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**Efficacy of cyproheptadine for appetite stimulation in children with cystic fibrosis**

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**Background:** Cystic fibrosis (CF) is an autosomal-recessive disease that results in progressive lung disease and may lead to poor nutritional status secondary to pancreatic insufficiency (PI). Because of impaired digestion and malabsorption, weight loss and malnutrition are complications of CF, and have been linked to declining lung function and increased infection. This study aims to evaluate the impact of cyproheptadine on nutritional status and lung health in children with CF and PI.
**Methods:** A retrospective chart review was conducted on patients aged 1 to 21 with CF and PI initiated on cyproheptadine for appetite stimulation between 2013 and 2019. Fifty-two patients with poor nutritional status were analyzed, comparing changes in body mass index (BMI) z-scores or weight for length based upon age, lung function (forced expiratory volume in 1 second [$FEV_1$]), and pulmonary exacerbations for 1 year before and 1 year after starting cyproheptadine or until discontinuation.
**Results:** Patients initiated on cyproheptadine realized an improvement in BMI z-scores of 0.363 ($p = 0.002$) and weight-for-length z-scores of 0.96 ($p < 0.001$) after 12 months. Reduction in the number of exacerbations was demonstrated, with 1.41 fewer exacerbations per calendar year ($p < 0.001$) 12 months after cyproheptadine initiation. There were no significant changes in FEV1.
**Conclusions:** The results of this study indicate a clinical benefit with cyproheptadine for appetite stimulation based on use for at least 12 months. Cyproheptadine was found to be an appropriate therapy to improve nutritional status, as demonstrated by significant increase in BMI and weight-for-length z-scores, and was correlated with fewer exacerbations. These findings suggest that cyproheptadine is an effective treatment addition for providing alternative nutritional support in people with CF and PI as young as 1 year old.

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**Caregiver perceptions of a lifestyle education tool and subsequent behavior changes with elexacaftor/tezacaftor/ivacaftor initiation**

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**Background:** Elexacaftor/tezacaftor/ivacaftor (ELX/TEZ/IVA) is a cystic fibrosis (CF) transmembrane conductance regulator (CFTR) modulator currently approved for persons with CF aged 6 and older with at least one copy of the F508del mutation or another eligible mutation. ELX/TEZ/IVA should be taken every 12 hours with fat-containing (10–20 g) foods and pancreatic enzyme therapy for optimal absorption. In clinical trials, ELX/TEZ/IVA increased body mass index (BMI) by 1 $kg/m^2$. Some adolescents started on ELX/TEZ/IVA at our center had rapid weight gain leading to overweight or obese status. We developed a proactive educational tool to increase caregiver knowledge about nutrition, physical and mental wellbeing, and anticipated outcomes with ELX/TEZ/IVA use in children aged 6 to 11, with the goal of providing education and avoiding rapid weight gain.
**Methods:** As part of a quality improvement project, multidisciplinary clinical care team members and family partners created an educational tool (Figure 1) to educate patients and families on the impact of ELX/TEZ/IVA therapy on BMI and potential lifestyle changes. Several months after the ELX/TEZ/IVA educational session, a survey was sent via the patient portal in our hospital's electronic medical record to caregivers of children aged 6 to 11 started on ELX/TEZ/IVA. This survey assessed caregiver perceptions of the educational tool and subsequent behavioral changes at home after ELX/TEZ/IVA initiation.

