Parental Depression and Pancreatic Enzymes Adherence in Children With Cystic Fibrosis

David H. Barker, PhD a,b Alexandra L. Quittner, PhD c

BACKGROUND: Treatment adherence in cystic fibrosis (CF) is often poor; however, less is known about adherence to pancreatic enzymes, a critical component of the CF treatment regimen. Parent caregivers often report elevations in depression, and parental depression may adversely affect children’s adherence.

METHODS: This prospective study evaluated adherence to pancreatic enzymes in 83 patients (1–13 years). Adherence was measured across 3 months with electronic pill-caps. Weight was measured at baseline and a 3-month follow-up. Parental depressive symptoms were evaluated by using the Center for Epidemiologic Studies Depression Scale (CES-D).

RESULTS: Adherence to pancreatic enzymes was 49.4% ± 3.4%. Adherence was higher at school (94.4% ± 6.1%) than at home (42.3% ± 3.1%), and higher for toddlers (50.6% ± 5.2%) than for school-aged children (37.5% ± 3.7%). Parents reported high rates of depressive symptoms (30% in the clinical range, 18% with moderate symptoms). Children of parents with symptoms of depression versus those without were less adherent (34.8% ± 4.5% vs 48.5% ± 4.1%), and adherence to enzymes was significantly related to 3-month weight outcomes. Average gain in weight z scores across 3 months was 0.5 ± 0.2 for children who were >50% adherent and –0.1 ± 6.1 for children who were <33% adherent. Parental depression had a significant, indirect effect on weight via adherence (–0.005 ± 0.003 gain in weight z score per CES-D unit).

CONCLUSIONS: High rates of parental depressive symptoms, coupled with its negative effects on adherence, suggest that measuring and treating parental depression may improve children’s adherence to therapy.

WHAT’S KNOWN ON THIS SUBJECT: Families of children living with cystic fibrosis manage complex and time-consuming treatment regimens, and rates of adherence are often low. Parents report elevated rates of depression, and there is growing evidence that parental depression adversely affects children’s treatment adherence.

WHAT THIS STUDY ADDS: Adherence to pancreatic enzymes (measured with electronic monitors) was suboptimal and related to weight outcomes 3 months later. Parental depression adversely affected adherence to enzymes during meals and snacks given at home, which in turn, negatively affected weight outcomes.


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Nutrition and weight are important outcomes that have been linked to reduced morbidity, increased lung function, and better survival in patients with cystic fibrosis (CF). For children who are pancreatic insufficient, taking pancreatic enzyme supplements is an important component of their treatment regimen. The Cystic Fibrosis Foundation (CF) has provided guidelines that focus on nutrition in childhood; these guidelines suggest that children should consume 110% to 200% of the energy intake requirement for healthy peers. To meet these guidelines, it is recommended that children eat at least 3 meals and 3 snacks per day, and children who are pancreatic insufficient should take pancreatic enzyme supplements with each meal and snack. Unfortunately, adherence to dietary recommendations is often low, ranging from 16% to 28% depending on the recommendation. Adherence to pancreatic enzyme regimens is also low, ranging from 27% to 46%. Although effective behavioral interventions have been developed to improve nutritional outcomes in young children, less is known about adherence to pancreatic enzyme therapy.

Adherence occurs in the context of patients’ daily lives, with processes that either facilitate or impede adherence. The pediatric self-management framework (PSMF) organizes these processes into 4 domains: individual, family, community, and health care. These domains influence patients’ general self-management of their condition, affecting their adherence to prescribed treatment regimens and, in turn, their health outcomes. Within CF, a number of individual, family, and health care processes have been linked to poor treatment adherence, but less is known about the role of parental mental health.

There is accumulating evidence that caring for children with CF increases rates of depression among parents, which in turn affects parents’ quality of life. In addition to concerns about parental well-being, parent mental health may influence patient adherence in several ways, including adversely affecting family dynamics, disrupting parent–child communication, altering parents' beliefs about treatment efficacy, reducing available family support, and decreasing parental supervision of treatments. All of these processes have been linked to treatment adherence in CF. Given the elevated rates of depression documented in parents of children with CF and the theorized impact of parental depression on treatment adherence, the goal of the present article was to test whether parental depressive symptoms were predictive of adherence to enzyme regimens and whether that impact also affected short-term health outcomes. In accordance with the PSMF, we hypothesized that parental depressive symptoms would contribute to worse adherence, which in turn, would lead to worse weight outcomes. To test this hypothesis, adherence to pancreatic enzyme therapy was measured using electronic monitors, and a mediation model tested the link from parental depressive symptoms to short-term weight outcomes through enzyme therapy adherence.

