . . Investigators, G. (2019). Effectiveness of ivacaftor in cystic fibrosis patients with non-G551D gating mutations. *Journal of Cystic Fibrosis, 18*(1), 102-109.

Henry, B., Aussage, P., Grosskopf, C., & Goehrs, J.-M. (2003). Development of the Cystic Fibrosis Questionnaire (CFQ) for assessing quality of life in pediatric and adult patients. *Quality of Life Research, 12*(1), 63-76.

Hilliard, M. E., Eakin, M. N., Borrelli, B., Green, A., & Riekert, K. A. (2015). Medication beliefs mediate between depressive symptoms and medication adherence in cystic fibrosis. *Health Psychology, 34*(5), 496.

Hosseini, Z., Aghamolaei, T., & Ghanbarnejad, A. (2017). Prediction of health promoting behaviors through the health locus of control in a sample of adolescents in Iran. *Health Scope, 6*(2).

Ingersoll, K. S., & Cohen, J. (2008). The impact of medication regimen factors on adherence to chronic treatment: a review of literature. *Journal of Behavioral Medicine, 31*(3), 213-224.

Jack, K., McLean, S. M., Moffett, J. K., & Gardiner, E. (2010). Barriers to treatment adherence in physiotherapy outpatient clinics: a systematic review. *Manual Therapy, 15*(3), 220-228.

Janowski, K., Kurpas, D., Kusz, J., Mroczek, B., & Jedynak, T. (2013). Health-related behavior, profile of health locus of control and acceptance of illness in patients suffering from chronic somatic diseases. *PLOS one, 8*(5).

Kardas, P., Lewek, P., & Matyjaszczyk, M. (2013). Determinants of patient adherence: a review of systematic reviews. *Frontiers in Pharmacology, 4*, 91.

Kettler, L., Sawyer, S., Winefield, H., & Greville, H. (2002). Determinants of adherence in adults with cystic fibrosis. *Thorax, 57*(5), 459-464.

Konstan, M. W., & Ratjen, F. (2012). Effect of dornase alfa on inflammation and lung function: potential role in the early treatment of cystic fibrosis. *Journal of Cystic Fibrosis, 11*(2), 78-83.

Lahiri, T., Hempstead, S. E., Brady, C., Cannon, C. L., Clark, K., Condren, M. E., . . . Maguiness, K. (2016). Clinical practice guidelines from the cystic fibrosis foundation for preschoolers with cystic fibrosis. *Pediatrics, 137*(4), e20151784.

Lindgren, B. R., Snyder, M., Sabati, N., Adam, T., Pieczkiewicz, D., & Finkelstein, S. M. (2002). Health locus of control and adherence with home spirometry use in lung transplant recipients. *Progress in Transplantation, 12*(1), 24-29.

Llorente, R. P. A., García, C. B., & Martín, J. J. D. (2008). Treatment compliance in children and adults with cystic fibrosis. *Journal of Cystic Fibrosis, 7*(5), 359-367.

Mautner, D., Peterson, B., Cunningham, A., Ku, B., Scott, K., & LaNoue, M. (2017). How Multidimensional Health Locus of Control predicts utilization of emergency and inpatient hospital services. *Journal of Health Psychology, 22*(3), 314-323.

McNamara, P. S., McCormack, P., McDonald, A. J., Heaf, L., & Southern, K. W. (2009). Open adherence monitoring using routine data download from an adaptive aerosol delivery nebuliser in children with cystic fibrosis. *Journal of Cystic Fibrosis, 8*(4), 258-263.

Myers, L., & Myers, F. (1999). The relationship between control beliefs and self-reported adherence in adults with cystic fibrosis. *Psychology, Health & Medicine, 4*(4), 387-391.

Nafradi, L., Nakamoto, K., & Schulz, P. J. (2017). Is patient empowerment the key to promote adherence? A systematic review of the relationship between self-efficacy, health locus of control and medication adherence. *PLOS one, 12*(10).

Nasr, S. Z., Chou, W., Villa, K. F., Chang, E., & Broder, M. S. (2013). Adherence to dornase alfa treatment among commercially insured patients with cystic fibrosis. *Journal of Medical Economics, 16*(6), 801-808.

O'Sullivan, B. P., & Freeman, S. D. (2009). Cystic fibrosis. *The Lancet, 373*(9678), 1891-1904.

Oermann, C. M., Swank, P. R., & Sockrider, M. M. (2000). Validation of an instrument measuring patient satisfaction with chest physiotherapy techniques in cystic fibrosis. *Chest, 118*(1), 92-97.

Omeje, O., & Nebo, C. (2011). The influence of locus control on adherence to treatment regimen among hypertensive patients. *Patient Preference and Adherence, 5*, 141.

Osterberg, L., & Blaschke, T. (2005). Adherence to medication. *New England Journal of Medicine, 353*(5), 487-497.

Patterson, J. M., Goetz, D., Budd, J., & Warwick, W. J. (1993). Family correlates of a 10-year pulmonary health trend in cystic fibrosis. *Pediatrics, 91*(2), 383-389.

Pender, N. (1996). Health promotion in nursing Practice. 3rd. *Stamford: Appleton & Lange, 251*.

Pereira, L. S., Araújo, L. G., Sampaio, R. F., & Haddad, J. (2011). Factorial analysis of the Multidimensional Health Locus of control scale: form C for elderly. *Brazilian Journal of Physical Therapy, 15*(5), 363-370.

Quittner, A. L., Espelage, D. L., & Drotar, D. (2000). Measuring adherence to medical treatments in childhood chronic illness: Considering multiple methods and sources of information. *Journal of Clinical Psychology in Medical Settings, 7*(1), 41-54.

Quittner, A. L., Zhang, J., Marynchenko, M., Chopra, P. A., Signorovitch, J., Yushkina, Y., & Riekert, K. A. (2014). Pulmonary medication adherence and health-care use in cystic fibrosis. *Chest, 146*(1), 142-151.

Radtke, T., Nolan, S. J., Hebestreit, H., & Kriemler, S. (2015). Physical exercise training for cystic fibrosis. *Cochrane Database of Systematic Reviews*(6).

Richter, A., Anton, S. E., Koch, P., & Dennett, S. L. (2003). The impact of reducing dose frequency on health outcomes. *Clinical Therapeutics, 25*(8), 2307-2335.

Ryan, G., Singh, M., & Dwan, K. (2011). Inhaled antibiotics for long-term therapy in cystic fibrosis. *Cochrane Database of Systematic Reviews*(3).

Shei, R.-J., Mackintosh, K. A., Peabody Lever, J. E., McNarry, M. A., & Krick, S. (2019). Exercise Physiology Across the Lifespan in Cystic Fibrosis. *Frontiers in Physiology, 10*, 1382.

Southern, K., & Barker, P. (2004). Azithromycin for cystic fibrosis. *European Respiratory Journal, 24*(5), 834-838.

Stallings, V. A., Stark, L. J., Robinson, K. A., Feranchak, A. P., Quinton, H., on Growth, C. P. G., . . . Group, A. H. W. (2008). Evidence-based practice recommendations for nutrition-related management of children and adults with cystic fibrosis and pancreatic insufficiency: results of a systematic review. *Journal of the American Dietetic Association, 108*(5), 832-839.

Theofilou, P. (2012). Quality of life and mental health in hemodialysis and peritoneal dialysis patients: the role of health beliefs. *International Urology and Nephrology, 44*(1), 245-253.

Thomas, J., Cook, D., & Brooks, D. (1995). Chest physical therapy management of patients with cystic fibrosis. *Am J Respir Crit Care Med, 151,* 846-850.

Tripahi, M., Asthana, H., & Asthana, A. (2016). Health locus of control and health behaviours in Lung cáncer patients. *International Journal of Indian Psychology, 3*(3), 20-30.

Urquhart, J. (1997). The electronic medication event monitor. *Clinical Pharmacokinetics, 32*(5), 345-356.

Wainwright, C. E., Elborn, J. S., Ramsey, B. W., Marigowda, G., Huang, X., Cipolli, M., . . . Flume, P. A. (2015). Lumacaftor–ivacaftor in patients with cystic fibrosis homozygous for Phe508del CFTR. *New England Journal of Medicine, 373*(3), 220-231.

Wallston, K. A., Strudler Wallston, B., & DeVellis, R. (1978). Development of the multidimensional health locus of control (MHLC) scales. *Health Education Monographs, 6*(1), 160-170.

Wang, J., & Wang, X. (2012). *Structural equation modeling: Applications using Mplus*: John Wiley & Sons.

West, L. M., Theuma, R. B., & Cordina, M. (2018). Health locus of control: Its relationship with medication adherence and medication wastage. *Research in Social and Administrative Pharmacy, 14*(11), 1015-1019.

Williams, J. S., Lynch, C. P., Voronca, D., & Egede, L. E. (2016). Health locus of control and cardiovascular risk factors in veterans with type 2 diabetes. *Endocrine, 51*(1), 83-90.

Xu, W. M., Shi, Q. X., Chen, W. Y., Zhou, C. X., Ni, Y., Rowlands, D. K., . . . Wang, X. F. (2007). Cystic fibrosis transmembrane conductance regulator is vital to sperm fertilizing capacity and male fertility. *Proceedings of the National Academy of Sciences, 104*(23), 9816-9821.

Yankaskas, J. R., Marshall, B. C., Sufian, B., Simon, R. H., & Rodman, D. (2004). Cystic fibrosis adult care: consensus conference report. *Chest, 125*(1), 1S-39S.

Yeung, M., O'Connor, S., Parry, D., & Cochrane, G. (1994). Compliance with prescribed drug therapy in asthma. *Respiratory Medicine, 88*(1), 31-35.

Zindani, G. N., Streetman, D. D., Streetman, D. S., & Nasr, S. Z. (2006). Adherence to treatment in children and adolescent patients with cystic fibrosis. *Journal of Adolescent Health, 38*(1), 13-17.

Zou, H., Tian, Q., Chen, Y., Cheng, C., & Fan, X. (2017). Coping styles mediate the relationship between self-esteem, health locus of control, and health-promoting behavior in Chinese patients with coronary heart disease. *Journal of Cardiovascular Nursing, 32*(4), 331-338.

SOCIAL SUPPORT AND TREATMENT ADHERENCE IN INDIVIDUALS WITH CYSTIC FIBROSIS

by

BENJAMIN EDWIN BURGESS

SYLVIE MRUG

Format adapted for dissertation

Abstract

Objectives: Treatment adherence in individuals with cystic fibrosis (CF) is suboptimal. Social support from various sources (family, friends, significant others) is related to better adherence in other chronic illness populations, with lower depression suggested as a mediator of these relationships. This study examines the effects of social support on treatment adherence with depression as a mediator in adults with CF. ***Methods:*** Adults with CF (n = 123) completed measures of social support from family, friends, and significant others; depressive symptoms; and adherence to common CF treatments over three time points approximately three months apart. ***Analyses:*** Multivariate path models evaluated the direct and indirect relationships between social support and treatment adherence, with depressive symptoms as a mediator. ***Results:*** Contrary to the hypotheses, greater social support from all sources was related to lower adherence in some treatment domains (corticosteroid, diabetes, and nutritional adherence) over time. There was no evidence for an indirect effect of social support on adherence through depressive symptoms. ***Conclusions:*** The results suggest that greater social support is related to lower adherence in adults with CF. Future studies should examine mechanisms that explain the links between social support and lower treatment adherence, such as greater social engagement that reduces available time to complete treatments.

Keywords: Cystic Fibrosis; Chronic Illness; Treatment Adherence; Social Support; Depression

Social Support and Treatment Adherence in Individuals with Cystic Fibrosis

Cystic fibrosis (CF) is a progressive genetic disorder that leads to impairments in pulmonary and gastrointestinal function (O'Sullivan & Freeman, 2009) as well as infertility in most males (Xu et al., 2007). These impairments are caused by blockages in patients' airways, pancreatic ducts, and biliary systems due to the production of abnormally viscous mucus which accumulates in these areas (Bilton, 2008). Recurring bacterial infections result from these blockages, leading to scarring and deterioration of patients' airways and lungs. This leads to declines in pulmonary function and can result in pulmonary failure and need for lung transplant (O'Sullivan & Freeman, 2009). Gastrointestinal impairments disrupt nutritional absorption and lead to malnutrition (O'Sullivan & Freeman, 2009). As a result, CF-patients have trouble maintaining healthy body mass index (BMI) and are often underweight.

To combat these complications and slow health decline, individuals with CF must adhere to complex and time-consuming treatment regimens. These treatments most often include daily medications (e.g., antibiotics, corticosteroids, and disease-modifying medications), dietary recommendations (e.g., pancreatic enzyme therapy, high caloric diets, and supplements), airway-clearance techniques (e.g., use of the Vest), and the monitoring and treatment of secondary disorders (e.g., blood-glucose monitoring and insulin for CF-related diabetes). Patients' clinical care team monitors disease progression at periodic visits multiple times a year, adjusting treatments to meet patients' needs.

Treatment Adherence

Treatment adherence can be measured using a variety of methods, each with different strengths and weaknesses. It is important to consider these strengths and weaknesses because they affect the validity of research on adherence. For instance, self-report measures of treatment adherence are widely used due to their low cost and overall convenience. However, these measures of adherence are subject to social-desirability bias (overestimating adherence) and problems with recall, so they can be inaccurate (Kettler, Sawyer, Winefield, & Greville, 2002; Quittner, Espelage, & Drotar, 2000). More accurate techniques for measuring adherence include electronic monitoring systems, collection prescription records, and internal monitoring and blood assays. However, these methods are generally more costly and time-consuming, do not apply to all treatments, and are sometimes subject to equipment failure (DiCarlo et al., 2016; McNamara, McCormack, McDonald, Heaf, & Southern, 2009; Urquhart, 1997; Yeung, O'Connor, Parry, & Cochrane, 1994). Complications may also arise when attempting to compare treatment adherence across studies which used different methods of measuring adherence. Results regarding treatment adherence in individuals with CF are often difficult to compare because of differences in measuring and scoring adherence. For instance, some studies report adherence to different treatments separately while others collapse adherence into categories or global measure of adherence.

Despite limitations inherent in comparing treatment adherence across studies, some general conclusions may be drawn about adherence in individuals with CF. For instance, although evidence shows that the most common treatments for CF are effective at slowing disease progression (Bradley & Moran, 2008; Guimbellot et al., 2019;

Konstan & Ratjen, 2012; Radtke, Nolan, Hebestreit, & Kriemler, 2015; Ryan, Singh, & Dwan, 2011; Southern & Barker, 2004; Stallings et al., 2008; Thomas, Cook, & Brooks, 1995; Wainwright et al., 2015) and that adherence to these treatments predicts better pulmonary and gastrointestinal health outcomes (Barker & Quittner, 2016; Briesacher et al., 2011; Eakin, Bilderback, Boyle, Mogayzel, & Riekert, 2011; Eddy et al., 1998; Osterberg & Blaschke, 2005; Patterson, Goetz, Budd, & Warwick, 1993), overall adherence in this population is suboptimal (Eakin et al., 2011; Llorente, García, & Martín, 2008; Nasr, Chou, Villa, Chang, & Broder, 2013; Quittner et al., 2014). Further, adherence appears to differ by treatment. Broad research on treatment adherence suggests that patients are less likely to adhere to complex and time-consuming treatments (Ingersoll & Cohen, 2008), and this appears to be somewhat true for individuals with CF (Llorente et al., 2008). For instance, for pulmonary medications (treatments which are often administered using a nebulizer), medication possession ratio scores (calculated as a percentage of prescribed medications that patients obtained from the pharmacy) ranged from 49% to 76% in one study of children and adults with CF (Eakin et al., 2011), and only 62% of patients in another study were adherent to respiratory medications (Llorente et al., 2008). Further, in the latter study, adherence to chest physiotherapy, which is often time-consuming and limits mobility during application, was only 41% (Llorente et al., 2008). For digestive medications, a treatment which involves taking a prescribed number of pills during meals, 88% of patients were adherent (Llorente et al., 2008).

Social Support and Treatment Adherence

Various personal and treatment factors have been evaluated as predictors of treatment adherence in patients with chronic illness. For instance, social support has been

considered as an important predictor of individual health, in part due to its links with health behaviors such as treatment adherence. In this research context, social support can be broadly defined as the provision of social resources to an individual with a given illness (generally by friends, family, and health providers) and may be influenced by the structure of the patient's environment (e.g., marital status, living arrangement, and social media; Langford, Bowsher, Maloney, & Lillis, 1997; Uchino, Cacioppo, & Kiecolt-Glaser, 1996). Social support may affect health and health behavior through a number of mechanisms. For instance, all forms of support may reduce stress for the patient which could circumvent harmful coping mechanisms (e.g., smoking and excessive drinking) and even promote general health behaviors (Cohen, 2004). This stress-buffering effect of social support may promote better psychosocial outcomes through the reduction of depression and anxiety. Indeed, evidence suggests that social support is related to reduced depression and anxiety symptoms in healthy individuals (Santini, Koyanagi, Tyrovolas, Mason, & Haro, 2015), as well as patients with CF (Anderson, Flume, & Hardy, 2001). Depression is associated with decreased health behaviors, including treatment adherence in chronic illness populations generally (DiMatteo, Lepper, & Croghan, 2000; Jack, McLean, Moffett, & Gardiner, 2010) and in individuals with CF specifically (Knudsen et al., 2016; Smith, Modi, Quittner, & Wood, 2010). Thus, improving social support would be expected to decrease depressive symptoms and increase adherence behavior. Additionally, social support may help facilitate health behaviors by providing tangible resources, such as assisting with their treatment or providing financial assistance.

In general, higher social support appears to facilitate better treatment adherence. According to one meta-analysis of research spanning from 1948 to 2001, higher social

support from various sources and in various forms (instrumental, structural, emotional, etc.) predicted greater adherence to medical treatment in patients with chronic illness (DiMatteo, 2004). However, relatively little research has tested the relationship between different forms of social support and treatment adherence in individuals with CF. Further, the majority of this research has examined the relationship between family support and adherence in children and adolescents, with little research conducted in adults with CF. What evidence is available suggests that family support (higher family cohesion, better quality of relationships, and greater family adaptability) is associated with higher adherence and greater attendance of periodic clinic visits (DeLambo, Ievers-Landis, Drotar, & Quittner, 2004; Eddy et al., 1998; Patterson et al., 1993).

It is less clear what impact social support from friends, spouses, and patients' care teams has on adherence for individuals with CF. As in other illnesses, these sources of support may be expected to facilitate greater adherence. However, alternative effects may be present in individuals with CF. Kettler and colleagues (2002) suggest that while a good relationship with one's CF care team may lead to trust and good communication over years of care (both of which can facilitate treatment adherence), it may also lead to team members omitting important information they have already discussed with the patient even if reviewing that information would be beneficial.