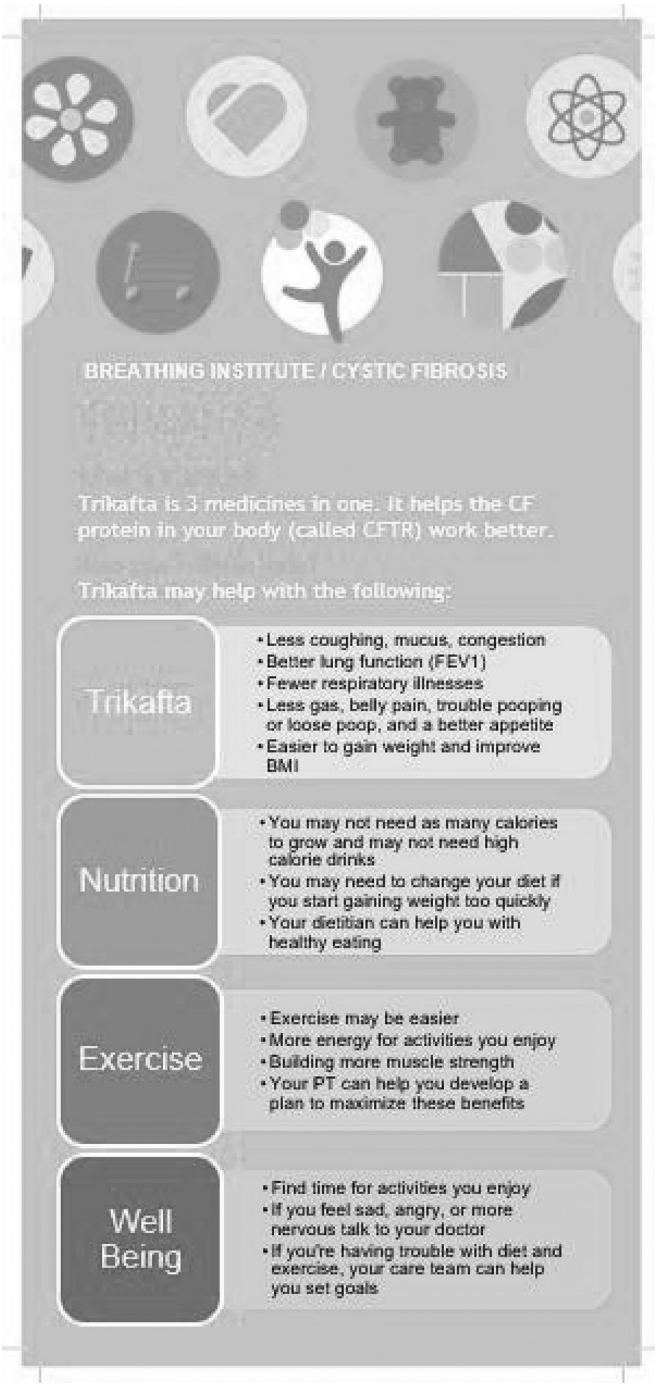


**Figure 1.** Elexacaftor/tezacaftor/ivacaftor (Trikafta) education tool

**Results:** We received 37 survey responses. Twenty-eight (76%) remembered receiving the educational tool and found it helpful, seven (19%) did not remember receiving it, and two (5%) did not find it helpful. Two-thirds requested that future educational materials be provided electronically. Caregivers reported potential side effects ($n = 26$) as the biggest concern with ELX/TEZ/IVA initiation, and some were concerned about insurance coverage ($n = 13$) or lack of improvement with treatment ($n = 11$). Nutritional and lifestyle changes that were made after ELX/TEZ/IVA

initiation included increasing fat at breakfast ($n = 14$), switching ELX/TEZ/IVA dose from bedtime snack to dinner ($n = 13$), and increasing activity levels ($n = 8$). Fifty-seven percent of respondents did not report making any dietary changes to reduce caloric intake; the most common reported changes were choosing healthier snacks (11%), stopping oral supplements (9%), and switching to lower-fat milk (9%). Caregivers identified multiple improvements with ELX/TEZ/IVA use, including eating more food at meals ($n = 18$), fewer stomach aches ($n = 11$), more actively playing ($n = 11$), eating bigger snacks ($n = 10$), and sleeping better ($n = 8$). BMI will be measured as the next step of this project (with data available before the North American Cystic Fibrosis Conference).

**Conclusions:** Using a standardized education tool, we hoped to increase CF caregiver knowledge before ELX/TEZ/IVA initiation. Families in our CF clinic received this educational tool well, and it aided our medical team when initiating discussion about starting ELX/TEZ/IVA. Most caregivers reported dietary or lifestyle changes after beginning ELX/TEZ/IVA therapy and some improvements in eating, activity, and sleeping. As Food and Drug Administration approval of ELX/TEZ/IVA expands to lower age ranges, appropriate nutritional and lifestyle education will be required to ensure normal growth in young children treated with CFTR modulators.

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## Clinical characteristics of children with cystic fibrosis who receive gastrostomy tubes

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**Background:** Gastrostomy tubes are commonly used to optimize enteral nutrition in patients with cystic fibrosis (CF), but few studies have explored the characteristics of children with CF who undergo gastrostomy tube placement.

**Methods:** We compared clinical characteristics, including demographic characteristics, method of diagnosis, nutritional interventions, and chronic pulmonary medication use, of patients who received gastrostomy tube with those of patients who did not from 2003 to 2019 within the Cystic Fibrosis Foundation (CFF) Patient Registry (CFFPR). Date of gastrostomy tube placement is not available in the CFFPR, so we defined year of gastrostomy tube placement as the first year in which the presence of a gastrostomy tube was indicated. Being malnourished was defined according to Centers for Disease Control and Prevention weight-for-age z-scores (WFAz <−1). We used chi-square tests for categorical variables and Student t-tests for continuous variables.