**METHODS**

**Participants**

The present study used preintervention data from a multicenter trial conducted between 2001 and 2007; the trial was designed to evaluate an in-clinic problem-solving intervention targeting adherence to multiple aspects of the CF regimen in children ages 1 to 13 years. Of the 115 families contacted, 28 declined participation, 87 were randomized to undergo study, and 83 were prescribed pancreatic enzyme supplements. Eligibility criteria included: (1) age 1 to 13 years; (2) diagnosis of CF confirmed by sweat test results; and (3) at least 1 year since diagnosis. Given the high rates of stress and depressive symptoms documented soon after the diagnosis, we chose not to include families who had a child with a recent diagnosis. Data were collected during a 3-month period after enrollment (before participating in the adherence intervention). Demographic and medical characteristics are listed in Table 1.

**Procedures**

This study was approved by local institutional review boards at 3 CF centers in Florida. Medical characteristics of patients with CF attending these clinics were as follows: mean forced expiratory volume in 1 second (percent predicted), 86% to 91%; and mean BMI percentile, 43% to 47%. During the first clinic visit of the study, the primary caregiver provided demographic information and completed the depression measure. Measures of patient health status were collected, and families were provided with electronic pill bottles, which recorded the date and time of each bottle opening; caregivers were instructed to put the month’s supply of enzyme supplements into these bottles. Participants returned for their next scheduled clinic visit 3 months later, during which measures of health status were again recorded, and data for bottle openings across the 3 months were downloaded.

**Measures**

**Center for Epidemiologic Studies Depression Scale**

The Center for Epidemiologic Studies Depression Scale (CES-D) is a widely used measure for screening depression in community samples.
It comprises 20 items, assessing depressed mood, fatigue, loss of appetite, and sleep disturbance. Participants rated the frequency of these symptoms over the last week on a 4-point scale. The CES-D has strong internal consistency (Cronbach’s α = 0.85–0.90; present sample, α = 0.88) and provides a clinical cutoff of ≥16.

Medication Event Monitoring System

The Medication Event Monitoring System (MEMS) records the date and time of each bottle opening, enabling investigators to better understand the pattern of pill taking between clinic visits. To use the MEMS, enzyme medications were transferred to a standard bottle, and the monitoring cap was placed on the bottle. Each cap stored up to 1800 dose events that were downloaded into a database managed by Aardex Ltd. Parents were provided multiple bottles with MEMS caps.

Electronic monitors offer a continuous, long-term measurement of a specific adherence behavior (eg, pill taking) and are considered the gold standard for measuring oral medication adherence. They provide daily data about the number and timing of positive events (opening the pill bottle). When an event was recorded, it is likely that the patient both ate a meal or snack and took the medication. Unfortunately, the bottle does not record the number of enzymes taken with each meal. Moreover, the bottles provide no information about negative events, which makes it difficult to determine why an event (ie, a bottle opening) is missing. Events could be missing for a number of reasons: patients did not eat a meal or snack and thus did not take the enzymes; patients ate but did not take the enzymes; patients did not use the electronic bottle to dispense the medication; or the bottle failed to record the events. To minimize these difficulties, careful records were maintained of technical difficulties, parental depression and child age were subdivided into meaningful categories. Parents were divided into 3 groups: few to no symptoms (CES-D <10; n = 43), subclinical symptoms (10 ≤ CES-D < 16; n = 15), and clinically elevated symptoms (CES-D ≥16; n = 25). Children were divided into 3 age groups: early childhood (age <5 years, n = 30), middle-childhood (ages 5–9 years, n = 35), and preadolescence (age ≥9 years, n = 18). To maintain statistical power while controlling for multiple comparisons, planned comparisons were used to test the differences in treatment adherence among the parental depression and child age categories. The planned comparisons