The relationship between other social factors (e.g., friendship quality and peer conformity) and treatment adherence may inform how social support from friends and peers could relate to treatment adherence in individuals with CF. For instance, some individuals with CF (6-40% of participants) report that treatments are neglected because they interfere with family and social commitments (Llorente et al., 2008; White, Stiller,

& Haensel, 2007). If individuals with CF spend time developing and maintaining relationships with friends, they may perceive high social support from friends. However, this increased time spent with friends might also cause them to neglect some of their treatments, especially those that are most time-consuming. Consistent with these speculations, higher levels of positive friendship qualities (e.g., companionship, intimacy, and support) within friendships of adolescents with CF were related to lower adherence (Helms, Dellon, & Prinstein, 2015). The authors suggested that positive experiences with friends may be associated with spending more time with friends and thus having less time for treatments. While this explanation has not been evaluated in further research, spending time with friends may similarly foster perceptions of higher social support. Therefore, social support from friends might be expected to be related to lower adherence in individuals with CF. In a qualitative study of children and adolescents with CF, social pressure to conform to peer behavioral norms and skipping treatments to spend time with friends were among key themes that arose as barriers to treatment adherence (Foster et al., 2001). Specifically, participants reported feeling embarrassed and self-conscious, or even being mocked, when taking medications in front of their peers. Older participants reported intentionally skipping treatments to spend time with friends. In another study of barriers to treatment adherence in adolescents with CF, 33% of participants avoided performing treatments in public and 25% chose to spend time with friends instead of performing treatments at some point (Bregnballe, Schiøtz, Boisen, Pressler, & Thastum, 2011). It is unclear if social interactions would similarly take up time for adults with CF, reducing adherence, or if the positive resources provided by social support from friends and peers would lead to increased adherence. Further, it is not known whether adults with

CF have the same reservations about displaying their illness around their friends and whether they may prioritize their health over spending time with friends (or find a way to accomplish both goals). More research is needed on the relationship between social support, friendship engagement, peer conformity, and adherence in adults with CF. However, the current study will focus on the role that social support (from friends and other sources) has in predicting treatment adherence.

Given the evidence for the relationship between social support and treatment adherence in adolescents with CF and other chronic illness groups, social support may influence treatment adherence in adults with CF as well. However, there is a lack of research addressing the role of social support in treatment adherence in adults with CF. Further, little is known about sources of support other than family in individuals with CF, some of which may have the potential to uniquely affect adherence in adults (e.g., spousal support). Longitudinal research designs have not often been utilized in this area of research but are important in determining the direction of associations between social support and adherence.

Aims and Hypotheses

The current study addresses gaps in the literature by aiming to determine if social support is related to treatment adherence in adults with CF concurrently and over time. Specifically, this study examines whether the sources of social support (i.e., family, friends, and significant other) play a role when predicting treatment adherence to different treatments, and if reduced depression can partially explain these relationships. Social support from family, friends, and significant other is hypothesized to predict greater adherence across treatments. Further, depression is hypothesized to mediate these

relationships, such that greater social support will predict fewer depressive symptoms, which in turn will predict greater adherence. Finally, because adherence differs by treatment type and these different types of adherence may be differentially related to social support and depression, adherence to different treatments is examined separately in this study.

METHODS

Participants and Procedures

Participants for this study were recruited from outpatient pulmonary clinics and inpatient units at the University of Alabama at Birmingham Hospital and Children's Hospital of Alabama. These units collectively serve about 230 adults with CF. Eligibility criteria for the study included a diagnosis of CF and age of 18 years or older. Participants were asked to complete three surveys administered approximately three months apart. Of 176 patients approached, 158 (90%) agreed to participate and 123 (70%) completed the baseline survey (T1). Of the 123 who completed the baseline survey, 111 (90%) completed the second survey (T2) and 98 of those (88%) completed the third survey (T3). Participants had a mean age of 31.8 years (SD=11.4 years; age range: 19-67 years), 47% were male, 93% were White, and 7% were African American.

The Institutional Review Board approved all study procedures. Participants provided written informed consent during recruitment and later completed online or paper questionnaires (data collection was conducted during 2016 and 2017). They were compensated for their time with a $30 Visa gift card for each questionnaire completed.

Measures

Treatment Adherence. Treatment adherence was measured at all time points using a modified version of the Treatment Adherence Questionnaire-CF (Quittner et al., 2000). This questionnaire evaluates patient adherence to 16 common treatments that CF-

patients complete. For each treatment, participants indicated how often they missed the treatment on a 7-point scale (1 – *Not at All* to 7 – *3 or more times per day*). Higher scores indicate higher non-adherence. Participants' medical records were used to screen their responses to treatments where prescription information was available. If a participant responded to a question about a medication that they had not been prescribed at the time they completed the questionnaire, their response was coded as missing because their adherence to that treatment was not applicable. Complete prescription information for oral and inhaled antibiotics was unavailable, so adherence scores for these items were omitted from the study. Principal components analysis (PCA) was attempted to reduce the 14 remaining items into fewer components for the study analyses, but high missingness (i.e., only 4 cases had responses for every treatment item) prevented the PCA from being conducted. Instead, the 14 items were grouped into clusters based on theoretical similarity and high bivariate correlations ($r \geq .50$). See *Table 2.1* for bivariate correlations among the individual adherence items. Seven treatment domains (five considered CF-specific and two considered broad health behaviors) were identified using this method. These domains included: 1) respiratory care to open and clear airways (airway clearance therapy and aerosols to thin mucus, clear mucus, and open airways; 4 items, $\alpha = .94$, .93 and .94); 2) respiratory care to address inflammation (inhaled corticosteroids; single item); 3) nutritional care (nutritional supplements, snacks, and meals; 3 items, $\alpha = .71$, .81, and .73); 4) diabetes care (insulin and blood glucose monitoring 2 items, $r = .71$, .35, and .64); 5) pancreatic enzyme therapy (vitamins and enzymes; 2 items, $r = .74$, .71, and .70); 6) disease modifying medications (single item); and 7) exercise (single item). Mean scores were calculated for each treatment domain and

reverse-coded so that higher scores indicated greater adherence. These composite treatment domain scores comprised all adherence items except for inhaled and oral antibiotics.

Social Support. Social support was assessed at T1 using the Multidimensional Scale of Perceived Social Support (Zimet, Dahlem, Zimet, & Farley, 1988), a 13-item questionnaire that measures three dimensions of perceived social support: family (e.g., *My family really tries to help me*), friends (e.g., *I count on my friends when things go wrong*), and significant other (e.g., *There is a special person who is around when I am in need*). The items in this measure largely address functional support. Participants indicated their agreement with each item using a 5-point scale (1 – *Rarely or Never* to 5 – *Always*). Scores were computed for each domain by averaging the items. Reliability was excellent for each domain (family: $\alpha = .93$, friends: $\alpha = .95$, significant other: $\alpha = .96$). Participants also indicated how many people lived in their household (structural support) when informed consent was obtained.

Depressive Symptoms. Symptoms of depression were assessed at T1 and T2 using the 6-item depression subscale of the Brief Symptom Inventory 18 (BSI-18), a shortened form of the BSI (Derogatis & Melisaratos, 1983). Responses to items from the subscale (e.g., *How much were you distressed by feelings of worthlessness?*) were made on a 5-point scale (1 – *Not at all* to 5 – *Extremely*). Items were averaged, with good reliability at baseline ($\alpha = .88$) and Time 2 ($\alpha = .91$).

Demographics. Demographic information (i.e., gender, household income level, marital status, education, and age) was collected from participants after informed consent

was obtained. Recruitment location (inpatient vs. outpatient) and clinic location type (adult, child, or transition clinic) were recorded.

Statistical Analyses

Preliminary Analyses. Descriptive statistics were computed for demographics and variables of interest. Sample representativeness was addressed by comparing participants to those who declined participation on available demographic variables (i.e., age and gender) using independent samples t-tests and chi-square tests of independence. Participants recruited from inpatient units and outpatient clinics were compared on demographics and variables of interest. Attrition analyses compared those who did vs. did not complete the follow-up questionnaires at T2 and T3 on all demographic and baseline variables. Changes in treatment adherence over the three time points of the study were evaluated using paired samples t-tests. Bivariate correlations were computed for all demographics and variables of interest, including stability of adherence measures over time. Finally, assumptions of the main analyses (normality, homoscedasticity, and multicollinearity) were tested.

Primary Analyses. Multivariate path models, conducted in Mplus version 7.11, were used to evaluate the relationships between social support, depression, and treatment adherence. The first model evaluated the cross-sectional main effects of social support on treatment adherence. The three social support subscales (family, friends, and significant other) measured at baseline were included as predictors of six adherence composite scores at baseline. Adherence to disease modifying medications was not modeled due to the small number of individuals reporting this type of adherence (n = 28-30). Covariates included demographic variables (age, marital status, household income, and number of

people in participant's household) that were related to model variables. A second model evaluated the longitudinal main effects of social support on treatment adherence. Baseline measures of each social support subscale were included as predictors of six adherence composite scores at Time 3, adjusting for Time 2 adherence as well as demographic variables that were related to model variables.

The third model tested the indirect effects of baseline social support on treatment adherence at Time 3 through depression at Time 2. Baseline measures of each social support subscale were included as predictors of depression at Time 2 and the six adherence composite scores at Time 3, with Time 2 depression also predicting Time 3 treatment adherence (see Figure 2.1). Due to the complexity of the models and modest sample size, separate models were fitted for each adherence outcome. Covariates included demographic variables (age, marital status, household income, and number of people in participant's household) that were related to model variables as determined by bivariate correlation. Additionally, previous levels of adherence (Time 2) and depressive symptoms (Time 1) were controlled for in the mediation model. The indirect effects from social support to adherence through depression were tested using bias-corrected bootstrapping with 5000 resamples, based on current recommendations (Preacher & Hayes, 2008; Rucker, Preacher, Tormala, & Petty, 2011). This procedure does not assume normality of sampling distributions of the indirect effects and can be used with small samples.

RESULTS

Preliminary Analyses

Descriptive statistics for demographic and model variables can be found in *Table 2.2*. The average friends support (M = 3.91) was lower than family (M = 4.35, $t(113)$ = 5.07, $p < .001$) and significant other support (M = 4.34, $t(113)$ = 3.58, p = .001). However, all social support scores were generally high, with average scores for family and significant other support falling between *much of the time* and *always*, and average scores for friends support falling between *sometimes* and *much of the time*. Depressive symptoms were generally low (Baseline M = 1.53, Time 2 M = 1.52), with the averages falling between *not at all* and *a little bit*. Adherence varied by treatment. Average adherence was between 5 and 7 for most adherence measures (baseline M = 5.43-6.45, Time 3 M = 5.80-6.70), though average exercise adherence was slightly lower (M = 4.96). This indicates that participants reported missing their treatments *1-2 times per week* to *not at all* on average. Further, participants' adherence scores were negatively skewed except for exercise adherence. Of participants prescribed each treatment, 17% to 70% reported some non-adherence at baseline and 18% to 69% reported some non-adherence at Time 3.

Comparisons of participants and non-participants indicated that individuals who completed the baseline survey were significantly older (M_{age} = 32.0 years) than non-participants (M_{age} = 27.7 years), $t(148.340)$ = 2.85, p = .005, and more likely to be

females, χ^2 (1) = 4.14, p = .042. Participants who were recruited from inpatient hospitals exercised less at baseline than those recruited from outpatient clinics, t(111) = -2.65, p = .009. Attrition analyses indicated that participants with lower levels of education were more likely to drop out by Time 2 (p < .05). Further, participants who completed questionnaires at all 3 time points had higher baseline friends social support (M = 4.0 vs M = 3.4) and were significantly older (M_{age} = 32.9 vs M_{age} = 27.9) than those who did not complete a survey for each time point (p < .05). Paired samples t-tests indicated that exercise adherence increased (M = 5.0 vs 5.5) from baseline to Time 2, and disease modifying medication adherence increased (M = 6.3 vs 6.7) from baseline to Time 3 (p < .05). Depressive symptoms and other adherence measures did not change significantly from baseline to Time 2 and Time 3 or from Time 2 to Time 3.

See *Table 2.3* for bivariate correlations among each social support subscale, depressive symptoms, and treatment adherence domain scores. Greater family, friends, and significant other social support were each related to higher adherence in one or more treatment domains at baseline (r = .20 to .32, p < .05), but only baseline friends social support was related to greater adherence at Time 3 (exercise adherence, r = .21, p = .047). Each baseline social support domain was moderately correlated with fewer depressive symptoms at baseline and Time 2 (r = -.29 to -.50, p < .01). Baseline and Time 2 depressive symptoms were also related to lower adherence in multiple treatment domains at baseline and Time 3 (r = -.19 to -.40, p < .05).

Normality was violated for each treatment domain score. Therefore, maximum likelihood estimation with robust standard errors (MLR), which is robust to violations of normality, was used in all models. No other major assumptions were violated.

Primary Analyses

Demographic covariates in the primary analyses included age, household income, marital status (married vs. not married), and number of people in household, because they were correlated with multiple predictor and outcome variables. See Table 2.4 for the standardized regression coefficients from the cross-sectional multivariate model testing the main effects of social support on adherence. After controlling for relevant demographic covariates, significant other social support predicted higher adherence to pancreatic enzymes (β = .26, p = .003). No other significant pathways between the social support measures and adherence emerged. Among the covariates, older age predicted lower corticosteroids adherence (β = -.43, p = .001) and lower exercise adherence (β = -.45, p < .001), greater household income predicted higher exercise adherence (β = .32, p = .002), and being married predicted higher airway clearance therapy adherence (β = .23, p = 020).

See *Table 2.5* for standardized regression coefficients from the longitudinal multivariate model testing the main effects of baseline social support on adherence at Time 3. After controlling for baseline adherence, time between baseline and Time 3, and relevant demographic variables, baseline friends support predicted lower diabetes care adherence at Time 3 (β = -.29, p = .005), and baseline significant other social support predicted lower adherence to corticosteroids (β = -.30, p = .006). No other significant pathways between the social support measures and follow-up adherence emerged. Among the covariates, more people living in participant's household at baseline predicted lower adherence to airway clearance therapy (β = -.38, p = .001) and lower nutritional adherence (β = -.18, p = .041); greater baseline household income predicted greater

airway clearance therapy adherence (β = .39, *p* = .001) and greater nutritional adherence (β = .31, *p* = .030); and older age predicted lower exercise adherence (β = -.30, *p* = .031).

See *Table 2.6* for the standardized regression coefficients from the mediation model testing the indirect effect of baseline social support on Time 3 treatment adherence through Time 2 depressive symptoms. After controlling for relevant demographic covariates and baseline depressive symptoms, none of the social support dimensions predicted depressive symptoms at Time 2. Further, after controlling for demographic covariates and Time 2 treatment adherence, only higher family social support at baseline predicted lower nutritional adherence at Time 3 (β = -.26, *p* = .047). None of the baseline social support dimensions predicted adherence for any other treatment domain at Time 3 directly or indirectly through Time 2 depressive symptoms. Depressive symptoms at Time 2 predicted lower nutritional care adherence at Time 3 (β = -.23, *p* = .029). Among the covariates, baseline household income predicted greater airway clearance therapy adherence at Time 3 (β = .40, *p* = .005) and greater nutritional adherence (β = .32, *p* = .046); more people living in participant's household at baseline predicted lower airway clearance therapy adherence at Time 3 (β = -.38, *p* = .002); and higher baseline age predicted lower exercise adherence at Time 3 (β = -.31, *p* = .040).

DISCUSSION

This study examined the relationships between social support and adherence to routine treatments over a 6-month period in adults with CF. The study further evaluated the mediating effect of depressive symptoms in this relationship. Different sources of social support (family, friends, and significant other) were measured, and each was expected to relate to higher overall adherence. In investigating these relationships, this study also evaluated the potential indirect effects of social support through depressive symptoms. Higher social support was expected to be related to fewer depressive symptoms at 3-month follow-up and that fewer depressive symptoms would be related to increased adherence at 6-month follow-up. However, only friends social support was related to treatment adherence. Specifically, friends support was related to lower adherence to diabetes treatments over time. Additionally, greater depressive symptoms were related to lower adherence in the nutritional domain over time.

Social Support and Adherence

Social support from family, friends, and significant other was related to nutritional, corticosteroid, and diabetes adherence, respectively. Specifically, social support from each of these sources was related to lower adherence over time. Additionally, having more people living in participants' household was related to lower adherence to airway clearance therapy over time. These results echo those reported in previous studies which suggest that various social influences (e.g., family and friend

engagement, friendship quality, and peer conformity) from family and friends can reduce adherence in adolescent and individuals with CF (Bregnballe et al., 2011; Foster et al., 2001; Helms et al., 2015; Llorente et al., 2008; White et al., 2007). It is possible that spending more time with friends may increase individuals' perceptions of social support from friends, but it may also interfere with their adherence behavior by reducing the time they have to complete their treatments. Further, individuals with CF may experience problems with social conformity related to their illness when spending time with friends. For instance, they may feel self-conscious or uncomfortable taking their medications in front of their peers or in other social situations because this brings attention to their illness. Thus, individuals with CF may neglect treatments when spending time with friends, leading to both higher perceptions of social support and lower treatment adherence. Indeed, in previous studies adolescents reported sometimes neglecting treatments to spend time with friends (Bregnballe et al., 2011; Foster et al., 2001; George et al., 2010). The results of the current study suggest that peer conformity or family and friend engagement may interfere with adherence in adults with CF as well. However, the current study did not measure peer conformity, or the amount of time participants spent with friends and family, so future research should include these variables to better understand the relationships between social support and treatment adherence.

In the current study, friends social support was related to lower adherence to diabetes treatment, perhaps because patients may be uncomfortable completing blood glucose monitoring and taking their insulin while spending time with friends. Additionally, patients may not want to measure glucose levels and take medications subcutaneously around others (especially in public spaces), because of their association

with blood and the perceived or actual risk of infection. Further, patients may not have access to treatment materials when spending time with friends (e.g., in public or at a friend's house). For instance, insulin must be refrigerated, so if patients plan to take this medication while spending time with friends, they must be able to properly store it during this time. This may not be possible in public places, and patients may not want to store their medication in friends' refrigerator because it may bring unwanted attention to their illness. Future research should evaluate the amount of time patients spend with friends and family as well as their attitudes about sharing their health status and performing treatments around others in order to determine if and how these factors relate to patient adherence.

The present study also suggests that living with more people may disrupt adherence to airway clearance therapy and nutritional treatments. Airway clearance therapy is very time consuming, so living in a household with multiple people may prevent patients from having the time or space to complete treatments as often as necessary. For instance, social interaction with family members may distract patients from this treatment. Moreover, family commitments, such as caring for children, may take time away from airway clearance therapy and other time-consuming treatments (e.g., neglecting meals while caring for children). The latter influence may be more relevant for adults with CF than for children and adolescents with CF. Patients living with others may also have less control over what meals are prepared, which may affect their eating behavior. Future research should evaluate the relationship between treatment adherence and cohabitation with friends or family (with respect to time and space management) and the role that family responsibilities may play in this relationship. Future research should

consider the amount of time patients spend with friends and family as well as their attitudes about sharing their health status and performing treatments around others in order to determine if and how these factors relate to patient adherence.

Family social support was related to lower nutritional treatment adherence over time in the current study. This contradicts previous studies which have found associations between family support and better treatment adherence and other health behaviors in individual with CF (DeLambo et al., 2004; Eddy et al., 1998; Patterson et al., 1993). However, for two of these studies (DeLambo et al., 2004; Eddy et al., 1998), only cross-sectional associations were evaluated, so the direction of the relationships is impossible to determine. Perhaps family support and treatment adherence are bi-directionally related, and adherence facilitates social support or alters perceptions of social support through some other mechanism (e.g., by improving health-related quality of life).