**Results:** There were 10,185 total children with CF in the CFFPR who met inclusion criteria, including 2,337 (22.9%) with a gastrostomy tube. Mean age at gastrostomy tube placement was 4.25 (95% CI, 4.12–4.39). Children who received a gastrostomy tube were more likely than those who did not to be diagnosed via meconium ileus (28% vs 16%) or failure to thrive (22% vs 11%), have only Class I to III CF transmembrane conductance regulator (CFTR) mutations (87% vs 78%), have ever used dornase alfa (30% vs 21%), and have been malnourished in the year of entry into the CFFPR (65% vs 35%). There were no substantial differences in sex, age at diagnosis, race or ethnicity, pancreatic enzyme replacement therapy, use of antireflux therapies or supplemental feedings, infection with *Pseudomonas aeruginosa*, or use of Medicaid or state insurance [Table 1].

**Conclusions:** To our knowledge, this is the first CFFPR data analysis describing patient characteristics associated with gastrostomy tube placement. Our findings may inform providers and parents in making clinical decisions with respect to children with CF at risk for gastrostomy tube placement, with particular attention to early malnourishment as a potentially modifiable risk factor that may help to avoid gastrostomy tube placement.

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## Re-evaluating the expression profile of SLC26A3 (down-regulated in adenoma) chloride/bicarbonate exchanger in the small intestine using human models: Implications for cystic fibrosis

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**Background:** Small-intestinal bicarbonate secretion aids in epithelial protection, digestion, and absorption. The cystic fibrosis (CF) transmembrane conductance regulator (CFTR), together with putative anion transporter-1 (PAT-1) and down-regulated in adenoma (DRA) chloride/bicarbonate exchangers, regulate intestinal bicarbonate transport in the small intestine. Prior mouse studies have suggested that PAT-1 is the primary chloride/bicarbonate exchanger in the small intestine, with DRA predominant in the colon. Data on the expression profiles of PAT-1 and DRA in human small intestine are limited. This is especially relevant for people with CF, in whom we have identified that chloride/bicarbonate exchange can compensate for loss of CFTR-mediated bicarbonate transport in the duodenum. The aim of the current study is to examine the expression profile of PAT-1 and DRA in the human small intestine and determine whether they are altered in CF.

**Methods:** We analyzed existing single-cell ribonucleic acid sequencing (sc-RNA-seq) metadata annotations on human small intestine and colon [1–3] using the Seurat R toolkit. Data available for each segment were as follows: duodenum (5944 cells, 5 subjects), ileum (6167 cells, 2 subjects), and colon (4472 cells, 2 subjects). CFTR, PAT-1, and DRA messenger (m)RNA and protein expression were also examined in human enteroids and biopsies using quantitative polymerase chain reaction and confocal immunofluorescence. $CFTR_{inh}$-172 was used for CFTR inhibition.

**Results:** Duodenal and ileal datasets showed higher expression of DRA mRNA than of PAT-1 mRNA (~3–4x in duodenum, ~2x in ileum). The expression profile across all segments was DRA > CFTR > PAT1. DRA expression in the colon was comparable with that in the duodenum and higher than the ileum. PAT-1 was higher in the duodenum and ileum than in the colon. DRA and PAT-1 were predominantly expressed in enterocytes. DRA was also expressed in BEST4+ cells. DRA protein was robust in villus enterocytes in human duodenal biopsies ($n = 3$). In patient-derived duodenal enteroids, DRA was expressed in crypt-like (undifferentiated) and villus-like (differentiated) enteroids ($n = 3$ each), with 20 times as much mRNA expression in the Day 5 differentiated enteroids. DRA mRNA expression was approximately 10 times as high as PAT-1 in Day 5 differentiated enteroids. Upon CFTR inhibition ($CFTR_{inh}$-172, 20 mM, 40 minutes) in apical-out enteroids, there was a significant increase in DRA membrane localization.

**Conclusions:** In humans, DRA is expressed throughout the small intestine —in the duodenum at levels comparable to the colon. Thus, in humans, DRA may play a more prominent role in small intestinal bicarbonate secretion than previously appreciated based on mouse data. Our observations that DRA is increased upon loss of CFTR function is consistent with a recent report of increased DRA in CF ileum [4]. Work examining DRA and PAT-1 expression and function in non-CF and CF intestine in humans to identify CFTR-independent means to restore defective intestinal bicarbonate secretion in CF is ongoing.

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