A Randomized Controlled Trial of an Outpatient Protocol for Transitioning Children from Tube to Oral Feeding: No Need for Amitriptyline

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Objective To assess the role of amitriptyline in the effectiveness of an outpatient protocol for weaning medically complicated children from tube to oral feeding.

Study design Twenty-one children seen in multidisciplinary outpatient feeding teams across 4 sites were recruited to a randomized placebo-controlled trial of a 6-month outpatient treatment protocol with behavioral, oral-motor, nutrition, and medication components.

Results All of the children who completed the 6-month program (73%) were weaned to receive only oral feeding, regardless of group assignment. The transition from tube to oral feeding resulted in decreases in body mass index percentile and pain, some improvements in quality of life, and no statistically significant changes in cost.

Conclusions Amitriptyline is not a key component of this otherwise effective outpatient, interdisciplinary protocol for weaning children from tube to oral feeding. *(J Pediatr 2016;172:136-41)*.

Trial registration ClinicalTrials.gov: NCT01206478.

Feeding problems that require medical intervention occur in 3%-10% of children.[1] Premature infants are overrepresented among children with feeding problems.[2] Improved preterm infant survival has increased the prevalence of feeding problems in older infants and toddlers.[3] In addition, severe feeding problems occur in 40%-70% of children with chronic medical conditions.[4,5] Neonates with long intensive care hospitalizations may miss early eating learning opportunities and may associate eating with pain or discomfort.[6] Gastric and gastrojejunal tube feeding requirements may persist for months or years secondary to these early medical issues resulting in chronic oral food refusal. As the prevalence of gastric tube feeding has increased, so have the challenges associated with transitioning a child from tube to oral feeding.[7,8]

There are several methods for achieving the transition from tube to oral feeding.[9] Many programs consist of rigorous behavioral outpatient treatment or inpatient stays.[8,10-12] Lengthy hospitalization and intensive outpatient treatments cause family disruption, emotional distress, and financial burden.[13] Few studies, other than case reports,[14-16] have examined the effectiveness of outpatient feeding programs for transitioning children from tube to oral feeding.[13] A recent systematic review suggests that appetite manipulation and behavioral therapy are efficacious for outpatient tube weaning.[9]

A randomized outpatient study compared 7 weekly outpatient sessions of behavior therapy to a traditional nutritional intervention for chronic oral food refusal. The behavioral treatment group had a 47% success rate compared with 0% in the nutritional group.[13]

An interdisciplinary treatment protocol to transition children from tube to oral feeding was developed by our team.[17] The initial 9 patients to undergo this multidisciplinary, multicomponent treatment all transitioned to oral feeding immediately following treatment, and 8 patients (89%) maintained this 6 months after treatment.

Because 2 medications were involved in the treatment, a randomized controlled trial using only 1 of the medications (amitriptyline) was considered a necessary step to further evaluate the role of medication in the patient.

Amitriptyline is used to treat chronic neuropathic pain, cyclic vomiting syndrome, and migraine headache in all age groups, except infants and toddlers.[18] Currently, there is only anecdotal data on the use of amitriptyline in infants and toddlers. At low doses, there are no reports of death or serious side effects such as cardiac arrhythmias. Amitriptyline was theorized to be a key component of the multidisciplinary treatment protocol.

This study aimed to assess the efficacy of amitriptyline as 1 component of a 24-week outpatient protocol for transitioning children from tube to oral feeding. We hypothesized that children receiving amitriptyline would more likely transition to oral feeding (defined as consuming at least 90% of their daily calories orally) than those receiving placebo. A secondary aim was to assess the role of pain in the efficacy of the protocol. We hypothesized that children receiving amitriptyline

ITQOL	Infant Toddler Quality of Life
NCCPC-R	Noncommunicating Children's Pain Checklist-Revised

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would demonstrate less pain, as reported by their parents/caregivers, and this would contribute to successful transition to oral feeding.