In the present study, significant other social support was related to lower adherence to corticosteroids over time. No other studies have addressed the role of significant other social support in predicting adherence in individuals with CF. A meta-analysis of the links between social support and adherence behaviors in various illness groups suggests that married individuals are more adherent to medications than single individuals (DiMatteo, 2004). The results from the current study showing that being married was related to greater concurrent adherence to airway clearance are consistent with these meta-analytic results. However, marital status does not indicate the quality of a marriage or individuals' perceptions of support from their spouse, so the results of the meta-analysis are not directly comparable to the association between significant other support and lower corticosteroid adherence. In a study with individuals with diabetes,

higher quality of marriage was related to better concurrent dietary and exercise self-care, but again the direction of these effects cannot be determined in this cross-sectional study (Trief, Ploutz-Snyder, Britton, & Weinstock, 2004). Further, the focus of the other studies was on marital relationships, but in this project lower corticosteroid adherence was related to higher significant other social support, which included support from non-spousal significant others. For participants who are dating but not married to a partner, this relationship may be more like their other friendships, and spending time with their partner may lead to lower adherence due to embarrassment or not wanting to draw attention to their illness. Future research should evaluate differences in the effects of dating and marital relationships on treatment adherence in individuals with CF.

In the present study, social support from family, friends, and significant others were each correlated with greater concurrent adherence to one or more treatments (airway clearance therapy, nutritional care, diabetes care, and enzyme therapy), and each source of support was related to greater airway clearance therapy. Further, significant other social support predicted greater concurrent pancreatic enzyme therapy while controlling for other related factors. Given these concurrent associations and lack of prospective relationships between social support and changes in adherence, it is possible that treatment adherence leads to increased social support over time. For instance, if patients are sufficiently adherent to their treatments, their health condition is likely improved (compared to if they are not adherent), allowing them to devote more time and effort to their social relationships. Alternatively, both social support and adherence may result from some other variable or variables (e.g., psychosocial adjustment, disease severity, engagement with other responsibilities, etc.). Future studies should evaluate the

bidirectional relationships between social support and treatment adherence over time, as well as other possible causal factors that may help explain the associations between social support and adherence.

Social support was expected to predict greater adherence behaviors indirectly through reduced depressive symptoms. This indirect relationship was not supported by the results of the current study. No other studies have addressed this indirect effect in chronic illness populations, but evidence suggests that social support is related to lower depression, concurrently and prospectively, in healthy individuals (Santini et al., 2015). In individuals with CF specifically, greater social support has also been related to lower concurrent depressive symptoms (Anderson et al., 2001). However, social support was not related to changes in depressive symptoms over time in the current study. These incongruent results may be due to differences in study design. For instance, the relationship between social support and depressive symptoms was evaluated using longitudinal data in this study, whereas Anderson et al. utilized a cross-sectional design. Therefore, the results of the previous study may be explained by fewer depressive symptoms leading to higher social support or the influence of other variables. Further, the current study controlled for a number of relevant variables (age, marital status, household income, and number of people in participants' household) when evaluating the longitudinal relationship between social support and depressive symptoms. It is unclear if the previous study accounted for these or other variables which may have affected the significance of the relationship observed in the study (Anderson et al., 2001).

While perceived social support from family, friends, and significant other was generally high in the present study, friends support was significantly lower on average.

This contrasts with reports of healthy individuals showing similar levels of social support across family, friends, and significant others (Zimet et al., 1988). Developmental processes may account for the differences across each source of support in the present study compared to Zimet et al. The sample from this previous study was comprised of college students (ages 17-22) (Zimet et al., 1988), so their level of friend support would be expected to be comparable to, if not higher than, support from other sources. By contrast, the current study was composed of young adults (ages 19-67), many of whom may not have as much time to spend with friends as young adults do.

However, friends support may also be lower than family and significant other support because illness factors (time-consuming treatments, negative health, and hospitalization periods) prevent individuals with CF from devoting time to developing and maintaining friendships. This is seen in adolescents with CF and other chronic conditions who face the risk of social isolation due to illness-related absences from school and extracurricular activities (Yeo & Sawyer, 2005). Additionally, this disruption of normal peer interaction at an early age may affect social development of individuals with CF from childhood to adulthood. Compared to healthy children, children with CF have more difficulties with social adjustment related to friendships (Kostakou et al., 2014). Perhaps these difficulties persist into adulthood and disrupt patients' ability to develop new friendships. Additionally, individuals with CF may have a stronger bond with immediate family and romantic partners and receive more support from these sources because of their current or past proximity to patients. Specifically, individuals with CF may have a more developed relationship with parents and siblings than friends because their family members are able to spend more time with them when they are sick

and have helped care for them throughout their childhood and adolescence. Further, individuals with CF may feel more supported by a partner or spouse because they live together in a committed relationship and interact daily.

Depressive Symptoms and Adherence

In the present study, participants with more depressive symptoms were less likely to adhere to nutritional recommendations (eating regular meals, dietary supplements, and snacks). Depression is generally characterized by decreases in motivation which affect normal and illness-related health activities (e.g., treatment adherence), as well as physical and emotional health, appetite, and dietary behaviors (American Psychiatric Association, 2013; DiMatteo et al., 2000; Jack et al., 2010; Penninx, Milaneschi, Lamers, & Vogelzangs, 2013). The results of the present study are consistent with research illustrating that more depressive symptoms are related to lower levels of treatment adherence, broadly in individuals with chronic illness (DiMatteo et al., 2000) and specifically in individuals with CF (Knudsen et al, 2016; Smith et al., 2010). For dietary concerns specifically, depression is associated with changes in appetite. For instance, depression is commonly associated with increases and decreases in appetite as well as weight gain and loss in healthy individuals, although these symptoms and outcomes are more prominent in adolescents than adults (Rice et al., 2019). In adolescent and young adults with CF, depression is associated with a decrease in BMI (Snell, Fernandes, Bujoreanu, & Garcia, 2014), which may result from changes in eating behavior, as the current study suggests. In individuals with CF, depression occurs at 2-3 times the rate it occurs in healthy individuals (Quittner et al., 2014), so its potential effect on appetite and eating behaviors can affect this population disproportionally. Additionally, loss of

appetite and subsequent weight loss is particularly problematic for individuals with CF because impaired nutritional absorption requires pancreatic enzyme therapy and a high calorie diet in order to maintain healthy body weight (Smyth & Rayner, 2017).

Implications

Healthcare providers who serve individuals with CF should be aware of social influences that can affect their patients' treatment adherence. In addition to the positive impact that social support can have on patients' lives, clinicians should consider the potential negative effects that may result from interactions with friends and family. Specifically, the current study suggests that closer relationships with friends (receiving emotional and function support) may reduce adherence to some treatments, particularly those that are time consuming or that are difficult or uncomfortable to perform in public. Clinicians may encourage their patients to make time for their medications when socializing or encourage them to communicate to friends the importance of taking their medications, as well as when and how often they should be administering their treatments. To address the potential adherence challenges that patients living with others may face, clinicians can work with these patients to develop and implement strategies for meeting adherence goals. For instance, clinicians and patients can identify relevant household barriers to adherence and brainstorm ways of overcoming these barriers, discussing the outcomes at future clinic visits. Given the increased prevalence of depression in individuals with CF, clinicians should also consider the effects that depression may have on adherence to dietary recommendations, as well as patients' nutritional outcomes. Clinicians could evaluate their patients' mental health status (e.g., screening for depression) and refer patients to mental health services if necessary. This

could serve as a preventive measure for avoiding poor nutritional outcomes that may otherwise result from psychosocial adjustment problems. Additionally, clinics that serve individuals with CF can incorporate mental health services and professionals into their routine care in order to address this and other mental health concerns.

Limitations

There are some limitations in the current study which must be discussed. Self-report measures were used for main variables, including treatment adherence, social support, and perceived disease severity. This may be problematic for some of these measures. For instance, self-report measures of adherence can introduce bias due to social-desirability concerns (Kettler et al., 2002; Quittner et al., 2000). This may have led to participants over-reporting adherence in the current study, which could affect the validity of the findings. In order to avoid this social-desirability bias problem, the phrasing of the treatment adherence questions was altered to normalize non-adherence. Specifically, the treatment adherence measure was modified to ask participants how often they missed each treatment (as opposed to how often they performed each treatment), because this was expected to result in more accurate reports of adherence. However, the validity of this measure of adherence is unknown. The use of mean domain scores for adherence is another potential limitation of the current study. Theoretical and empirical similarity of the items in each domain drove the creation of each domain cluster, and combining items into meaningful clusters helped reduce the number of analyses. However, this approach may have prevented the detection of unique relationships between social support and adherence to individual treatments. Additionally, the relatively small sample likely may have contributed to a reduced power to detect smaller-

sized relationships between social support, depression, and treatment adherence. Further, small sample size and model complexity prohibited the testing of multiple adherence outcomes in the same mediation model. Therefore, these models did not control for adherence across other domains. However, it is important to note that the relatively small sample size is typical for studies conducted with CF patients. Additionally, the current study could not evaluate the relationships between social support and adherence to disease modifying medications due to the small number of participants taking these medications.

Patients' care teams play an important supportive role in their lives, likely influencing adherence behaviors and psychosocial outcomes. However, the current study did not measure this source of support and thus could not determine its role in adherence to different treatments. Additionally, this study used a measure of general perceived social support. Measuring social support specific to CF may have been more relevant to treatment adherence. For instance, perhaps illness specific support from patients' family, friends, and significant others (e.g., directly aiding in adherence, transporting patients to clinic and hospital appointments, or providing emotional support directed toward patients' condition) would be more likely to predict increased treatment adherence than general social support. This support might even be expected to improve patients' coping and decrease depressive symptoms if patients' depression is primarily the result of illness-related stressors.

Conclusions

Treatment adherence is suboptimal in individuals with CF. Therefore, it is important to study factors that may contribute to adherence and non-adherence in this

population. This is one of the first studies to address the effects of multiple sources of social support on treatment adherence in adults with CF. Additionally, this study evaluated these relationships across a range of treatment domains, which is necessary because adherence rates differ by treatment in this population and treatment efficacy is likely dependent on the performance of multiple treatments. The results of this study suggest that social support from friends is related to decreased adherence to diabetes medications and that living with more people may decrease adherence to airway clearance therapy and nutritional recommendations. Additionally, higher depressive symptoms are related to lower adherence to nutritional care (consuming regular meals, dietary supplements, and snacks). Clinicians should provide their patients with mental health resources and include mental health professionals on care teams in order to screen for psychosocial adjustment problems and address depression-related non-adherence. Further, clinicians may want to implement a cooperative, problem-solving approach to address potential barriers to patients' adherence (e.g., number of individuals in patients' household). Future studies should continue to evaluate the role of social support in treatment adherence, focusing on possible bidirectional relationships between social support and adherence behavior, as well as mechanisms that may explain their connections (e.g., emotion regulation and social desirability). Additionally, more robust and standard measures of treatment adherence should be implemented in order to more accurately evaluate predictors of adherence and compare results across studies.

REFERENCES

Anderson, D. L., Flume, P. A., & Hardy, K. K. (2001). Psychological functioning of adults with cystic fibrosis. *Chest, 119*(4), 1079-1084.

Association, A. P. (2013). *Diagnostic and statistical manual of mental disorders (DSM-5®)*: American Psychiatric Pub.

Barker, D. H., & Quittner, A. L. (2016). Parental depression and pancreatic enzymes adherence in children with cystic fibrosis. *Pediatrics, 137*(2), e20152296.

Bilton, D. (2008). Cystic fibrosis. *Medicine, 36*(5), 273-278.

Bradley, J. M., & Moran, F. (2008). Physical training for cystic fibrosis. *Cochrane Database of Systematic Reviews*(1).

Bregnballe, V., Schiøtz, P. O., Boisen, K. A., Pressler, T., & Thastum, M. (2011). Barriers to adherence in adolescents and young adults with cystic fibrosis: a questionnaire study in young patients and their parents. *Patient Preference and Adherence, 5*, 507.

Briesacher, B. A., Quittner, A. L., Saiman, L., Sacco, P., Fouayzi, H., & Quittell, L. M. (2011). Adherence with tobramycin inhaled solution and health care utilization. *BMC Pulmonary Medicine, 11*(1), 5.

Cohen, S. (2004). Social relationships and health. *American Psychologist, 59*(8), 676.

DeLambo, K. E., Ievers-Landis, C. E., Drotar, D., & Quittner, A. L. (2004). Association of observed family relationship quality and problem-solving skills with treatment

adherence in older children and adolescents with cystic fibrosis. *Journal of Pediatric Psychology, 29*(5), 343-353.

Derogatis, L. R., & Melisaratos, N. (1983). The brief symptom inventory: an introductory report. *Psychological Medicine, 13*(3), 595-605.

DiCarlo, L. A., Weinstein, R. L., Morimoto, C. B., Savage, G. M., Moon, G. L., Au-Yeung, K., & Kim, Y. A. (2016). Patient-centered home care using digital medicine and telemetric data for hypertension: feasibility and acceptability of objective ambulatory assessment. *The Journal of Clinical Hypertension, 18*(9), 901-906.

DiMatteo, M. R. (2004). Social support and patient adherence to medical treatment: a meta-analysis. *Health Psychology, 23*(2), 207.

DiMatteo, M. R., Lepper, H. S., & Croghan, T. W. (2000). Depression is a risk factor for noncompliance with medical treatment: meta-analysis of the effects of anxiety and depression on patient adherence. *Archives of Internal Medicine, 160*(14), 2101-2107.

Eakin, M. N., Bilderback, A., Boyle, M. P., Mogayzel, P. J., & Riekert, K. A. (2011). Longitudinal association between medication adherence and lung health in people with cystic fibrosis. *Journal of Cystic Fibrosis, 10*(4), 258-264.

Eddy, M. E., Carter, B. D., Kronenberger, W. G., Conradsen, S., Eid, N. S., Bourland, S. L., & Adams, G. (1998). Parent relationships and compliance in cystic fibrosis. *Journal of Pediatric Health Care, 12*(4), 196-202.

Foster, C., Eiser, C., Oades, P., Sheldon, C., Tripp, J., Goldman, P., . . . Trott, J. (2001). Treatment demands and differential treatment of patients with cystic fibrosis and

their siblings: patient, parent and sibling accounts. *Child: Care, Health and Development, 27*(4), 349-364.

George, M., Rand-Giovannetti, D., Eakin, M. N., Borrelli, B., Zettler, M., & Riekert, K. A. (2010). Perceptions of barriers and facilitators: self-management decisions by older adolescents and adults with CF. *Journal of Cystic Fibrosis, 9*(6), 425-432.

Guimbellot, J., Solomon, G. M., Baines, A., Heltshe, S. L., VanDalfsen, J., Joseloff, E., . . . Investigators, G. (2019). Effectiveness of ivacaftor in cystic fibrosis patients with non-G551D gating mutations. *Journal of Cystic Fibrosis, 18*(1), 102-109.

Helms, S. W., Dellon, E. P., & Prinstein, M. J. (2015). Friendship quality and health-related outcomes among adolescents with cystic fibrosis. *Journal of Pediatric Psychology, 40*(3), 349-358.

Ingersoll, K. S., & Cohen, J. (2008). The impact of medication regimen factors on adherence to chronic treatment: a review of literature. *Journal of Behavioral Medicine, 31*(3), 213-224.

Jack, K., McLean, S. M., Moffett, J. K., & Gardiner, E. (2010). Barriers to treatment adherence in physiotherapy outpatient clinics: a systematic review. *Manual Therapy, 15*(3), 220-228.

Kettler, L., Sawyer, S., Winefield, H., & Greville, H. (2002). Determinants of adherence in adults with cystic fibrosis. *Thorax, 57*(5), 459-464.

Knudsen, K., Pressler, T., Mortensen, L., Jarden, M., Skov, M., Quittner, A., . . . Boisen, K. (2016). Associations between adherence, depressive symptoms and health-related quality of life in young adults with cystic fibrosis. *SpringerPlus, 5*(1), 1-8.

Konstan, M. W., & Ratjen, F. (2012). Effect of dornase alfa on inflammation and lung function: potential role in the early treatment of cystic fibrosis. *Journal of Cystic Fibrosis, 11*(2), 78-83.

Kostakou, K., Giannakopoulos, G., Diareme, S., Tzavara, C., Doudounakis, S., Christogiorgos, S., . . . Kolaitis, G. (2014). Psychosocial distress and functioning of Greek youth with cystic fibrosis: a cross-sectional study. *BioPsychoSocial Medicine, 8*(1), 13.

Langford, C. P. H., Bowsher, J., Maloney, J. P., & Lillis, P. P. (1997). Social support: a conceptual analysis. *Journal of Advanced Nursing, 25*(1), 95-100.

Llorente, R. P. A., García, C. B., & Martín, J. J. D. (2008). Treatment compliance in children and adults with cystic fibrosis. *Journal of Cystic Fibrosis, 7*(5), 359-367.

McNamara, P. S., McCormack, P., McDonald, A. J., Heaf, L., & Southern, K. W. (2009). Open adherence monitoring using routine data download from an adaptive aerosol delivery nebuliser in children with cystic fibrosis. *Journal of Cystic Fibrosis, 8*(4), 258-263.

Nasr, S. Z., Chou, W., Villa, K. F., Chang, E., & Broder, M. S. (2013). Adherence to dornase alfa treatment among commercially insured patients with cystic fibrosis. *Journal of Medical Economics, 16*(6), 801-808.

O'Sullivan, B. P., & Freeman, S. D. (2009). Cystic fibrosis. *The Lancet, 373*(9678), 1891-1904.

Osterberg, L., & Blaschke, T. (2005). Adherence to medication. *New England Journal of Medicine, 353*(5), 487-497.

Patterson, J. M., Goetz, D., Budd, J., & Warwick, W. J. (1993). Family correlates of a 10-year pulmonary health trend in cystic fibrosis. *Pediatrics, 91*(2), 383-389.

Penninx, B. W., Milaneschi, Y., Lamers, F., & Vogelzangs, N. (2013). Understanding the somatic consequences of depression: biological mechanisms and the role of depression symptom profile. *BMC Medicine, 11*(1), 129.

Preacher, K. J., & Hayes, A. F. (2008). Asymptotic and resampling strategies for assessing and comparing indirect effects in multiple mediator models. *Behavior Research Methods, 40*(3), 879-891.

Quittner, A. L., Espelage, D. L., & Drotar, D. (2000). Measuring adherence to medical treatments in childhood chronic illness: Considering multiple methods and sources of information. *Journal of Clinical Psychology in Medical Settings, 7*(1), 41-54.

Quittner, A. L., Zhang, J., Marynchenko, M., Chopra, P. A., Signorovitch, J., Yushkina, Y., & Riekert, K. A. (2014). Pulmonary medication adherence and health-care use in cystic fibrosis. *Chest, 146*(1), 142-151.

Radtke, T., Nolan, S. J., Hebestreit, H., & Kriemler, S. (2015). Physical exercise training for cystic fibrosis. *Cochrane Database of Systematic Reviews*(6).