**TABLE 1 Parent and Child Demographic and Medical Characteristics**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
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<tr>
<td>Parent demographic characteristics (n = 83)</td>
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<tr>
<td>Primary caregiver</td>
<td>83%</td>
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<td>Father</td>
<td>12%</td>
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<tr>
<td>Other</td>
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<tr>
<td>Parental education, y</td>
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<td>Family income (in $10,000)</td>
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<td>Public insurance recipients</td>
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<td>Families with multiple children with CF</td>
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<tr>
<td>No. of children in family</td>
<td>1.1 ± 0.9</td>
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<tr>
<td>Child demographic characteristics (n = 83)</td>
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</tr>
<tr>
<td>Child age, y</td>
<td>6.4 ± 3.0</td>
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<tr>
<td>Child gender (% male)</td>
<td>51%</td>
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<td>Child enrolled in school</td>
<td>89%</td>
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<tr>
<td>Weight percentile</td>
<td>41.3 ± 28.5</td>
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<tr>
<td>Height percentile</td>
<td>35.1 ± 28.6</td>
</tr>
<tr>
<td>BMI percentile</td>
<td>52.0 ± 29.3</td>
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<tr>
<td>FEV1, percent predicted</td>
<td>87.9 ± 25.1</td>
</tr>
</tbody>
</table>

Unless otherwise indicated, data are presented as mean ± SD. FEV1, forced expiratory volume in 1 second.

* Calculated for the 50 children who were old enough to complete a pulmonary function test.

**Health Outcomes**

Weight was measured at the beginning of each clinic visit; these measures were transformed into z scores by using the National Center for Health Statistics 2000 normative data. Spirometry was performed by a trained technician, and forced expiratory volume in 1 second (percent predicted) was calculated by using Hankinson’s formula. Children aged <6 years were not able to reliably perform spirometry (n = 33).

**Statistical Analysis**

The primary hypotheses were tested by using a mediation analysis. Mediation was selected because it allowed us to evaluate whether parental depressive symptoms lowered enzyme therapy adherence, and thus influencing changes in weight z scores (a.k.a., indirect effect; Figure 1). Child age was also included as a mediator because of the relationship between age and treatment adherence. Robust SEs were generated by using resampling estimates derived from 2000 random draws. Resampling estimates have been shown to be less biased and more powerful than other tests of indirect effects in samples <200. Unstandardized regression coefficients are reported throughout.

To help illustrate the relationships tested by using the mediation model, additional analyses were performed in which parental depressive symptoms, child age, and enzyme therapy adherence were subdivided into meaningful categories. Parents were divided into 3 groups: few to no symptoms (CES-D < 10; n = 43), subclinical symptoms (10 ≤ CES-D < 16; n = 15), and clinically elevated symptoms (CES-D ≥16; n = 25). Children were divided into 3 age groups: early childhood (age <5 years, n = 30), middle-childhood (ages 5–9 years, n = 35), and preadolescence (age ≥9 years, n = 18). To maintain statistical power while controlling for multiple comparisons, planned comparisons were used to test the differences in treatment adherence among the parental depression and child age categories. The planned comparisons
first tested the difference between the 2 highest categories and then tested the difference between the lowest category and the average of the highest categories. To better understand the relationship between enzyme therapy adherence and weight outcomes, adherence was divided into 5 groups based on the average number of daily bottle openings (<1, 2, 3, 4, and ≥5).

Because parental depressive symptoms are most likely to influence adherence to treatments administered at home, adherence to enzyme therapy was calculated separately for home and for school. The parent study from which these data were drawn included minimal information about school start times, after-school care, or day care arrangements, but it did indicate if the child was attending school at each study assessment. Given the lack of specific information regarding the school and day care arrangements or school accommodations, we used a general definition of adherence during school hours and only provide descriptive statistics about adherence at school. Time at school was defined as 8:00 AM to 2:00 PM on weekdays for children attending school (89% of children). These children were expected to have 1 meal at school and 2 meals and 4 snacks at home.

Missing data were managed by using 10 multiple imputations with Barnard and Rubin’s adjustment to degrees of freedom for small samples. Descriptive statistics were calculated using both the existing and imputed data; they are displayed in Table 2, with the percentage of missing data per measure. All parameter estimates reported in the Results were derived from the multiply imputed data. Averages of the imputed data sets were used to generate figures. Multiple imputations were generated by using SAS PROC MI and analyzed by using PROC MIXED and PROC MIANALYZE (SAS Institute, Inc, Cary, NC). Tests of mediation were performed by using Mplus version 4.0 (Muthén & Muthén, Los Angeles, CA).

RESULTS
Descriptive Statistics
Parental Depressive Symptoms
Thirty percent of parents in this study scored above the clinical cutoff score, placing them in the clinically elevated range of depression (CES-D ≥16). An additional 18% endorsed subclinical symptoms (10 ≤ CES-D < 16) (Table 2). The 3 most highly endorsed items were: (1) My sleep was restless; (2) I had trouble keeping my mind on what I was doing; and (3) I felt that everything I did was an effort.