Methods

Patients were identified through interdisciplinary feeding teams at each site. Institutional Review Board approval (12261) and ClinicalTrials.gov registration were obtained prior to enrollment. Once a child met the inclusion/exclusion criteria, families were invited to participate and consent obtained. Baseline measures were obtained by clinical trials staff at each site, after which the statistician assigned the child to placebo/amitriptyline using randomization software and conveyed this information to the pharmacy, keeping research and clinical staff blind to assignment. Medication and instructions were identical regardless of group assignment and included a dose based on subject weight (0.33 mg/kg qhs).[19] The dose was increased weekly by 0.33 mg/kg until the final dose equaled 1 mg/kg. Shelf life of the active compounded liquid is 1 month, so refills were provided to both groups (placebo/amitriptyline) each month. The amitriptyline and placebo preparation were identical for taste, look, and smell. Feeding schedules were changed such that patients were fed their usual total volume and usual formula by continuous drip over 12 hours into the small intestine. Families were encouraged to contact team members with questions or concerns at any time throughout the study. Families who consented to the protocol were offered $50 for each major clinical visit (weeks 0, 10, and 24; $150 total) as reimbursement for transportation, effort for measure completion, and other costs.

Families received a weekly phone call from a research team member to assess the child's parent-reported weight, feeding habits, progress, and any negative side effects. If serious problems arose, providers were unblinded to the group assignment, the subject was withdrawn, and patients received all necessary treatment.

Families had 8 outpatient clinic visits after signing consent, each of which took approximately 1 hour (Figure 1). Visits were led by clinical research staff, and measures were completed as indicated, as well as medical monitoring at every clinic visit, which included electrocardiogram (ECG), vital signs, height, weight, blood draws (complete blood count with differential, comprehensive metabolic profile), and morning cortisol (at weeks 10, 15, and 19 only). During the week 10 visit, the team prescribed the appetite stimulant megesterol (3 mg/kg two times a day). Five days after beginning the appetite stimulant, tube feedings were reduced by 1 hour each night, such that within 12 days patients were receiving no calories through their tubes. Megesterol was discontinued after 6 weeks. Amitriptyline was discontinued 6 months from when it was started by weekly titration to smaller doses over 1 month, unless the treating physician decided otherwise based upon clinical indicators.

Families were instructed to sit the patient at a table or in a high chair at home for at least 3 meals daily for approximately 10-20 minutes. Parents were instructed to present a variety of foods including some that are preferred, and some that are not, varying textures as appropriate for patient skill. Although feeding highly nutritious foods is important, for the purpose of switching from tube to oral feedings, the primary focus was on increasing oral caloric intake. It was stressed that parents never force anything into their child's mouth, including food.

Criteria for patient inclusion were 9 months to 9 years of age, having a history of chronic oral food refusal (3 months of refusing to eat more than 50% of their caloric required orally), and having been tube fed for 3 months or longer. Patients with known gastrointestinal disorders, which would negatively affect their progress (such as esophageal stricture or chronic intestinal pseudo-obstruction) were excluded, as were children with uncontrolled seizures or heart disease with cardiac conduction abnormalities. Patients unable to meet the behavioral and occupational therapy criteria for necessary oral-motor skills and behavioral control (Table I) were excluded or were trained to meet the inclusion criteria and then enrolled. Finally, patients were to be withdrawn from the protocol at any time if their weight loss exceeded 10% of initial body weight.

Measures

Percentage of kilocalories obtained orally was obtained using the 24-hour food recall, a standardized 5-pass method developed by the US Department of Agriculture for use in national dietary surveillance. This measure has been widely used in several large trials, and data suggest it is the most valid and reliable method of dietary assessment for children.[20] The data were collected at week 0, week 10, and week 24 using

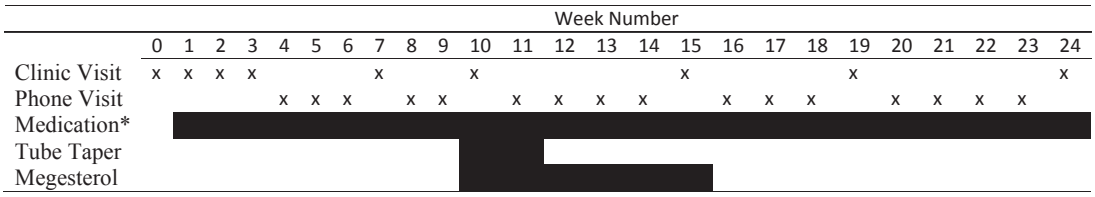

Figure 1. Procedures timeline. *Medication was randomly assigned (placebo, amitriptyline) and included a 3-week taper up in weeks 1, 2 and 3.