Rucker, D. D., Preacher, K. J., Tormala, Z. L., & Petty, R. E. (2011). Mediation analysis in social psychology: Current practices and new recommendations. *Social and Personality Psychology Compass, 5*(6), 359-371.

Ryan, G., Singh, M., & Dwan, K. (2011). Inhaled antibiotics for long-term therapy in cystic fibrosis. *Cochrane Database of Systematic Reviews*(3).

Santini, Z. I., Koyanagi, A., Tyrovolas, S., Mason, C., & Haro, J. M. (2015). The association between social relationships and depression: a systematic review. *Journal of Affective Disorders, 175*, 53-65.

Smith, B. A., Modi, A. C., Quittner, A. L., & Wood, B. L. (2010). Depressive symptoms in children with cystic fibrosis and parents and its effects on adherence to airway clearance. *Pediatric Pulmonology, 45*(8), 756-763.

Smyth, R. L., & Rayner, O. (2017). Oral calorie supplements for cystic fibrosis. *Cochrane Database of Systematic Reviews*(5).

Snell, C., Fernandes, S., Bujoreanu, I. S., & Garcia, G. (2014). Depression, illness severity, and healthcare utilization in cystic fibrosis. *Pediatric Pulmonology, 49*(12), 1177-1181.

Southern, K., & Barker, P. (2004). Azithromycin for cystic fibrosis. *European Respiratory Journal, 24*(5), 834-838.

Stallings, V. A., Stark, L. J., Robinson, K. A., Feranchak, A. P., Quinton, H., on Growth, C. P. G., . . . Group, A. H. W. (2008). Evidence-based practice recommendations for nutrition-related management of children and adults with cystic fibrosis and pancreatic insufficiency: results of a systematic review. *Journal of the American Dietetic Association, 108*(5), 832-839.

Thomas, J., Cook, D., & Brooks, D. (1995). Chest physical therapy management of patients with cystic fibrosis. *Am J Respir Crit Care Med, 151*, 846-850.

Trief, P. M., Ploutz-Snyder, R., Britton, K. D., & Weinstock, R. S. (2004). The relationship between marital quality and adherence to the diabetes care regimen. *Annals of Behavioral Medicine, 27*(3), 148-154.

Uchino, B. N., Cacioppo, J. T., & Kiecolt-Glaser, J. K. (1996). The relationship between social support and physiological processes: a review with emphasis on underlying mechanisms and implications for health. *Psychological Bulletin, 119*(3), 488.

Urquhart, J. (1997). The electronic medication event monitor. *Clinical Pharmacokinetics, 32*(5), 345-356.

Wainwright, C. E., Elborn, J. S., Ramsey, B. W., Marigowda, G., Huang, X., Cipolli, M., . . . Flume, P. A. (2015). Lumacaftor–ivacaftor in patients with cystic fibrosis homozygous for Phe508del CFTR. *New England Journal of Medicine, 373*(3), 220-231.

White, D., Stiller, K., & Haensel, N. (2007). Adherence of adult cystic fibrosis patients with airway clearance and exercise regimens. *Journal of Cystic Fibrosis, 6*(3), 163-170.

Xu, W. M., Shi, Q. X., Chen, W. Y., Zhou, C. X., Ni, Y., Rowlands, D. K., . . . Wang, X. F. (2007). Cystic fibrosis transmembrane conductance regulator is vital to sperm fertilizing capacity and male fertility. *Proceedings of the National Academy of Sciences, 104*(23), 9816-9821.

Yeo, M., & Sawyer, S. (2005). Chronic illness and disability. *BMJ, 330*(7493), 721-723.

Yeung, M., O'Connor, S., Parry, D., & Cochrane, G. (1994). Compliance with prescribed drug therapy in asthma. *Respiratory Medicine, 88*(1), 31-35.

Zimet, G. D., Dahlem, N. W., Zimet, S. G., & Farley, G. K. (1988). The multidimensional scale of perceived social support. *Journal of Personality Assessment, 52*(1), 30-41.

DISEASE SEVERITY AND TREATMENT ADHERENCE IN INDIVIDUALS WITH CYSTIC FIBROSIS

by

BENJAMIN EDWIN BURGESS

SYLVIE MRUG

Format adapted for dissertation

Abstract

Objectives: Individuals with cystic fibrosis (CF) must complete complex and time-consuming treatments in order to maintain health and slow disease progression, but adherence is suboptimal in this population. Clinical and perceived disease severity may help explain individual differences in treatment adherence. This study examines linear and non-linear relationships between disease severity and adherence in individuals with CF. ***Methods:*** Adults with CF (n = 123) completed measures of perceived disease severity and adherence to common treatments for CF. Additionally, common clinical measures of CF severity, including percentage predicted forced expiratory volume in one second (%FEV_1) and body mass index (BMI), were obtained from participant' medical records. ***Analyses:*** Multivariate regression analyses evaluated the linear and quadratic effects of disease severity on treatment adherence cross-sectionally and over a 3-month period. ***Results:*** The direction of the linear relationships between each measure of disease severity and adherence were not consistent. However, perceived severity and %FEV_1 were quadratically related to adherence to corticosteroids as well as nutritional recommendations and diabetes treatments, with greater adherence observed at low and high levels of severity. ***Conclusions:*** The results suggest that the relationship between disease severity and treatment adherence is more complex than a linear association and that disease severity may be quadratically associated with treatment adherence over time.

Keywords: Cystic Fibrosis; Treatment Adherence; Disease Severity; Quadratic; U-shaped

Disease Severity and Treatment Adherence in Individuals with Cystic Fibrosis

Cystic fibrosis (CF) is a progressive, genetic disorder which causes impaired pulmonary and gastrointestinal function, as well as infertility in most males (O'Sullivan & Freeman, 2009; Xu et al., 2007). These complications arise due to production and build-up of abnormally viscous mucus in the airways, pancreatic ducts, and biliary systems, which result in bacterial infection in patients' lungs and airways (Bilton, 2008). Patients' respiratory function declines over time, sometimes leading to pulmonary failure and need for lung transplant (O'Sullivan & Freeman, 2009). Additionally, malnutrition and declining BMI result from impaired gastrointestinal and pancreases function due to build-up of mucus (O'Sullivan & Freeman, 2009). In order to address these complications, individuals with CF are prescribed a wide range of treatments which generally include antibiotics, nebulized medications, pancreatic enzymes and vitamin replacement, chest physiotherapy techniques, and blood-glucose monitoring. The primary goal of these treatments and therapies is to slow disease progression and preserve pulmonary and gastrointestinal function. However, these treatments also address secondary disorders related to CF (e.g., CF-related diabetes). Patients also periodically meet with clinicians to assess health their status and monitor their disease progression. During each of these routine visits, clinical measures of pulmonary function (forced expiratory volume in one second; FEV_1) and nutritional status (body mass index; BMI), as well as microbiological assessment of expectorated sputum, are taken. Patients are admitted to inpatient units when experiencing pulmonary exacerbation, pneumothorax,

massive hemoptysis, or other complications. Patients are generally hospitalized for up to two weeks for pulmonary exacerbation, but may remain in the hospital for longer periods, depending on the complications.

Treatment Adherence

Clinical trials support the efficacy of the most common treatments for CF (Bradley & Moran, 2008; Guimbellot et al., 2019; Konstan & Ratjen, 2012; Radtke, Nolan, Hebestreit, & Kriemler, 2015; Ryan, Singh, & Dwan, 2011; Southern & Barker, 2004; Stallings et al., 2008; Thomas, Cook, & Brooks, 1995; Wainwright et al., 2015), so increased adherence to these therapies is expected to slow decline in health for individuals with CF. Indeed, measures of global adherence have been shown to predict higher FEV_1, better weight management (BMI), and fewer exacerbations and hospitalizations over time in this population (Barker & Quittner, 2016; Briesacher et al., 2011; Eakin, Bilderback, Boyle, Mogayzel, & Riekert, 2011; Eddy et al., 1998; Osterberg & Blaschke, 2005; Patterson, Goetz, Budd, & Warwick, 1993). However, studies often fail to find a direct relationship between adherence to individual therapies and the complication they aim to address (Eakin et al., 2011). Because of this, it has been suggested that the effectiveness of treatments to slow the decline of health for individuals with CF may rely on the collective effects of patients' treatments (Eakin et al., 2011). Therefore, it is important to evaluate multiple measures of adherence.

Adherence can be measured using a variety of methods, each with corresponding advantages and disadvantages. For instance, self-report measures of adherence (e.g., treatment diary, questionnaire recall, interview, and report from a third-party such as a family member) are convenient and inexpensive. However, they are subject to reporter-

bias (typically overestimating adherence) and problems with participant recall, which may result in inaccurate measurements of adherence (Kettler, Sawyer, Winefield, & Greville, 2002; Quittner, Espelage, & Drotar, 2000). By contrast, more objective measures of adherence (e.g., electronic monitoring systems, prescription records, and internal monitoring and blood assays) are generally more accurate. However, these measures are often limited by the method of treatment administration and are usually less convenient and more expensive than self-reports (DiCarlo et al., 2016; McNamara, McCormack, McDonald, Heaf, & Southern, 2009; Urquhart, 1997; Yeung, O'Connor, Parry, & Cochrane, 1994). Variations across studies in how treatment adherence is measured and scored can make direct comparisons of adherence rates difficult across multiple patient populations, including individuals with CF. However, it is clear that adherence for individuals with CF is suboptimal and varies by treatment (Eakin et al., 2011; Llorente, García, & Martín, 2008; Nasr, Chou, Villa, Chang, & Broder, 2013; Quittner et al., 2014). For example, in one study, median possession ratio scores for different pulmonary medications ranged from 49% to 76% in adults and children with CF. In another study, compliance rates were 62% for respiratory medications and 41% for chest physiotherapy, but 88% for digestive medications taken during meals (Llorente et al., 2008).

Disease Severity and Treatment Adherence

In order to reduce non-adherence and increase adherence in patient populations, research has evaluated many factors that may affect treatment adherence. A frequently studied factor is the severity of an individual's condition, which has been generally linked with greater adherence to medications and other treatments across various illness groups

(e.g., tuberculosis, multiple sclerosis, heart disease, HIV, cancer, and mental illnesses) (Kardas, Lewek, & Matyjaszczyk, 2013). Additionally, a person's perception of the threat or severity of the illness (distinct from their beliefs about their own symptoms and health status related to that illness) may also impact their adherence, with higher disease threat being associated with greater adherence (DiMatteo, Haskard, & Williams, 2007). However, the effect of disease severity on adherence may differ by disease, with greater severity being associated with *lower* adherence for individuals with more serious conditions (e.g., more debilitating and life-threatening diseases), but *higher* adherence for individuals with less serious conditions (DiMatteo et al., 2007).

Despite continual advances in treatment and increased life expectancy for individuals with CF, this illness poses significant risks to patient health and quality of life. Given the seriousness of the condition, greater severity might be expected to relate to lower adherence. However, research supporting this relationship is inconclusive. For instance, some research in individuals with CF suggests that greater clinically measured disease severity, evaluated using Shwachman-Kulczycki scores (global measure of physical fitness, pulmonary healthy, and nutritional status), is associated with lower overall treatment adherence to respiratory medication, chest physiotherapy, and nutritional supplements (Llorente et al., 2008). The authors suggested that perhaps individuals with greater disease severity are less adherent because their treatments do not provide an immediate benefit in addressing their increasing symptoms. In this study's sample, greater disease severity was also associated with older age. Given that older, more ill patients have more treatments to complete and that greater complexity of treatments is related to lower adherence (Ingersoll & Cohen, 2008), increased treatment

burden may also explain why higher severity predicted lower adherence. However, other evidence suggests that increased treatment complexity is associated with *greater* adherence in individuals with CF, rather than lower adherence (Quittner et al., 2014). Therefore, the role of treatment complexity in the relationship between disease severity and adherence is unclear in this population. In contrast to the results of Llorente and colleagues (2008), another cross-sectional study observed a positive relationship between perceived disease severity and adherence to chest physical therapy (CPT) in children and adults with CF, suggesting that greater perceived severity is associated with higher adherence (Oermann, Swank, & Sockrider, 2000). Further, a study of children and adolescents with CF reported that greater disease severity (measured by FEV_1) was associated with higher adherence to airway clearance/aerosolized medications (DeLambo, Ievers-Landis, Drotar, & Quittner, 2004). However, the cross-sectional design of each of these studies makes it difficult to understand the causal relationships between disease severity and treatment adherence.

In order to untangle the possible reciprocal effects that treatment adherence and disease severity may have on one another, it is important to consider the prospective associations between disease severity and subsequent treatment adherence, while controlling for baseline adherence. As discussed above, some research has addressed the effect of adherence on later health outcomes in individuals with CF, but research evaluating the longitudinal effect of disease severity on adherence in this population is limited. One longitudinal study examining adherence to nebulized medications among adults with CF found that participants with adherence greater than 50% over a three-month period tended to have higher $\%FEV_1$ at baseline (mean $\%FEV_1$ = 79.7-83.5%)

than patients with low adherence (mean %FEV_1 = 49.5%; Hoo et al., 2019). In a study of adolescents with CF, patient adherence to nebulized medication was measured over a month period, and higher pulmonary function (as measured by FEV_1) predicted greater adherence to participants' nebulized medication (Modi, Marciel, Slater, Drotar, & Quittner, 2008). Thus, with some exceptions, lower clinically measured disease severity appears to predict greater adherence in individuals with CF in both cross-sectional and longitudinal studies.

In addressing the potential relationship between disease severity and treatment adherence, it is important to consider the different ways disease severity can be conceptualized and measured. The two most common methods of measuring disease severity in research with CF patients are clinical measures of health (e.g., FEV_1 and BMI) and patients' self-perceptions of their health. Individuals' perceptions of disease severity, which may not always align with clinical measures (Abbott, Dodd, & Webb, 1995), may be expected to have a greater impact on their decisions to perform their treatments. Therefore, perceived severity may be a stronger predictor of their adherence. Research with lung transplant patients—including individuals with CF—indicates that transplant-specific adherence decreases shortly after lung transplant despite physician recommendations, although increasing again over time (Teichman, Burker, Weiner, & Egan, 2000). It is possible that patients view their treatments as less necessary after successful transplantation, because of a decrease in perceived disease severity (Llorente et al., 2008). However, the health perceptions of participants with CF (past, present, and future health perceptions) did not relate to their adherence to chest physiotherapy, exercise, pancreatic enzyme therapy, and vitamin therapy in another study (Abbott,

Dodd, & Webb, 1996). Therefore, it is unclear whether perceptions of disease severity impact adherence in individuals with CF. Because little research evaluating the relationship between disease severity and adherence in individuals with CF considers patients' perceived disease severity, the present study will evaluate both clinical measures of severity and perceived severity as predictors of adherence.

Lastly, it has been suggested that the relationship between perceived severity and adherence may be nonlinear for individuals with life threatening illnesses like CF (Abbott et al., 1996). As discussed above, individuals with low perceived severity might be expected to be less adherent than those with moderate to high severity. However, individuals with particularly high levels of disease severity might implement avoidance coping, ignoring or downplaying the severity of their illness and disregarding their care providers' recommendations. This might affect their health behaviors, leading to lower adherence rates instead of higher rates. Such a nonlinear relationship between disease severity and adherence may help explain why greater disease severity has been related to lower adherence for more serious illnesses like CF (DiMatteo et al., 2007; Hoo et al., 2019; Llorente et al., 2008). The present study will evaluate the quadratic effect of disease severity on adherence.

Aims and Hypotheses

The current study evaluates concurrent and longitudinal associations between disease severity and adherence to the most common treatments for CF (e.g., airway clearance therapy, nutritional care, pancreatic enzyme therapy, and CF related diabetes treatments). Because a positive association has most frequently been reported in previous research in this area, greater severity is expected to predict higher adherence.

Additionally, given the potential for disease severity to have a nonlinear relationship with treatment adherence, this study will evaluate the quadratic effect of disease severity on adherence to different treatments. Participants with both the lowest and greatest severity are expected to be less adherent than participants with moderate disease severity, both concurrently and over time. In evaluating these effects, both clinical and perceived disease severity will be used as predictors of treatment adherence. Perceived severity is expected to be more consistently related to treatment adherence and have a stronger effect on adherence than clinical measures of severity.

METHODS

Participants and Procedures

The current study was comprised of 123 participants with CF recruited between 2016 and 2017 from outpatient clinics and inpatient units at the University of Alabama at Birmingham Hospital and Children's Hospital of Alabama. These hospitals collectively serve about 230 adults with CF. Patients were eligible for the study if they were 18 years or older and diagnosed with CF. A total of 176 participants were approached for the study. Of these, 158 (90%) agreed to participate and were asked to complete two surveys administered approximately three months apart. A total of 123 (70%) participants completed the first survey, and 111 (90%) of these completed the follow-up survey. The 123 participants had a mean age of 31.8 years (SD = 11.4 years; age range: 19-67 years), 47% were male, 93% were White, and 7% were African American.

The Institutional Review Board approved all study procedures. Participants provided written informed consent during recruitment and later completed online or paper questionnaires. They were compensated for their time with a $30 Visa gift card for each questionnaire completed.

Measures

Treatment Adherence. A modified form of the Treatment Adherence Questionnaire-CF (Quittner et al., 2000) was used to measure treatment adherence. Each of the 16 items in this questionnaire addresses adherence to a particular treatment or

component of participants' treatment routines (e.g., adherence to various aerosols, airway clearance, meal and exercise recommendations, and pancreatic enzymes). Participants responded to each item using a 7-point scale, indicating how often they missed each treatment (*Not at All* to *3 or more times per day*). Participants' medical records were used to determine what treatments they were prescribed. This information was used to determine if participants' responses were congruent or incongruent with their medical records. For instance, if participants' medical records indicated that they were not prescribed a given medication, but they responded to the item measuring adherence to that medication, the response was coded as missing. For oral and inhaled antibiotics, insufficient information was available in patients' records to determine how frequently and over what period each participant was prescribed these medications. Therefore, these adherence items were not included in the study.

In order to reduce the number of outcomes for the primary analyses, an attempt was made to reduce the 14 remaining treatment adherence items into fewer components using principal components analysis (PCA). However, PCA was not possible due to high missingness across treatment items (i.e., only 4 cases had responses to every treatment item). Instead, strong bivariate correlations ($r \geq .50$) between theoretically related items were used to cluster items into seven treatment domains. For each participant, mean domain scores were calculated as an average of the items in each domain. To aid in interpretation, these scores were reverse-coded so that higher scores indicated greater adherence. These domains included: 1) respiratory care to open and clear airways (airway clearance therapy and aerosols to thin mucus, clear mucus, and open airways; 4 items, α = .94 and .93); 2) respiratory care to address inflammation (inhaled corticosteroids; single

item); 3) nutritional care (nutritional supplements, snacks, and meals; 3 items, α = .71 and .81); 4) diabetes care (insulin and blood glucose monitoring 2 items, *r* = .71 and .35); 5) pancreatic enzyme therapy (vitamins and enzymes; 2 items, *r* = .74 and .71); 6) disease modifying medications (single item); and 7) fitness maintenance (exercise; single item).