Enzyme Adherence
Using the CFF recommendations, children were, on average, 49% (95% confidence interval [CI]: 43–56) adherent to their enzyme regimen, which is equivalent to taking enzymes with 3.0 (CI: 2.6 to 3.7) meals or snacks per day. Importantly, only 4 children (5%) routinely met or exceeded the recommendations (Fig 1). Adherence was worse at home (42% [CI: 36 to 48] or 2.5 [CI: 2.2 to 2.9] bottle openings per day) than at school (94% [CI: 82–106] or 0.9 [CI: 0.8 to 1.1] bottle opening per day). Of the 74 children attending school, 54% averaged >1 bottle opening per day at school, 38% averaged <1, and 8% recorded no bottle openings.

Relationships Among Child Age, Parental Depressive Symptoms, Enzyme Adherence at Home, and Weight Gain
Parental depressive symptoms were hypothesized to negatively affect adherence to pancreatic enzyme therapy administered at home. As expected, the mediation model indicated that higher numbers of depressive symptoms led to worse adherence at home (−0.8 [CI: −1.5 to −0.1] percent adherence per unit change in CES-D) (Fig 2). There was no significant difference between parents endorsing subclinical versus clinically elevated symptoms of depression (Cohen’s d = 0.02, P = .60); there was a significant difference between parents who endorsed few to no symptoms and those who either endorsed subclinical or clinically elevated symptoms (d = 0.56, P = .02). Children with parents endorsing few to no symptoms were 49% (CI: 40 to 57) adherent (2.9 [CI: 2.4 to 3.4] bottle openings per day) compared with children whose parents endorsed subclinical or clinically elevated symptoms (35% [CI: 26 to 44] adherent; 2.1 [CI: 1.5 to 2.6] bottle openings per day) (Fig 3).

Child age was also significantly related to children’s therapy adherence at home (−3.1 [CI: −5.2 to −1.1] percent adherence per
year of age) (Fig 2), with older children demonstrating worse adherence. No significant difference was found between children in the middle-childhood age range versus preadolescent age range (\(d = 0.43, P = .08\)), but there was a difference between children in early childhood versus those in middle-childhood to preadolescence (\(d = 0.59, P = .02\)). Younger children exhibited higher rates of adherence (51% [CI: 40 to 61] adherent; 3.0 (CI: 2.4 to 3.7) bottle openings per day) than older children (38% [CI: 30 to 45] adherent; 2.3 (CI: 1.8 to 2.7) bottle openings per day).

Mediation analyses also suggest that adherence to enzymes affected gains in weight z scores (0.007 [CI: 0.003 to 0.010] per percentage point of adherence) (Fig 2). Children who were >50% adherent to their enzyme prescriptions at home (\(n = 18\)) exhibited an average gain of 0.5 (CI: 0.2 to 0.8) standardized unit at the next clinic visit, whereas children who were <33% adherent (\(n = 15\)) exhibited an average loss of 0.1 (CI: 0.0 to 0.2) standardized unit (Fig 4).

After controlling for initial weight z scores, the indirect effect of parental depressive symptoms on change in weight z scores via enzyme adherence was significant (\(-0.005\) [CI: \(-0.010\) to \(-0.001\)] gain per unit change in CES-D) (Fig 2). This indirect path suggests that parents endorsing elevated depressive symptoms had children who gained less weight over 3 months than children of parents reporting no depressive symptoms. The indirect effect from child age to child weight gain via enzyme adherence was also significant (\(-0.02\) [CI: \(-0.04\) to \(-0.01\)] gains per year of age). The full model accounted for 22% of the variance in enzyme therapy adherence at home and 37% of the variance in weight gain. Adherence accounted for 30% of the variance in weight gain, and parental depressive symptoms accounted for 7% of the variance in adherence.

**DISCUSSION**

The present study evaluated rates of adherence to pancreatic enzyme regimens in children with CF by using electronic monitors. We examined how child age and parental depressive symptoms were related to both adherence and weight for age at the next clinic visit. Results were consistent with a recent international study reporting elevated rates of depression in parents of children and adolescents living with CF, with nearly one-third of this sample screening above the clinical cutoff. Adding to the current literature, the results suggest that parental depressive symptoms and age mediated the relationship between enzyme adherence and weight gain.
Adherence to enzyme therapy and increased caloric intake are important but challenging treatment recommendations for managing nutrition and weight in children with CF. The CFF recommends that these children consume 110% to 200% of the energy intake requirement for healthy peers and eat at least 3 meals and 3 snacks per day to achieve this elevated intake. Using electronic monitors, participants' adherence was estimated at 42% (2.5 bottle openings) at home and 94% (0.9 bottle opening) at school. Only 7% of children met recommendations for the entire day. These low levels of adherence are concerning, given the importance of weight gain and growth in young children with CF and their long-term association with lung function. Moreover, it seems that adherence rates >50% at home are required for modest gains in weight (Fig 4). Only 46% of the participants were at or above this threshold. Adherence to enzyme recommendations accounted for 30% of the variability in changes in weight, which is substantial.

Consistent with the PSMF, our results suggest that parental depressive symptoms predicted lower adherence to pancreatic enzyme regimens, resulting in worse short-term weight outcomes. Our study did not measure the processes by which parental depression may influence self-management, but it likely occurs through the dynamic interplay between self-management processes identified by the PSMF, including family functioning, parent-child communication, parental beliefs about treatment efficacy, family support, and parental supervision of treatments. There is evidence from 2 cross-sectional studies in pediatric patients with CF that the relationship between depression and treatment adherence may depend on...
the treatment being considered. Both studies reported that parental depression was paradoxically associated with better adherence to airway clearance and offered an explanation that parents may experience “burn out” as they try to facilitate good management of the disease. Given our results, an alternative explanation could be that parents who are depressed may selectively adhere to what they deem the most important elements of the treatment regimen, or they may rally to perform the larger tasks while letting slip other important but less salient components of the regimen (eg, providing enzyme supplements). Although more research is needed to understand the mechanisms through which parental mental health influences self-management, evidence is accumulating that parental mental health is an important contributor to patient self-management in CF.

Results from our study must be considered in light of its limitations. First, although the data were collected prospectively, it was an observational study. Additional studies are required to confirm the suggested links between parental depressive symptoms and adherence to pancreatic enzyme regimens. Second, this study did not measure energy or fat intake, dosing of enzymes, or how well families followed dosing recommendations, thus limiting our ability to comment on the interplay between treatment efficacy and treatment adherence. Third, we used data from the self-identified primary caregiver but did not assess the roles and responsibilities of all caregivers in the home. Finally, families were not randomly sampled from the national registry; generalizing these results to the larger CF population therefore requires caution.

CONCLUSIONS

Results of this study are consistent with previous studies that have reported elevated rates of depressive symptoms in parents caring for children with CF. Our results add to this body of evidence by linking parental depressive symptoms with adherence to enzyme regimens and short-term weight gain. Parents who endorsed mild to clinically significant depressive symptoms had children who took their enzyme supplements with 5.2 fewer meals per week than children of parents endorsing few to no symptoms. Given the relationship between enzyme therapy adherence and weight gain, this poor adherence resulted in fewer gains in weight for children of depressed versus nondepressed parents. Recently, data from TIDES (The International Depression/Anxiety Epidemiological Study) led to the development of an international guideline on mental health in CF, which recommended annual screening of parent caregivers for symptoms of depression and anxiety. These results, coupled with the elevated rates of depressive symptoms in parents of children with CF found across 9 countries (37% of mothers and 31% of fathers) and the availability of effective interventions for depression, strongly indicate that identifying and treating parental mental health issues (eg, depression) may be an important pathway for improving treatment adherence during childhood. Interventions aimed at improving adherence and evidence-based interventions to address depression are currently being tested in multicenter studies.

ABBREVIATIONS

CES-D: Center for Epidemiologic Studies Depression Scale
CF: cystic fibrosis
CFF: Cystic Fibrosis Foundation
MEMS: Medication Event Monitoring System
PSMF: pediatric self-management framework

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REFERENCES


Numerous studies have shown that parental mental health is an important contributor to patient self-management in cystic fibrosis (CF). Our results add to this evidence by linking parental depressive symptoms to adherence to enzyme regimens and short-term weight gain. Parents who endorsed mild to clinically significant depressive symptoms had children who took their enzyme supplements with fewer meals per week than children of parents endorsing few to no symptoms. Given the relationship between enzyme therapy adherence and weight gain, this poor adherence resulted in fewer gains in weight for children of depressed versus nondepressed parents. This highlights the importance of screening and treating parental mental health issues to improve adherence and outcomes in CF.


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