Disease Severity. Clinical and self-reported measures of disease severity were used for the current study. Clinical measures of disease severity included forced expiratory volume during the first second of exhalation (FEV_1) and body mass index (BMI) at baseline. These measures are commonly used to track disease progression in individuals with CF. They are recorded by clinicians during patients' routine pulmonary clinic visits and were retrieved from participants' medical records for use in this study. FEV_1 indicates the volume that a participant can exhale during the first second of a forced expiratory maneuver. It is used to calculate percentage predicted FEV_1 ($\%FEV_1$) scores for each patient which represent participants' FEV_1 as percentage of their predicted scores based on age, height, and sex. Higher scores indicate less pulmonary obstruction (normal/mild: ≥70%; moderate: 40%-69%; severe: <40%; CFF, 2016). BMI scores are calculated using individuals' weight and height and are used as a marker of healthy weight and to screen for issues of nutritional absorption. Higher scores indicate greater weight (<18.5: underweight; 18.5-25: normal healthy weight; 25-30: overweight; >30: obese). Self-reported disease severity was measured using a question asking about participants' perceived severity (*How do you think your health is now?*) (Henry, Aussage, Grosskopf, & Goehrs, 2003). Participants responded to this question using a 4-point scale (*Excellent* to *Poor*). Higher scores indicate greater perceived severity.

Demographics. Demographic information (i.e., gender, household income level, marital status, education, and age) was collected from participants after informed consent was obtained. Further, recruitment site (inpatient vs. outpatient) and clinic location type (adult, child, or transition clinic) were recorded.

Statistical Analyses

Preliminary Analyses. Descriptive statistics were computed for demographics and variables of interest, including screening for sufficient variability. Sample representativeness was addressed by comparing participants to individuals who were approached but did not participate on age using an independent samples t-test and gender using a chi-square test of independence. Participants recruited from inpatient units and outpatient clinics were compared to determine if they differed on demographics and variables of interest. Attrition analyses compared those who did vs. did not complete the follow-up questionnaire on all demographic and baseline variables. Change in treatment adherence from baseline to follow-up was evaluated using paired samples t-tests. Bivariate correlations were computed for all demographics and variables of interest; they also evaluated stability over time for adherence measures. Finally, assumptions of the main analyses (normality, homoscedasticity, and multicollinearity) were tested.

Primary Analyses. Hierarchical multivariate linear regressions, conducted in Mplus version 7.11, were used to evaluate the linear and quadratic relationships between disease severity (perceived severity, $\%FEV_1$, and BMI) and treatment adherence. The first model tested cross-sectional relationships. At Step 1 of this model, baseline measures of each severity measure were included as predictors of six adherence composite scores also at baseline (disease modifying medications were not included in

the models due its small sample size disrupting model convergence; n = 28-30). Covariates were also entered at Step 1 and included demographic variables (age and household income) that were related to disease severity and/or adherence as determined by bivariate correlations. At Step 2, a quadratic term for each centered severity measure was added to test nonlinear relationships between disease severity and adherence. To reduce model complexity, these quadratic effects were tested one at a time. Thus, Step 2a included a quadratic term for perceived severity, Step 2b included a quadratic term for $\%FEV_1$, and Step 2c included a quadratic term for BMI. Missing data were handled with full information maximum likelihood (FIML), a method that uses all available data and produces less bias than other methods of addressing missingness (e.g., listwise or pairwise deletion; Enders & Bandalos, 2001; Wang & Wang, 2012). However, due to convergence issues for Step 2b (testing the quadratic effects of $\%FEV_1$ on adherence), separate models had to be conducted for each adherence measure and FIML was only used for missing values on the outcome variables, but not the predictors.

The second model tested the linear and quadratic effects of disease severity on treatment adherence over a 3-month period. At Step 1, the three baseline measures of disease severity (perceived severity, $\%FEV_1$, and BMI) were included as predictors of the six adherence composite scores at 3-month follow-up. Step 1 also included covariates—demographic variables (age and household income) that were related to disease severity and/or adherence as determined by bivariate correlation and baseline treatment adherence. At separate Steps 2, one quadratic term for each centered severity measure was included to test nonlinear relationships between disease severity and adherence. Step 2a included a quadratic term for perceived severity, Step 2b included a quadratic term for

$\%FEV_1$, and Step 2c included a quadratic term for BMI. Missing data were handled with full information maximum likelihood (FIML). Again, due to convergence issues, separate models were conducted for each adherence measure when testing the quadratic effects of $\%FEV_1$ on treatment adherence, and FIML was only used for missing values on the outcome variables, but not the predictors.

RESULTS

Preliminary Analyses

Descriptive statistics for demographic and model variables can be found in *Table 2*. The average for %FEV_1 was 61.97, indicating moderate severity for pulmonary condition on average. Within the sample, 35.5% of patients fell in the normal/mild obstruction range, 41.1% in the moderate obstruction range, and 18.5% in the severe obstruction range. The average BMI was 23.48, indicating that patients had normal healthy body weight on average. Specifically, 7.3% of the participants were underweight, 59.7% had normal healthy weight, 20.2% were overweight, and 8.1% were obese. The average for perceived severity was 2.37, indicating that participants thought their health was *fair* to *good* on average. Specifically, 58.9% of participants indicated that their health was good or excellent, and 41.1% indicated their health was poor or fair. The mean of most treatment domain scores fell between 5 and 7 (baseline *M* = 5.71-6.45, follow-up M = 5.83-6.64). This indicates that participants reported missing their treatments *1-2 times per week* to *not at all* on average. For most domains, with the exception of exercise, participants' adherence scores were negatively skewed. Of participants prescribed each treatment, 21% to 60% reported some non-adherence at baseline and 18% to 69% reported some non-adherence at follow-up.

Comparisons of participants and non-participants indicated that individuals who completed the baseline survey were significantly older (M_{age} = 32.0 vs 27.7 years,

t(148.340) = 2.85, *p* = .005) and more likely to be females (53% vs 36%, χ^2 (1) = 4.14, *p* = .042). Participants who were recruited from inpatient units exercised less at baseline than those recruited from outpatient clinics, *t*(111) = -2.65, *p* = .009. Attrition analyses indicated that participants were more likely to drop out before the follow-up assessment if they had lower level of education, *t*(67.04) = -4.82, *p* < .001, and lower adherence to diabetes treatments at baseline, *t*(57) = -2.06, *p* = .044. Paired samples t-tests indicated that only exercise adherence differed from baseline to follow-up, with higher exercise adherence seen at follow-up, *t*(101) = -2.372, *p* = .020.

See *Table 3.3* for bivariate correlations between disease severity, and treatment adherence domain scores. Greater perceived disease severity was related to lower %FEV_1 (*r* = -.18, *p* = .047) and less adherence in the nutritional care (*r* = -.26, *p* = .006) and exercise domains (*r* = -.36, *p* < .001) at baseline, as well as less adherence in the nutritional care domain at follow-up (*r* = -.28, *p* = .003), but it was unrelated to BMI (*r* = -.07, *p* = .484). Greater baseline %FEV_1 was related to higher baseline BMI (*r* = .26, *p* = .005) and lower adherence to pancreatic enzyme therapy at follow-up (*r* = -.24, *p* = .012). BMI was not correlated with any of the adherence measures. Most of the adherence domain measures were moderately correlated over time (*r* range = .35 to .63, *p* < .01).

Normality was violated for each treatment domain score. Therefore, maximum likelihood estimation with robust standard errors (MLR), which is robust to violations of normality, was used in all models. No other major assumptions were violated.

Primary Analyses

Covariates in the primary analyses included age and household income, because they were correlated with multiple predictor and outcome variables. See *Table 3.4* for standardized regression coefficients from the cross-sectional hierarchical multivariate regression models. At Step 1, baseline age predicted lower adherence to corticosteroid (β = -.31, p = .003), nutritional (β = -.21, p = .037), and exercise adherence (β = -.26, p = .011), but higher pancreatic enzyme adherence (β = .22, p = .008). Household income predicted greater airway clearance (β = .26, p = .019) and nutritional adherence (β = .22, p = .040). Greater baseline perceived severity predicted lower exercise adherence (β = -.23, p = .009), $\%FEV_1$ predicted lower airway clearance (β = -.20, p = .026), and BMI predicted higher enzyme therapy adherence (β = .20, p = .003). At Step 2a, the quadratic effect of perceived severity predicted corticosteroid adherence (β = .21, p = .002). At Step 2b, the quadratic effect of $\%FEV_1$ predicted nutritional adherence (β = .21, p = .016). Both quadratic relationships were U-shaped, indicating that those with the highest and lowest baseline perceived or pulmonary disease severity reported greater treatment adherence, but those with moderate severity (perception of *Good* to *Fair* health or 50-70% $\%FEV_1$) had lower adherence (see Figure 3.1). No significant quadratic effects were discovered for BMI in Step 2c.

See *Table 3.5* for standardized regression coefficients from the longitudinal multivariate regression models. At Step 1, baseline age predicted decreased exercise adherence (β = -.28, p = .034). Greater perceived severity predicted increased adherence to pancreatic enzyme therapy (β = -.31, p = .001). Baseline $\%FEV_1$ predicted increased adherence to diabetes treatment (β = .25, p = .015) and decreased adherence to pancreatic

enzyme therapy at follow-up (β = -.31, p = .028). At Step 2b, the quadratic effect of baseline %FEV_1 predicted adherence to diabetes treatment at follow-up (β = .29, p = .009). Again, the quadratic effect was U-shaped. Participants with the highest and lowest baseline %FEV_1 had greater follow-up adherence to diabetes treatment, whereas those with moderate %FEV_1 had lower adherence (see Figure 3.1). No significant quadratic effects were discovered for perceived severity at Step 2a or BMI at Step 2c.

DISCUSSION

This study examined the relationship between disease severity and adherence to routine treatments, both concurrent and over a 3-month period, in individuals with CF. Both clinical measures of disease severity and participants' perception of their health condition were utilized. In general, greater disease severity was expected to predict greater adherence, with participants' perceptions of severity expected to be more consistently related to adherence behavior than clinical measures of severity. The prospective nonlinear relationship between severity and adherence was also tested. An inverted U-shaped relationship was expected between disease severity and treatment adherence, indicating that participants with the highest and lowest severity are least adherent to their treatments and participants with moderate severity are most adherent. The results indicate that each measure of disease severity was related to one or more measure of treatment adherence, but higher severity was not consistently related to higher treatment adherence. Further, $\%FEV_1$ and perceived severity showed quadratic relationships with individual adherence domains (corticosteroid, diabetes, and nutritional adherence). However, the direction of the non-linear associations was contrary to hypotheses. The relationship between disease severity and treatment adherence was U-shaped, indicating that participants with the highest and lowest severity were more adherent to their treatments than participants with moderate levels of severity. Finally, perceived severity was expected to be more consistently related to adherence than the clinical measures of adherence, but this pattern was not confirmed in the results.

Linear Effect of Disease Severity

For individuals with CF, clinicians use $\%FEV_1$ and BMI scores to evaluate disease severity and progression. To reiterate, $\%FEV_1$ is a measure of the volume of air that can be expelled in one second as a percentage of the value predicted for a given patient, so greater $\%FEV_1$ indicates better pulmonary function (i.e., lower disease severity). Further, many individuals with CF have difficulty maintaining healthy weight due to impaired nutritional absorption which results in many patients being underweight. Therefore, higher BMI is used as an indicator of healthy nutritional absorption (i.e., lower disease severity). Most adherence outcomes in the current study had at least one significant association with either clinically measured disease severity or participant reported severity. Some of the observed linear relationships suggest that greater disease severity is related to higher adherence. For instance, lower $\%FEV_1$ (i.e., more severe pulmonary obstruction) was related to higher concurrent adherence to airway clearance therapy and increased adherence to pancreatic enzyme therapy at 3-month follow-up. Further, greater perceived severity was related to increased adherence to enzyme therapy at 3-month follow-up. By contrast, greater perceived severity was related to lower concurrent adherence to exercise, and lower (i.e., worse) $\%FEV_1$ was related to decreased adherence to diabetes treatment over the 3-month follow-up.

Greater disease severity (e.g., greater number of symptoms and higher perception of severity) is often linked to higher adherence in patients with chronic illness (Kardas et al., 2013). However, research in individuals with CF is inconclusive on this point, with some evidence suggesting that disease severity is related to higher adherence (DeLambo et al., 2004; Oermann et al., 2000) and other evidence suggesting severity is related to

lower adherence (Llorente et al., 2008). The cross-sectional design of these studies may partially explain their conflicting results. Specifically, their results may reflect bi-directional effects between disease severity and treatment adherence. Greater severity would be expected to predict greater adherence, because patients are motivated to complete treatments in order to treat their symptoms. The immediate and long-term effects of greater treatment adherence would be expected to improve patients' symptoms, decreasing disease severity and slowing disease progression. This bidirectional relationship of disease severity and treatment adherence may also partially explain the conflicting results of the concurrent relationships in the present study (i.e., worse %FEV1 predicting higher airway clearance adherence but higher perceived severity predicting lower exercise adherence).

However, there were also conflicting results for the prediction of treatment adherence from disease severity over time. For perceived severity, greater disease severity was related to increased pancreatic enzyme treatment adherence over time. For $\%FEV_1$, greater severity was related to increased adherence to enzyme treatment but decreased adherence to diabetes treatment over time. Some evidence suggests that greater severity predicts worse adherence for particularly serious illnesses (DiMatteo et al., 2007). Given the seriousness of CF, it seems plausible that this effect would be seen in this illness. Limited research has evaluated the longitudinal effect of disease severity on treatment adherence in individuals with CF, but what evidence does exist suggesting that greater severity (measured using FEV_1) predicts lower adherence (Hoo et al., 2019; Modi et al., 2008). These results are consistent with the linear relationship observed between $\%FEV_1$ and diabetes adherence in the current study. However, they conflict with the

longitudinal associations observed between disease severity (perceived severity and $\%FEV_1$) and increased enzyme therapy over time in the current study. Further, a uniform direction in the effects of disease severity on treatments would be expected across treatment types and measures of severity, but that was not the case in the present study. Therefore, other explanations are needed to shed light on the discrepancy, such as the presence of non-linear relationships between disease severity and adherence (Abbott et al., 1996).

Quadratic Effect of Disease Severity

Some research suggests that the relationship between disease severity and treatment adherence is nonlinear and differs at different levels of severity (Abbott et al., 1996). Specifically, it has been suggested that very low severity may not sufficiently motivate individuals to complete their treatments and that particularly high severity may cause patients to implement avoidance coping, neglecting their treatments as a result. Additionally, there may be a moderate range where disease severity is sufficiently high to encourage adherence but not so high that it demoralizes and demotivates patients or causes them to apply avoidance coping. The nonlinear relationship between disease severity and treatment adherence was evaluated in order to test this hypothesis. Indeed, perceived severity was nonlinearly related to concurrent adherence to corticosteroids, and $\%FEV_1$ was nonlinearly related to concurrent adherence to nutritional recommendations and diabetes adherence over a 3-month period. However, for each of these relationships, high and low disease severity was associated with greater adherence, and moderate severity was associated with lower adherence. This appears inconsistent with the notion

that patients believe they are healthy enough to forgo some treatment when they are well and avoid treatments when they are extremely sick.

For the concurrent associations between disease severity (perceived severity and $\%FEV_1$) and treatment adherence (corticosteroids and nutritional recommendations), it is impossible to determine the direction of the effects. In fact, the potential bi-directional effect of disease severity and treatment adherence may partially explain these associations. Specifically, a positive effect of treatment adherence may explain why participants with lower adherence had moderate severity and why those with greater adherence had lower severity. These results are consistent with evidence suggesting that higher treatment adherence promotes better health in individuals with CF (Barker & Quittner, 2016; Briesacher et al., 2011; Eakin et al., 2011; Eddy et al., 1998; Osterberg & Blaschke, 2005; Patterson et al., 1993). The motivating effect of disease severity may then explain why participants with high severity had higher adherence.

The potential bi-directional effects of treatment adherence and disease severity do not explain the longitudinal quadratic relationships in the present study. Instead, these results offer stronger evidence for a quadratic effect of disease severity on treatment adherence. However, the observed associations are not consistent with the hypothesized inverted U-shaped relationship between disease severity and treatment adherence. Therefore, other explanations are needed to account for the observed relationship. For instance, perhaps adherence is high when patients' severity is low because their treatments have proven to be effective at maintaining their health (therefore, patients remain adherent). This is consistent with qualitative studies with adult and adolescent CF patients which indicate that the perception of a given therapy as ineffective contributes to

individuals' non-adherence (Conway, Pond, Watson, & Hamnett, 1996; DiMatteo et al., 2007). Further, in the present study, participants who had moderate %FEV_1 and perceived disease severity may have been less adherent than those with low and high severity because their condition leads to the belief that they cannot control their health and they become less adherent as a result. Thus, these individuals may utilize avoidance coping, neglecting treatments and downplaying their illness. While this was expected to occur at highest levels of severity, perhaps this avoidance occurs at moderate levels of severity and continues as patients' health declines. Finally, individuals with the most severe condition may have high adherence because those with severe symptoms are more likely to be hospitalized or may have more clinic visits during this time. Perhaps this facilitates higher adherence as clinicians and medical professionals monitor and aid inpatients while they complete treatments. It is unclear if this was the case in the present study. Participants who were recruited from inpatient hospital units vs. outpatient clinics did not differ in adherence to nutritional, corticosteroid, or diabetes adherence. However, inpatient status at recruitment may not accurately reflect when participants completed the questionnaires for this study, especially for the 3-month follow-up responses. Therefore, it is unclear if increases in adherence during hospitalization account for the association between high severity and treatment adherence. Finally, consideration of the treatments that %FEV_1 predicted (diabetes and nutritional adherence) may also inform our interpretation of the current study's results. For the participants in the current study with particularly low %FEV_1, increased adherence to diabetes treatments and higher adherence to nutritional care (treatments that do not directly or primarily address pulmonary health) may reflect their attempts to exert some control over their health as

they face increased pulmonary decline. Future research should continue to evaluate the prospective nonlinear relationships between disease severity and treatment adherence in individuals with CF. This research should focus on what role factors like control beliefs, perceived treatment efficacy, coping, and the bi-directional effects between disease severity and treatment adherence have in explaining these relationships.

Implications

The results of the current study may inform how healthcare providers approach the treatment of individuals with CF. For instance, participants with moderate severity appeared to have lower treatment adherence than those with lowest and highest severity. Knowing that adherence is related to later health outcomes, patients with moderate severity may be at increased risk of worsening disease severity. Therefore, clinicians should closely monitor adherence in these individuals and be mindful of potential contributors and barriers to patient adherence. For instance, various individual (e.g., patient knowledge, apprehension due to side-effect, and regimen complexity), interpersonal (e.g., social support and patient-provider relationship), and cognitive factors (e.g., control beliefs, depression, and anxiety) may need to be explored for their role in treatment adherence. It may be helpful for clinicians to discuss these factors with their patients and address any that are hindering adherence. For instance, clinicians may periodically review patients' treatment plans to make sure their patients understand how to manage specific aspects of their treatments (e.g., reviewing enzyme dosages, discussing what form of ACT is most convenient for patients, etc.). Additionally, clinics serving individuals with CF could integrate mental health services to address cognitive and psychosocial factors that may affect adherence.

Limitations

There are important limitations to consider when interpreting the results of the current study. For instance, self-reported disease severity has the potential to introduce bias into the results. Specifically, participants' reported severity may have been subject to social desirability influences or participants' denial of actual severity, leading to underreported severity. These biases may have attenuated the linear and quadratic associations between perceived disease severity and adherence. Further, the current measure of severity only addressed general severity, although its significant correlation with $\%FEV_1$ and not BMI suggests participants may largely be reporting perceived pulmonary severity. However, severity may also vary across different symptoms in individuals with CF, and it is possible that illness perceptions for different aspects of their health have a greater impact on adherence to different treatments. For instance, individuals' perceptions of their digestive health status may be more relevant to adherence to enzyme therapy and nutrition treatment compared to an overall disease severity perception. Likewise, their perceptions of their pulmonary health may be more likely to predict their respiratory treatment adherence and physical fitness health behaviors. Future research should address the roles of symptom-specific disease severity measures in treatment adherence.

Another measurement concern is the use of self-reported adherence, which may also have introduced bias (e.g., due to social desirability) into the study. Specifically, participants may have over-reported adherence (Kettler et al., 2002; Quittner et al., 2000), which may have affected the results of the current study (e.g., if patients with the greatest severity reported higher adherence than they actually had). This may be particularly

important to consider when interpreting the nonlinear relationships reported in this study. To reduce reporter bias, the adherence items were rephrased so that participants reported how often they missed each treatment (instead of how often they completed each treatment). This was done to normalize non-adherence and encourage accurate reporting, but the validity of this method needs to be established by comparing it to adherence measures with more direct questions. Additionally, despite being guided by theoretical and empirical similarity of items, the calculation and use of mean domain scores for adherence may also limit the results of the current study. Indeed, meaningful relationships may exist between disease severity and specific adherence behaviors which were collapsed into broader domains. However, the use of combined domain scores reduced the number of analyses or complexity of the models evaluated in the present study. Future research should address the role of disease severity in treatment adherence using alternative and more robust measures of disease severity and treatment adherence.

Small sample size is a common concern in research with CF patients, largely because of how small this population is. Thus, the relatively small sample size in the current study may have contributed to lower power to detect small effects. Further, the current study could not evaluate the potential relationships between disease severity and adherence to disease modifying medications, because too few participants were prescribed these treatments. Future research evaluating the relationships between disease severity and adherence could implement a multi-site study design to recruit larger samples.

Differences in overall disease severity across samples may impact the reproducibility of the current results. It is possible that other samples with generally

lower or higher disease severity than the current sample may not obtain the same quadratic associations observed in this study. Thus, comparisons of results across studies need to consider the study-specific distributions of disease severity.

Conclusions

Treatment adherence is suboptimal in individuals with CF, so it is important to study predictors of treatment adherence in this population. This was the first study to evaluate the prospective nonlinear effects of disease severity (clinically measured and patient perceived) on treatment adherence in this population. Further, adherence was measured separately for most common treatments, reflecting the fact that adherence often differs by treatment. The results evaluating the linear effect of disease severity on treatment adherence were inconsistent, with both positive and negative associations evident (concurrently and over time). Inconsistencies in concurrent associations may be partially explained by possible bi-directional relationships between disease severity and treatment adherence. Nonlinear effects of disease severity on treatment adherence may help explain inconsistencies in both concurrent and longitudinal associations. Indeed, multiple non-linear relationships between disease severity and adherence—both concurrently and over time—were obtained in the present study. Specifically, the relationship between severity and adherence appeared to be U-shaped across all reported quadratic associations, with the highest adherence seen when disease severity was low or high and lowest adherence seen when severity was moderate. This relationship was observed for two measures of severity (%FEV_1 and perceived severity), and three of the six treatment domains evaluated (corticosteroids, nutritional recommendations, and diabetes management). Given the results of this study, future research should continue to

examine prospective nonlinear relationships between disease severity and treatment adherence to replicate and extend the results of the current study. Further, future research should evaluate factors that may explain these relationships and implement more robust measures of adherence, as well as perceptions of disease severity reported for specific symptoms or complications (e.g., perceptions of gastrointestinal vs. pulmonary disease severity).

REFERENCES

Abbott, J., Dodd, M., & Webb, A. (1995). Different perceptions of disease severity and self care between patients with cystic fibrosis, their close companions, and physician. *Thorax, 50*(7), 794-796.

Abbott, J., Dodd, M., & Webb, A. K. (1996). Health perceptions and treatment adherence in adults with cystic fibrosis. *Thorax, 51*(12), 1233-1238.

Barker, D. H., & Quittner, A. L. (2016). Parental depression and pancreatic enzymes adherence in children with cystic fibrosis. *Pediatrics, 137*(2), e20152296.

Bilton, D. (2008). Cystic fibrosis. *Medicine, 36*(5), 273-278.

Bradley, J. M., & Moran, F. (2008). Physical training for cystic fibrosis. *Cochrane Database of Systematic Reviews*(1).

Briesacher, B. A., Quittner, A. L., Saiman, L., Sacco, P., Fouayzi, H., & Quittell, L. M. (2011). Adherence with tobramycin inhaled solution and health care utilization. *BMC Pulmonary Medicine, 11*(1), 5.

Conway, S., Pond, M., Watson, A., & Hamnett, T. (1996). Knowledge of adult patients with cystic fibrosis about their illness. *Thorax, 51*(1), 34-38.

DeLambo, K. E., Ievers-Landis, C. E., Drotar, D., & Quittner, A. L. (2004). Association of observed family relationship quality and problem-solving skills with treatment adherence in older children and adolescents with cystic fibrosis. *Journal of Pediatric Psychology, 29*(5), 343-353.

DiCarlo, L. A., Weinstein, R. L., Morimoto, C. B., Savage, G. M., Moon, G. L., Au-Yeung, K., & Kim, Y. A. (2016). Patient-centered home care using digital medicine and telemetric data for hypertension: feasibility and acceptability of objective ambulatory assessment. *The Journal of Clinical Hypertension, 18*(9), 901-906.

DiMatteo, M. R., Haskard, K. B., & Williams, S. L. (2007). Health beliefs, disease severity, and patient adherence: a meta-analysis. *Medical Care*, 521-528.

Eakin, M. N., Bilderback, A., Boyle, M. P., Mogayzel, P. J., & Riekert, K. A. (2011). Longitudinal association between medication adherence and lung health in people with cystic fibrosis. *Journal of Cystic Fibrosis, 10*(4), 258-264.

Eddy, M. E., Carter, B. D., Kronenberger, W. G., Conradsen, S., Eid, N. S., Bourland, S. L., & Adams, G. (1998). Parent relationships and compliance in cystic fibrosis. *Journal of Pediatric Health Care, 12*(4), 196-202.

Enders, C. K., & Bandalos, D. L. (2001). The relative performance of full information maximum likelihood estimation for missing data in structural equation models. *Structural Equation Modeling, 8*(3), 430-457.

Guimbellot, J., Solomon, G. M., Baines, A., Heltshe, S. L., VanDalfsen, J., Joseloff, E., . . . Investigators, G. (2019). Effectiveness of ivacaftor in cystic fibrosis patients with non-G551D gating mutations. *Journal of Cystic Fibrosis, 18*(1), 102-109.

Henry, B., Aussage, P., Grosskopf, C., & Goehrs, J.-M. (2003). Development of the Cystic Fibrosis Questionnaire (CFQ) for assessing quality of life in pediatric and adult patients. *Quality of Life Research, 12*(1), 63-76.

Hoo, Z. H., Gardner, B., Arden, M. A., Waterhouse, S., Walters, S. J., Campbell, M. J., . . . Wildman, M. J. (2019). Role of habit in treatment adherence among adults with cystic fibrosis. *Thorax, 74*(2), 197-199.

Ingersoll, K. S., & Cohen, J. (2008). The impact of medication regimen factors on adherence to chronic treatment: a review of literature. *Journal of Behavioral Medicine, 31*(3), 213-224.

Kardas, P., Lewek, P., & Matyjaszczyk, M. (2013). Determinants of patient adherence: a review of systematic reviews. *Frontiers in Pharmacology, 4*, 91.

Kettler, L., Sawyer, S., Winefield, H., & Greville, H. (2002). Determinants of adherence in adults with cystic fibrosis. *Thorax, 57*(5), 459-464.

Konstan, M. W., & Ratjen, F. (2012). Effect of dornase alfa on inflammation and lung function: potential role in the early treatment of cystic fibrosis. *Journal of Cystic Fibrosis, 11*(2), 78-83.

Llorente, R. P. A., García, C. B., & Martín, J. J. D. (2008). Treatment compliance in children and adults with cystic fibrosis. *Journal of Cystic Fibrosis, 7*(5), 359-367.

McNamara, P. S., McCormack, P., McDonald, A. J., Heaf, L., & Southern, K. W. (2009). Open adherence monitoring using routine data download from an adaptive aerosol delivery nebuliser in children with cystic fibrosis. *Journal of Cystic Fibrosis, 8*(4), 258-263.

Modi, A. C., Marciel, K. K., Slater, S. K., Drotar, D., & Quittner, A. L. (2008). The influence of parental supervision on medical adherence in adolescents with cystic fibrosis: developmental shifts from pre to late adolescence. *Children's Health Care, 37*(1), 78-92.

Nasr, S. Z., Chou, W., Villa, K. F., Chang, E., & Broder, M. S. (2013). Adherence to dornase alfa treatment among commercially insured patients with cystic fibrosis. *Journal of Medical Economics, 16*(6), 801-808.

O'Sullivan, B. P., & Freeman, S. D. (2009). Cystic fibrosis. *The Lancet, 373*(9678), 1891-1904.

Oermann, C. M., Swank, P. R., & Sockrider, M. M. (2000). Validation of an instrument measuring patient satisfaction with chest physiotherapy techniques in cystic fibrosis. *Chest, 118*(1), 92-97.

Osterberg, L., & Blaschke, T. (2005). Adherence to medication. *New England Journal of Medicine, 353*(5), 487-497.

Patterson, J. M., Goetz, D., Budd, J., & Warwick, W. J. (1993). Family correlates of a 10-year pulmonary health trend in cystic fibrosis. *Pediatrics, 91*(2), 383-389.

Quittner, A. L., Espelage, D. L., & Drotar, D. (2000). Measuring adherence to medical treatments in childhood chronic illness: Considering multiple methods and sources of information. *Journal of Clinical Psychology in Medical Settings, 7*(1), 41-54.

Quittner, A. L., Zhang, J., Marynchenko, M., Chopra, P. A., Signorovitch, J., Yushkina, Y., & Riekert, K. A. (2014). Pulmonary medication adherence and health-care use in cystic fibrosis. *Chest, 146*(1), 142-151.

Radtke, T., Nolan, S. J., Hebestreit, H., & Kriemler, S. (2015). Physical exercise training for cystic fibrosis. *Cochrane Database of Systematic Reviews*(6).

Ryan, G., Singh, M., & Dwan, K. (2011). Inhaled antibiotics for long-term therapy in cystic fibrosis. *Cochrane Database of Systematic Reviews*(3).

Southern, K., & Barker, P. (2004). Azithromycin for cystic fibrosis. *European Respiratory Journal, 24*(5), 834-838.

Stallings, V. A., Stark, L. J., Robinson, K. A., Feranchak, A. P., Quinton, H., on Growth, C. P. G., . . . Group, A. H. W. (2008). Evidence-based practice recommendations for nutrition-related management of children and adults with cystic fibrosis and pancreatic insufficiency: results of a systematic review. *Journal of the American Dietetic Association, 108*(5), 832-839.

Teichman, B., Burker, E. J., Weiner, M., & Egan, T. M. (2000). Factors associated with adherence to treatment regimens after lung transplantation. *Progress in Transplantation, 10*(2), 113-121.

Thomas, J., Cook, D., & Brooks, D. (1995). Chest physical therapy management of patients with cystic fibrosis. *Am J Respir Crit Care Med, 151*, 846-850.

Urquhart, J. (1997). The electronic medication event monitor. *Clinical Pharmacokinetics, 32*(5), 345-356.

Wainwright, C. E., Elborn, J. S., Ramsey, B. W., Marigowda, G., Huang, X., Cipolli, M., . . . Flume, P. A. (2015). Lumacaftor–ivacaftor in patients with cystic fibrosis homozygous for Phe508del CFTR. *New England Journal of Medicine, 373*(3), 220-231.

Wang, J., & Wang, X. (2012). *Structural equation modeling: Applications using Mplus*: John Wiley & Sons.

Xu, W. M., Shi, Q. X., Chen, W. Y., Zhou, C. X., Ni, Y., Rowlands, D. K., . . . Wang, X. F. (2007). Cystic fibrosis transmembrane conductance regulator is vital to sperm

fertilizing capacity and male fertility. *Proceedings of the National Academy of Sciences, 104*(23), 9816-9821.

Yeung, M., O'Connor, S., Parry, D., & Cochrane, G. (1994). Compliance with prescribed drug therapy in asthma. *Respiratory Medicine, 88*(1), 31-35.

CONCLUSIONS

For individuals with CF, it is important to adhere to prescribed treatment regimens in order to slow disease progression and maintain health. However, in previous research, treatment adherence has been shown to be suboptimal in this population. Therefore, it is important to consider factors that contribute to adherence and non-adherence among individuals with CF. The current study evaluated the role of various cognitive factors (HLC, social support, disease severity, and depressive symptoms) in predicting adherence in adults with CF and discussed how these results can be applied in clinical settings. Considerations for future research were also addressed.

The results of the first study suggest that different domains of HLC are related to adherence to various treatments and that the results of some of these relationships depend on patients' perceptions of disease severity. The study supported the hypothesis that Internal HLC beliefs are related to higher treatment adherence for individuals with higher perceptions of disease severity. Although not expected, the results of the study also suggested that Chance HLC beliefs are related to lower adherence when perceived severity is low. Therefore, clinicians trying to encourage adherence may benefit from considering their patients' perceptions of disease severity and HLC beliefs. Future studies should continue to evaluate the direct and interactive effects of HLC and disease severity on treatment adherence.

The results of the second study suggest that social support from friends is related to decreased adherence to diabetes treatments. Further, they suggest that living with more people may decrease adherence to airway clearance therapies and nutritional recommendations. Depressive symptoms may also be related to lower adherence to nutritional care (meals, dietary supplements, and snacks). Clinicians may be able to help patients complete their treatments by aiding them in the development and implementation of strategies to overcome social barriers to adherence. Further, mental health professionals should be included on clinical care teams in order to address psychosocial adjustment problems and their potential effects on adherence. Future studies should continue to evaluate the relationships between social support and treatment adherence, with specific focus on mechanisms that may explain these relationships (e.g., emotion regulation and social desirability).

The results of the final study suggest that the relationship between disease severity and treatment adherence may be more complex than a linear association. Specifically, the results of the study suggest that the relationship between severity and adherence may be U-shaped with lowest adherence occurring when disease severity is moderate. This relationship was incongruent with the hypothesized non-linear association, expecting highest adherence at moderate severity. However, this U-shaped relationship was observed for two measures of severity (%FEV1 and perceived severity) and multiple domains of adherence (corticosteroids, nutritional recommendations, and diabetes management), supporting its validity. Moreover, these associations were observed concurrently and over time. Therefore, future studies should continue to examine prospective nonlinear relationships between disease severity and treatment

adherence, as well as mechanisms that may explain these relationships (e.g., avoidance coping).

There are also some general considerations for future research which are relevant to the results of each study. For instance, future research evaluating cognitive factors related to treatment adherence should use more robust, accurate, and standard measures of treatment adherence. Further, future studies should strive to recruit patients from multiple sites in order to increase sample size, statistical power, and generalizability of results.

Table 1.1
Bivariate Correlations among Individual Items for Treatment Adherence at Baseline

	M (*SD*)	n	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
1. Aerosols – Open Airways (RA)	2.02 (1.44)	108	-														
2. Aerosols – Clear Mucus (RA)	2.40 (1.69)	93	**.77*****	-													
3. Aerosols – Thin Mucus (RA)	2.25 (1.62)	95	**.70*****	**.82*****	-												
4. Airway Clearance (RA)	2.36 (1.52)	113	**.69*****	**.79*****	**.75*****	-											
5. Inhaled Antibiotics	1.86 (1.52)	69	.30*	**.59*****	**.82*****	**.65*****	-										
6. Oral Antibiotics	1.63 (1.25)	103	**.63*****	**.64*****	**.52*****	**.60*****	.42***	-									
7. Disease Modifying (DM)	1.73 (1.39)	30	**.72*****	.37	**.71*****	**.67*****	-.04	**.83*****	-								
8. Enzymes (E)	1.95 (1.50)	105	.48***	.38***	.25*	.35***	.11	**.54*****	**.79*****	-							
9. Vitamins (E)	2.00 (1.52)	115	**.55*****	**.46*****	.36***	.42***	.18	**.67*****	**.55****	**.74*****	-						
10. Meals (N)	2.00 (1.56)	115	.27**	.37***	.24*	.20*	-.05	.08	.42*	.25*	.17	-					
11. Snacks (N)	2.05 (1.67)	114	.15	.19	.08	.09	-.13	.00	.25	.10	.08	**.77*****	-				
12. Supplements (N)	2.11 (1.90)	110	.26**	.23*	.09	.18	-.07	.20*	-.15	.01	.24*	.24*	.41***	-			
13. Inhaled Steroids (RI)	1.55 (1.51)	58	.33*	.38**	.39**	**.52*****	.40*	.33*	.20	-.06	-.05	.18	.16	.23	-		
14. Blood Glucose Monitoring (D)	2.22 (1.70)	59	.35**	.38**	**.60*****	.41**	**.66*****	-.00	-.03	.09	.22	-.08	-.06	.13	**.56****	-	
15. Insulin (D)	2.12 (1.78)	59	.25	.39**	**.54*****	.39**	**.67*****	.04	-.10	.14	.24	-.05	-.02	.06	**.70*****	**.71*****	-
16. Exercise (F)	3.04 (1.95)	113	.12	.19	.19	.33***	.24	.15	.29	.18	.15	.22*	.35***	.45***	.40**	.26*	.15

*Note: *p < .05, **p < .01, ***p < .001; Bolded correlations are moderate correlations (r ≥ .50) for clustering; Treatment Domain Labels: RA = respiratory care to open and clear airways; RI = respiratory care to address inflammation; N = nutritional care; D = diabetes care; E = enzyme therapy; DM =disease modifying medications; F = fitness maintenance.*

Table 1.2
Descriptive Statistics

	Time 1	Time 2
	M (SD)	*M (SD)*
Age	31.79 (11.41)	-
$\%FEV_1$	61.97 (22.95)	-
BMI	23.48 (4.94)	-
Health Locus of Control – Internal	25.61 (5.13)	-
Health Locus of Control – Powerful Others	22.74 (4.78)	-
Health Locus of Control – Chance	15.65 (5.15)	-
Perceived Disease Severity	2.37 (0.80)	-
Adherence – Airway Clearance (n = 108 and 100)	5.71 (1.43)	5.83 (1.35)
Adherence – Corticosteroids (n = 58 and 58)	6.45 (1.51)	6.48 (1.08)
Adherence – Nutrition (n = 114 and 106)	5.94 (1.37)	6.14 (1.22)
Adherence – Diabetes (n = 59 and 55)	5.83 (1.61)	6.06 (1.32)
Adherence – Enzymes (n = 115 and 106)	6.01 (1.44)	6.23 (1.23)
Adherence – Exercise (n = 113 and 105)	4.96 (1.95)	5.50 (1.71)
Adherence – Disease Modifying (n = 30 and 28)	6.27 (1.39)	6.64 (0.99)
	n (%)	
Gender		
Male	58 (46.8)	
Female	66 (53.2)	
Ethnicity		
White	116 (93.5)	
African American	8 (6.5)	
Household Income		
<$10,000	16 (14.7)	
$0-$50,000	44 (40.4)	
$50,000-$100,000	34 (31.2)	
>$100,000	15 (13.8)	

Note: $\%FEV_1$ = forced expiratory volume in 1 second as a percentage of expected volume; BMI = body mass index; adherence ranges from 1 (missed treatment 3 or more times per day) to 7 (not at all); HLC ranges from 1 (strongly disagree) to 6 (strongly agree).

Table 1.3
Bivariate Correlations Between HLC, Perceived Severity, and Adherence Domains

	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19
1. Internal HLC	-																		
2. Powerful Others HLC	.33***	-																	
3. Chance HLC	-.16	.08	-																
4. Perceived Severity	-.23*	.02	.18*	-															
5. Age	-.18	.09	-.06	.28**	-														
6. %FEV_1	.14	.21*	-.03	-.18*	-.13	-													
7. T1 Airway Clearance	-.06	-.22*	-.15	-.08	.03	-.11	-												
8. T1 Corticosteroids	.14	-.03	-.04	-.08	-.28*	-.08	.47***	-											
9. T1 Nutrition	.13	.07	-.15	-.26**	-.18	.09	.24*	.23	-										
10. T1 Diabetes	-.09	.01	-.11	.05	.12	-.17	.50***	.71***	.00	-									
11. T1 Enzymes	.10	-.05	-.17	-.06	.22*	-.08	.51***	-.06	.22*	.22	-								
12. T1 Exercise	.20*	-.03	-.15	-.36***	-.29**	.08	.26**	.40**	.44***	.22	.16	-							
13. T1 Disease Modifying	-.14	-.40*	.02	-.12	.30	-.08	.71***	.20	.19	-.07	.75***	.29	-						
14. T2 Airway Clearance	-.13	-.16	-.18	-.07	-.12	-.13	.56***	.22	.10	.23	.07	.25*	.38	-					
15. T2 Corticosteroids	-.07	-.11	-.19	-.04	-.16	-.08	.37**	.38**	-.11	.59**	.14	.33*	-.02	.55***	-				
16. T2 Nutrition	-.09	-.11	-.10	-.28**	-.07	-.05	.30**	.17	.50***	.18	.13	.44***	.20	.24*	.04	-			
17. T2 Diabetes	.02	.09	-.27	-.03	-.10	.11	.40**	.41*	.06	.54***	.23	.32*	.01	.36**	.15	.31*	-		
18. T2 Enzymes	.03	-.07	-.11	.09	.08	-.24*	.41***	.21	.19	.07	.41***	.16	.34	.40***	.03	.18	.16	-	
19. T2 Exercise	-.02	-.11	-.15	-.12	-.32**	.03	.23*	.06	.02	.02	.01	.39***	.23	.44***	.44**	.36***	.29*	.06	-
20. T2 Disease Modifying	-.05	-.32	-.26	.11	.11	.08	.46*	.67*	.61**	.11	.50**	.41*	.63**	.63**	.19	.67***	.25	.65***	.40*

*Note: *p < .05, **p < .01, ***p < .001; %FEV_1 = forced expiratory volume in 1 second as a percentage of expected; T1 – baseline, T2 – 3-month follow-up*

Table 1.4

Standardized Coefficients from a Multivariate Regression Predicting Baseline Adherence Domains from HLC, Perceived Severity, and Covariates

	Predictors	Airway Clearance	Nutrition	Diabetes	Enzymes	Exercise
Step 1	Age	-.01	**-.25****	.14	**.20****	-**.21***
	Income	.23	**.22***	.02	.09	.12
	$\%FEV_1$	-.16	-.05	-.07	-.15	-.01
	BMI	.12	.12	-.11	**.21****	-.01
	Internal HLC	-.03	.02	-.07	.12	.10
	Powerful Others HLC	-.17	.09	.12	-.10	-.03
	Chance HLC	-.09	-.11	-.16	-.07	-.11
	Perceived Severity	-.02	-.12	.02	-.05	**-.23****
Step 2	Internal HLC X Severity	.04	-.01	.13	**.22***	**.18***
	Powerful HLC X Severity	.06	.04	-.10	-.16	-.14
	Chance HLC X Severity	.09	-.07	.16	**.25***	.01

*Note: *p < .05, **p < .01; Note: $\%FEV_1$ = forced expiratory volume in 1 second as a percentage of expected*

Table 1.5

Standardized Coefficients from a Multivariate Regression Predicting Adherence Domains at Follow-up from Baseline HLC, Perceived Severity, and Covariates

	Predictors	**Airway Clearance**	**Nutrition**	**Diabetes**	**Enzymes**	**Exercise**
Step 1	Age	-.15	.06	-.14	-.20	**-.31***
	Income	-.04	-.03	-.00	.17	.01
	$\%FEV_1$	-.03	-.10	**.26****	**-.22***	.02
	BMI	**-.22***	.01	-.17	-.09	-.14
	Days Between Surveys	**.12***	.01	.11	-.01	**.15***
	Internal HLC	-.15	**-.16***	-.13	-.02	-.11
	Powerful Others HLC	.05	-.07	.18	-.01	-.03
	Chance HLC	-**.18***	-.03	-.19	-.10	-.17
	Perceived Severity	.02	-.17	.01	**.26****	.08
Step 2	Internal HLC X Severity	.01	-.13	.04	-.10	-.03
	Powerful HLC X Severity	-.06	-.14	.13	.03	-.09
	Chance HLC X Severity	.13	.01	-.17	-.03	.08

*Note: *p < .05, **p < .01; Note: $\%FEV_1$ = forced expiratory volume in 1 second as a percentage of expected*

Table 2.1
Bivariate Correlations among Individual Items for Treatment Adherence at Baseline

	M (*SD*)	n	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
1. Aerosols – Open Airways	2.02 (1.44)	108	-														
2. Aerosols – Clear Mucus	2.40 (1.69)	93	**.77*****	-													
3. Aerosols – Thin Mucus	2.25 (1.62)	95	**.70*****	**.82*****	-												
4. Airway Clearance	2.36 (1.52)	113	**.69*****	**.79*****	**.75*****	-											
5. Inhaled Antibiotics	1.86 (1.52)	69	.30*	**.59*****	**.82*****	**.65*****	-										
6. Oral Antibiotics	1.63 (1.25)	103	**.63*****	**.64*****	**.52*****	**.60*****	.42***	-									
7. Disease Modifying	1.73 (1.39)	30	**.72*****	.37	**.71*****	**.67*****	-.04	**.83*****	-								
8. Enzymes	1.95 (1.50)	105	.48***	.38***	.25*	.35***	.11	**.54*****	**.79*****	-							
9. Vitamins	2.00 (1.52)	115	**.55*****	**.46*****	.36***	.42***	.18	**.67*****	**.55****	**.74*****	-						
10. Meals	2.00 (1.56)	115	.27**	.37***	.24*	.20*	-.05	.08	.42*	.25*	.17	-					
11. Snacks	2.05 (1.67)	114	.15	.19	.08	.09	-.13	.00	.25	.10	.08	**.77*****	-				
12. Supplements	2.11 (1.90)	110	.26**	.23*	.09	.18	-.07	.20*	-.15	.01	.24*	.24*	.41***	-			
13. Inhaled Steroids	1.55 (1.51)	58	.33*	.38**	.39**	**.52*****	.40*	.33*	.20	-.06	-.05	.18	.16	.23	-		
14. Blood Glucose Monitoring	2.22 (1.70)	59	.35**	.38**	**.60*****	.41**	**.66*****	-.00	-.03	.09	.22	-.08	-.06	.13	**.56****	-	
15. Insulin	2.12 (1.78)	59	.25	.39**	**.54*****	.39**	**.67*****	.04	-.10	.14	.24	-.05	-.02	.06	**.70*****	**.71*****	-
16. Exercise	3.04 (1.95)	113	.12	.19	.19	.33***	.24	.15	.29	.18	.15	.22*	.35***	.45***	.40**	.26*	.15

*Note: *p < .05, **p < .01, ***p < .001; Bolded correlations are moderate correlations (r ≥ .50) for clustering*

Table 2.2
Descriptive Statistics

	Time 1	Time 2	Time 3
	M (SD)	*M (SD)*	
Age	31.79 (11.41)	-	-
$\%FEV_1$	61.97 (22.95)	-	-
BMI	23.48 (4.94)	-	-
Family Social Support	4.35 (0.88)	-	-
Friend Social Support	3.91 (1.08)	-	-
Significant Others Social Support	4.34 (1.06)	-	-
Depressive Symptoms	1.53 (0.70)	1.52 (0.77)	-
Adherence – Airway Clearance (n = 88-108)	5.71 (1.43)	5.83 (1.35)	5.80 (1.43)
Adherence – Corticosteroids (n = 49-58)	6.45 (1.51)	6.48 (1.08)	6.49 (1.26)
Adherence – Nutrition (n = 92-114)	5.94 (1.37)	6.14 (1.22)	6.27 (1.17)
Adherence – Diabetes (n = 48-59)	5.83 (1.61)	6.06 (1.32)	6.19 (1.34)
Adherence – Enzymes (n = 91-115)	6.01 (1.44)	6.23 (1.23)	6.17 (1.33)
Adherence – Exercise (n = 91-113)	4.96 (1.95)	5.50 (1.71)	5.43 (1.48)
Adherence – Disease Modifying (n = 28-33)	6.27 (1.39)	6.64 (0.99)	6.70 (0.98)
	n (%)		
Gender			
Male	58 (46.8)		
Female	66 (53.2)		
Ethnicity			
White	116 (93.5)		
African American	8 (6.5)		
Income			
<$10,000	16 (14.7)		
$0-$50,000	44 (40.4)		
$50,000-$100,000	34 (31.2)		
>$100,000	15 (13.8)		

Note: $\%FEV_1$ = forced expiratory volume in 1 second as a percentage of expected volume; BMI = body mass index

Table 2.3
Bivariate Correlations among Social Support, Depression, and Adherence Domains

	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18
1. Family Support	-																	
2. Friends Support	**.57*****	-																
3. Sig. Other Support	**.44*****	**.28****	-															
4. T1 Depression	**-.40*****	**-.31****	**-.32****	-														
5. T2 Depression	**-.50*****	**-.33****	**-.29****	**.73*****	-													
6. T1 Airway Clearance	**.20***	**.27****	**.27****	-.14	**-.25***	-												
7. T1 Corticosteroids	.10	.13	.16	.00	-.08	**.47*****	-											
8. T1 Nutrition	.17	**.22***	.10	**-.19***	-.16	**.24***	.23	-										
9. T1 Diabetes	.03	.08	**.32***	-.16	-.20	**.50*****	**.72*****	.01	-									
10. T1 Enzymes	.04	.13	**.28****	**-.23***	-.17	**.51*****	-.06	**.22***	.22	-								
11. T1 Exercise	.06	.02	.05	-.08	-.02	**.26****	**.40****	**.44*****	.22	.16	-							
12. T1 Disease Modifying	-.27	-.22	-.08	.09	.06	**.71*****	.20	.19	-.07	**.75****	.29	-						
13. T3 Airway Clearance	.07	.02	.03	-.04	-.08	**.52*****	-.18	.09	.01	.17	**.24***	**.42***	-					
14. T3 Corticosteroids	-.04	-.12	-.11	.10	.06	.05	-.07	-.23	.21	.00	.06	-.22	**.47****	-				
15. T3 Nutrition	.05	.08	.10	-.08	**-.26***	.17	-.14	**.31****	.04	.12	.12	.26	**.30****	-.10	-			
16. T3 Diabetes	.23	-.02	.12	-.28	**-.39****	.29	-.14	.02	**.50****	.20	.27	.03	**.40****	**.54****	.28	-		
17. T3 Enzymes	.19	.16	.16	-.15	-.13	**.29****	.02	.07	.19	**.31****	.07	**.40***	**.60*****	.03	**.28****	**.30***	-	
18. T3 Exercise	.20	**.21***	.18	**-.23***	**-.25***	.19	.01	**.31****	-.07	.14	**.46*****	-.02	**.40*****	**.40****	**.25***	.14	**.25***	-
19. T3 Disease Modifying	-.12	-.06	-.14	-.02	-.08	**.71*****	-.07	.11	-.18	**.68*****	.06	**.76****	**.48****	-.14	**.58*****	-.07	**.60*****	-.03

*Note: *p < .05, **p < .01, ***p < .001*

154

Table 2.4

Coefficients from a Cross-sectional Multivariate Regression Model Predicting Baseline Adherence from Social Support and Covariates

	Adherence Domain					
Predictors	**Airway Clearance**	**Corticosteroids**	**Nutrition**	**Diabetes**	**Enzymes**	**Exercise**
Age	-.16	**-.43****	-.23	.10	.15	**-.45*****
Income	.16	.15	.21	.08	.07	**.32****
Married	**.23***	.16	.01	-.08	.07	.04
# People in Household	-.06	.01	.05	-.08	.04	-.04
Family Social Support	-.05	-.10	-.01	-.09	-.16	-.07
Friends Social Support	.20	.04	.11	.02	.13	-.11
Sig. Other Social Support	.16	.17	.07	.38	**.26****	.14

*Note: *p < .05, **p < .01, ***p < .001*

Table 2.5

Coefficients from a Longitudinal Multivariate Regression Model Predicting Adherence at T3 from Social Support at T1 and Covariates

	Adherence Domain					
Predictors	**Airway Clearance**	**Corticosteroids**	**Nutrition**	**Diabetes**	**Enzymes**	**Exercise**
Adherence (T2)	**.36****	.42	**.61*****	**.65*****	.19	**.38****
Age	-.10	-.13	.06	-.07	.02	**-.30***
Income	**.39****	-.13	**.31***	.26	.22	.08
Married	.01	.18	-.18	-.11	.01	.12
# People in Household	**-.38****	-.14	**-.18***	-.11	-.11	-.12
Days Between Surveys	-.01	-.37	.09	.06	.09	-.05
Family Social Support	.06	.20	-.13	.16	.11	-.02
Friends Social Support	-.12	.01	-.03	**-.29****	-.02	.11
Sig. Other Social Support	.02	**-.30****	.10	-.08	.10	.11

*Note: *p < .05, **p < .01, ***p < .001*

Table 2.6
Path Coefficients from a Mediation Model Linking Social Support at T1 to Adherence at T3 through Depression at T2

	Adherence Domain					
	Airway Clearance	**Corticosteroids**	**Nutrition**	**Diabetes**	**Enzymes**	**Exercise**
T1 Family Support → T3 Adherence	.09	.23	**-.26***	.01	.12	-.08
T1 Family Support → T2 Depression	-.25	-.22	-.25	-.25	-.25	-.25
T1 Family Support → T2 Depression → T3 Adherence	.02	-.01	.08	.08	.01	.04
T1 Friends Support → T3 Adherence	-.14	-.14	-.00	-.24	-.01	.10
T1 Friends Support → T2 Depression	.10	.07	.10	.11	.10	.10
T1 Friends Support → T2 Depression → T3 Adherence	.01	.00	-.03	-.03	.00	-.01
T1 Sig. Other Support → T3 Adherence	.04	-.29	.07	-.15	.09	.12
T1 Sig. Other Support → T2 Depression	-.03	-.02	-.03	-.03	-.03	-.03
T1 Sig. Other Support → T2 Depression → T3 Adherence	-.00	-.00	.01	.01	.00	.00
T2 Depression → T3 Adherence	.06	.03	**-.23***	-.20	.02	-.09
T2 Adherence → T3 Adherence	**.37****	.54	**.58*****	**.62*****	.21	**.37****
T1 Depression → T2 Depression	**.65*****	**.72*****	**.65*****	**.65*****	**.65*****	**.65*****
Age → T3 Adherence	-.10	-.01	.04	-.05	.01	**-.31***
Income → T3 Adherence	**.40****	-.01	**.32***	-.15	.21	.10
Married → T3 Adherence	.00	.44	-.17	.12	.01	.13
# in Household → T3 Adherence	**-.38****	-.19	-.23	.05	-.12	-.11

*Note: *p < .05, **p < .01, ***p < .001*

Table 3.1
Bivariate Correlations among Individual Items for Treatment Adherence at Baseline

	M (*SD*)	n	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
1. Aerosols – Open Airways (RA)	2.02 (1.44)	108	-														
2. Aerosols – Clear Mucus (RA)	2.40 (1.69)	93	**.77*****	-													
3. Aerosols – Thin Mucus (RA)	2.25 (1.62)	95	**.70*****	**.82*****	-												
4. Airway Clearance (RA)	2.36 (1.52)	113	**.69*****	**.79*****	**.75*****	-											
5. Inhaled Antibiotics	1.86 (1.52)	69	.30*	**.59*****	**.82*****	**.65*****	-										
6. Oral Antibiotics	1.63 (1.25)	103	**.63*****	**.64*****	**.52*****	**.60*****	.42***	-									
7. Disease Modifying (DM)	1.73 (1.39)	30	**.72*****	.37	**.71*****	**.67*****	-.04	**.83*****	-								
8. Enzymes (E)	1.95 (1.50)	105	.48***	.38***	.25*	.35***	.11	**.54*****	**.79*****	-							
9. Vitamins (E)	2.00 (1.52)	115	**.55*****	**.46*****	.36***	.42***	.18	**.67*****	**.55****	**.74*****	-						
10. Meals (N)	2.00 (1.56)	115	.27**	.37***	.24*	.20*	-.05	.08	.42*	.25*	.17	-					
11. Snacks (N)	2.05 (1.67)	114	.15	.19	.08	.09	-.13	.00	.25	.10	.08	**.77*****	-				
12. Supplements (N)	2.11 (1.90)	110	.26**	.23*	.09	.18	-.07	.20*	-.15	.01	.24*	.24*	.41***	-			
13. Inhaled Steroids (RI)	1.55 (1.51)	58	.33*	.38**	.39**	**.52*****	.40*	.33*	.20	-.06	-.05	.18	.16	.23	-		
14. Blood Glucose Monitoring (D)	2.22 (1.70)	59	.35**	.38**	**.60*****	.41**	**.66*****	-.00	-.03	.09	.22	-.08	-.06	.13	**.56****	-	
15. Insulin (D)	2.12 (1.78)	59	.25	.39**	**.54*****	.39**	**.67*****	.04	-.10	.14	.24	-.05	-.02	.06	**.70*****	**.71*****	-
16. Exercise (F)	3.04 (1.95)	113	.12	.19	.19	.33***	.24	.15	.29	.18	.15	.22*	.35***	.45***	.40**	.26*	.15

*Note: *p < .05, **p < .01, ***p < .001; Bolded correlations are moderate correlations (r ≥ .50) for clustering; Treatment Domain Labels: RA = respiratory care to open and clear airways; RI = respiratory care to address inflammation; N = nutritional care; D = diabetes care; E = enzyme therapy; DM =disease modifying medications; F = fitness maintenance.*

Table 3.2
Descriptive Statistics

	Time 1	Time 2
	M (SD)	*M (SD)*
Age	31.79 (11.41)	-
$\%FEV_1$	61.97 (22.95)	-
BMI	23.48 (4.94)	-
Perceived Disease Severity	2.37 (0.80)	-
Adherence – Airway Clearance (n = 108 and 100)	5.71 (1.43)	5.83 (1.35)
Adherence – Corticosteroids (n = 58)	6.45 (1.51)	6.48 (1.08)
Adherence – Nutrition (n = 114 and 106)	5.94 (1.37)	6.14 (1.22)
Adherence – Diabetes (n = 59 and 55)	5.83 (1.61)	6.06 (1.32)
Adherence – Enzymes (n = 115 and 106)	6.01 (1.44)	6.23 (1.23)
Adherence – Exercise (n = 113 and 105)	4.96 (1.95)	5.50 (1.71)
Adherence – Disease Modifying (n = 30 and 28)	6.27 (1.39)	6.64 (0.99)
	n (%)	
Gender		
Male	58 (46.8)	
Female	66 (53.2)	
Ethnicity		
White	116 (93.5)	
African American	8 (6.5)	
Household Income		
<$10,000	16 (14.7)	
$0-$50,000	44 (40.4)	
$50,000-$100,000	34 (31.2)	
>$100,000	15 (13.8)	

Note: $\%FEV_1$ = forced expiratory volume in 1 second as a percentage of expected volume; BMI = body mass index; adherence ranges from 1 (missed treatment 3 or more times per day) to 7 (not at all); HLC ranges from (strongly disagree) to (strongly agree).

Table 3.3
Bivariate Correlations among Disease Severity and Adherence Domain Measures

	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
1. Perceived Severity	-															
2. %FEV_1	**-.18***	-														
3. BMI	-.07	**.26****	-													
4. T1 Airway Clearance	-.08	-.11	.03	-												
5. T1 Corticosteroids	-.08	-.08	.12	**.47*****	-											
6. T1 Nutrition	**-.26****	.09	.15	**.24***	.23	-										
7. T1 Diabetes	.05	-.17	-.18	**.50*****	**.72*****	.01	-									
8. T1 Enzymes	-.06	-.08	.17	**.51*****	-.06	**.22***	.22	-								
9. T1 Exercise	**-.36*****	.08	.03	**.26****	**.40****	**.44*****	.22	.16	-							
10. T1 Disease Modifying	-.12	-.08	.05	**.71*****	.20	.19	-.07	**.75*****	.29	-						
11. T2 Airway Clearance	-.07	-.13	-.19	**.56*****	.22	.10	.23	.07	**.25***	.38	-					
12. T2 Corticosteroids	-.04	-.08	-.14	**.37****	**.38****	-.11	**.59****	.14	**.33***	-.03	**.55*****	-				
13. T2 Nutrition	**-.28****	-.05	.07	**.30****	.17	**.50*****	.18	.13	**.44*****	.20	**.24***	.04	-			
14. T2 Diabetes	-.03	.11	-.09	**.40****	**.41***	.06	**.54*****	.23	**.32***	.01	**.36****	.15	**.31***	-		
15. T2 Enzymes	.09	**-.24***	-.05	**.41*****	.21	.19	.07	**.41*****	.16	.34	**.40*****	.03	.18	.16	-	
16. T2 Exercise	-.12	.03	-.15	**.23***	.06	.02	.03	.01	**.39*****	.23	**.44*****	**.44****	**.36*****	**.29***	.06	-
17. T2 Disease Modifying	.11	.08	.04	**.46***	**.67***	**.61****	.11	**.50****	**.41***	**.63****	**.63****	.19	**.67*****	.25	**.65*****	**.40***

*Note: *p < .05, **p < .01, ***p < .001; %FEV_1 = forced expiratory volume in 1 second as a percentage of expected; T1 – baseline, T2 – 3-month follow-up*

Table 3.4

Regression Coefficients for Cross-sectional Effects of Baseline Disease Severity on Adherence Domains

	Predictors	**Airway Clearance**	**Corticosteroids**	**Nutrition**	**Diabetes**	**Enzymes**	**Exercise**
Step 1	Perceived Severity	-.01	-.01	-.13	-.01	-.12	**-.23****
	$\%FEV_1$	**-.20***	-.13	-.04	-.18	-.15	.03
	BMI	.09	.04	.16	.07	**.20****	-.03
	Baseline Age	-.05	**-.31****	**-.21***	-.08	**.22****	**-.26***
	Household Income	**.26***	.19	**.22***	-.03	.09	.16
Step 2a	Perceived Severity Squared	.07	**.21****	-.11	.09	-.12	.02
Step 2b	$\%FEV_1$ Squared	.15	.24	**.21***	.04	-.03	.14
Step 2c	BMI Squared	.13	.04	.07	.13	.11	.11

*Note: *p < .05, **p < .01, ***p < .001; $\%FEV_1$ = forced expiratory volume in 1 second as a percentage of expected.*

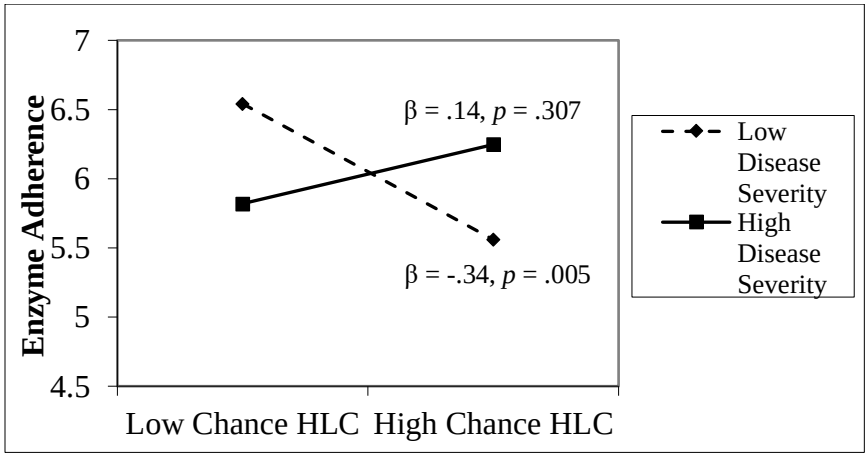
Table 3.5

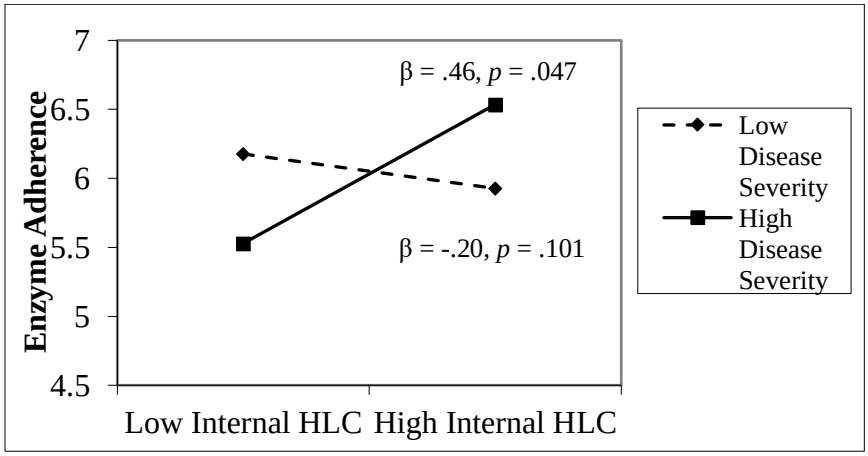
Regression Coefficients for Longitudinal Effects of Baseline Disease Severity on Adherence at 3-month Follow-up

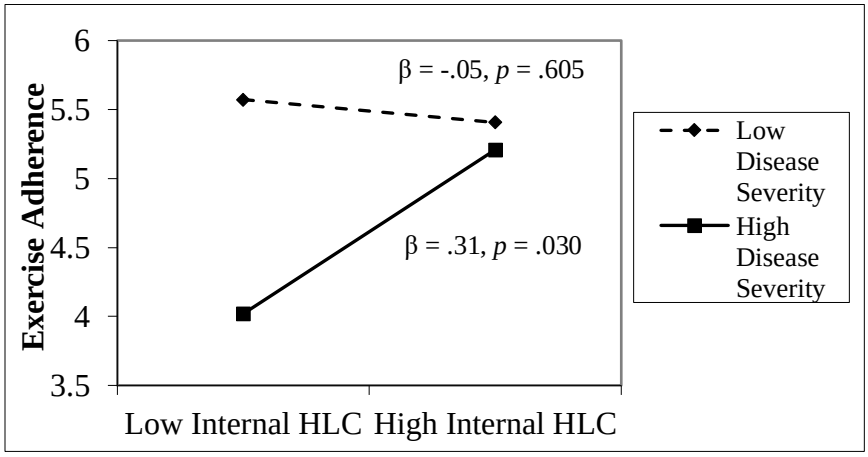
	Predictors	**Airway Clearance**	**Corticosteroids**	**Nutrition**	**Diabetes**	**Enzymes**	**Exercise**
Step 1	T1 Adherence	**.48*** **	**.51*** **	**.49*** **	**.52** **	**.56*** **	**.26***
	Perceived Severity	.00	-.00	-.17	-.04	**.26** **	.06
	$\%FEV_1$	-.05	-.05	-.12	**.25***	**-.21***	.00
	BMI	-.20	-.12	-.01	-.15	-.09	-.13
	Baseline Age	-.12	-.01	.08	-.13	-.20	**-.28***
	Household Income	-.03	.09	-.03	-.05	.17	.04
	Days Between T1 and T2	**.15***	.11	.02	.11	-.01	.16
Step 2a	Perceived Severity Squared	-.00	.12	-.01	.02	.07	.04
Step 2b	$\%FEV_1$ Squared	-.01	.08	.04	**.29** **	-.07	-.18
Step 2c	BMI Squared	-.08	.27	.08	.06	-.28	.09

*Note: *p < .05, **p < .01, ***p < .001; $\%FEV_1$ = forced expiratory volume in 1 second as a percentage of expected.*

Figure 1.1. *Simple Slopes for Interactions of HLC and Perceived Severity on T1 Adherence*



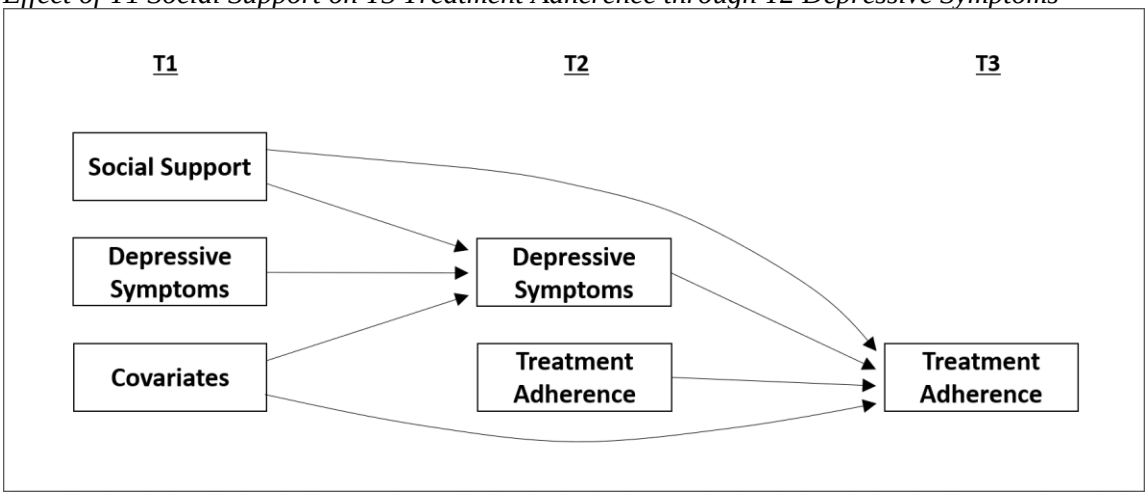




Note: Higher treatment values indicate higher adherence; consistent with the simple slopes analyses, 1.5 SD below and above mean is used for the graph illustrating the relationship between Internal HLC and enzyme adherence, and 1 SD below and above mean is used for each other graph.

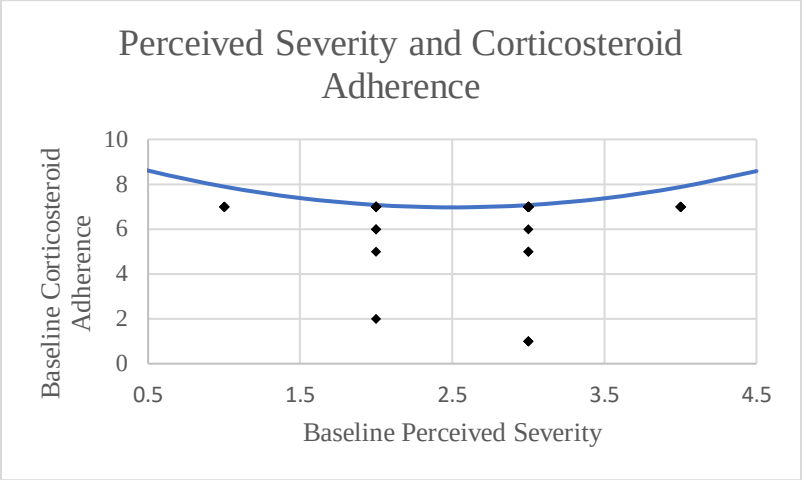
Figure 2.1

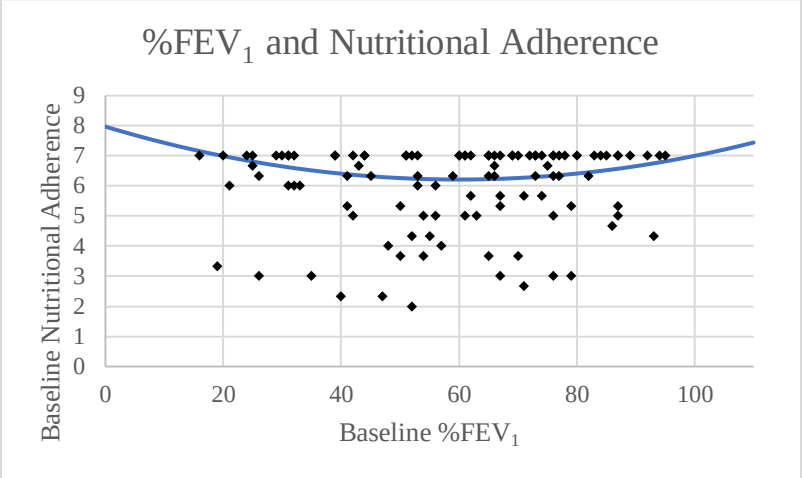
Effect of T1 Social Support on T3 Treatment Adherence through T2 Depressive Symptoms

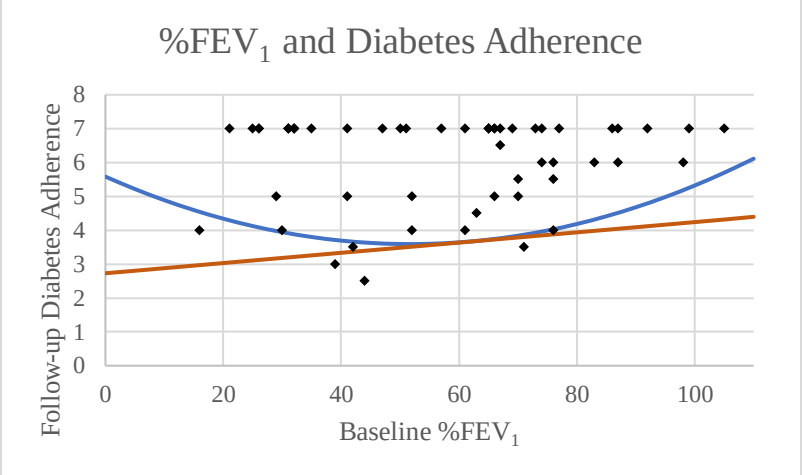


Note: Each social support domain (friends, family, and significant other) was included in every model; covariates included age, household income, marital status, and number of people in participant's household; analyses were conducted separately for each adherence domain.

Figure 3.1
Quadratic Effects of Disease Severity on Adherence







Note: The red line represents the linear effect of %FEV₁ on diabetes adherence (Step 1)

APPENDIX

IRB APPROVAL FORMS

THE UNIVERSITY OF ALABAMA AT BIRMINGHAM
Office of the Institutional Review Board for Human Use

470 Administration Building
701 20th Street South
Birmingham, AL 35294-0104
205.934.3789 | Fax 205.934.1301 |
irb@uab.edu

APPROVAL LETTER

TO: Mrug, Sylvie

FROM: University of Alabama at Birmingham Institutional Review Board
Federalwide Assurance # FWA00005960
IORG Registration # IRB00000196 (IRB 01)
IORG Registration # IRB00000726 (IRB 02)

DATE: 01-Oct-2018

RE: IRB-151013008
Coping and Health in Adults with Cystic Fibrosis

The IRB reviewed and approved the Continuing Review submitted on 28-Sep-2018 for the above referenced project. The review was conducted in accordance with UAB's Assurance of Compliance approved by the Department of Health and Human Services.

Type of Review:	Expedited
Expedited Categories:	
Determination:	Approved
Approval Date:	01-Oct-2018
Approval Period:	One Year
Expiration Date:	30-Sep-2019

THE UNIVERSITY OF ALABAMA AT BIRMINGHAM
Office of the Institutional Review Board for Human Use

470 Administration Building
701 20th Street South
Birmingham, AL 35294-0104
205.934.3789 | Fax 205.934.1301 |
irb@uab.edu

APPROVAL LETTER

TO: Mrug, Sylvie

FROM: University of Alabama at Birmingham Institutional Review Board
Federalwide Assurance # FWA00005960
IORG Registration # IRB00000196 (IRB 01)
IORG Registration # IRB00000726 (IRB 02)

DATE: 02-Jun-2019

RE: IRB-151013008
Coping and Health in Adults with Cystic Fibrosis

The IRB reviewed and approved the Revision/Amendment submitted on 29-May-2019 for the above referenced project. The review was conducted in accordance with UAB's Assurance of Compliance approved by the Department of Health and Human Services.

Type of Review:	Expedited
Expedited Categories:	7
Determination:	Approved
Approval Date:	02-Jun-2019
Expiration Date:	01-Jun-2022

Although annual continuing review is not required for this project, the principal investigator is still responsible for (1) obtaining IRB approval for any modifications before implementing those changes except when necessary to eliminate apparent immediate hazards to the subject, and (2) submitting reportable problems to the IRB. Please see the IRB Guidebook for more information on these topics.

Documents Included in Review:

- praf.190528.pdf