Table I. Oral-motor and behavioral skills

Name of skill	Descriptor
Age-appropriate strength and coordination of the oral cavity*	Adequate range of motion, strength and coordinated movement of the lips, tongue, jaw; if safety of swallow is in question, a study will be done to assess; child must have safe swallow to proceed
Head/neck/trunk support*	Strength and control of the head, neck, and trunk to provide midline stability of the body
Sensory processing*	No major overt sensory processing issues that interfere with daily life activities, specifically eating/feeding
Regular meals*	Coming to the meal setting at least 2-3 times per day, willingly
Limited grazing†	Child does not simply graze throughout the day, but participates in structured family mealtimes
Same location*	Daily meals take place in the same location
Meal Length†	Meal length falls between 10-20 minutes
Meal distractions†	There are few distractions during mealtime (ex. TV), that occur on a routine basis; a child who requires significant distraction in order to take bites is not eligible
Family mealtime†	The child and family eat meals together on a regular basis
Structured start and end†	The parent dictates the start and end of the meal with a simple command such as "It's time to eat" or "You may get down now"
Parent behavior during meals†	Parent behavior during meals is appropriate with limited coaxing and no yelling or threatening
Force feeding*	There is never any forcing of food or other objects into the child's mouth
Meal demeanor*	Child is neutral or positive in response to mealtime without crying or constantly turning head away from spoon
Good food presentation†	Appropriate amount/variety of foods are presented in a calm, relaxed manner; feeders announce each bite

*Required prior to starting protocol.
†Trained during first 10 weeks of protocol if not present at baseline.

standardized probes by highly trained research staff, and parents were presented with paper food models and measuring devices prior to interviews to reference during the recall. Recalls were analyzed with the Nutritional Data System for Research, v 2005; University of Minnesota, Minneapolis, Minnesota.

Noncommunicating Children's Pain Checklist-Revised (NCCPC-R) is a 30 item measure intended to assess pain in children who are unable to speak because of cognitive or physical impairments. Previous research indicates strong psychometric properties ($\alpha = 0.93$) and acceptable reliability across 3 time points in the current study ($\alpha = 0.80$) There are 7 subscales including vocal, social, facial, activity, body/limbs, physiological, and eating/sleeping.[21] This measure was completed by parents at week 0, week 10, and week 24.

Child quality of life was measured with the Infant Toddler Quality of Life (ITQOL) v 04.06 questionnaire, which has been validated for children as young as 2 months of age. The measure has 97 items which result in 9 multi-item scales, 2 global items, and 2 single item (only multi-item scales were included here). The ITQOL is a well-established, reliable (Cronbach $\alpha > .70$), and valid measure of infant and toddler quality of life. This measure was completed by parents at week 0 and week 24.

In order to assess cost of caring for their child, parents completed a simple questionnaire asking them the amount of money they spent on the medical care of their child in the previous week. Costs were broken out by medications, food, and other care items. This measure was completed by parents at week 0 and week 24.

Statistical Analyses

Descriptive statistics were run for the overall sample and to test for differences at baseline between groups. Analyses for aim 1 first assessed effectiveness of the protocol for the entire sample, regardless of group assignment using paired samples *t* test or signed rank test if normality assumption was violated for all primary outcome variables. To test for differences between groups, 2-sample *t* tests were run or the Wilcoxon rank-sum test was run if the normality assumption was not satisfied. To assess aim 2, a bivariate correlation was run between change in % kilocalories obtained orally and change in pain on the NCCPC-R. As this is a pilot study, corrections for multiple comparisons were not included. The analyses of 24-week pre-post change were based upon completers only. An a priori sample size calculation based upon the primary outcome variable of % kilocalories obtained orally (assuming a success rate in the amitriptyline group of 80%, and in the control group of 30%), revealed that a 1-sided Fisher exact test has 81% power of detecting the difference with 15 subjects in each group (total 30 patients).

Results

A total of 21 patients were randomized and enrolled September 2010 through December 1, 2014 (**Table II** and **Figure 2**; available at www.jpeds.com). Baseline characteristics are presented in **Table III** (available at www.jpeds.com). Twelve were assigned to placebo and 9 to amitriptyline; 10 were female (52.63%) and 17 were white (80.95%). The 2 groups (placebo, amitriptyline) were not significantly different at baseline on any key characteristics. Two patients withdrew prior to the baseline visit (10%), and 5 more patients withdrew during the study (5 placebo, 2 amitriptyline; 24%) leaving 14 completers (7 placebo, 7 amitriptyline). Reasons for withdrawal included not completing baseline paperwork (n = 2); seizure (n = 1, assigned to placebo), parent disagreement regarding suitability of patient for protocol (n = 1), poor compliance with protocol (n = 1), and weight loss (n = 2).

All patients who completed the protocol (regardless of group assignment) obtained 100% of their kilocalories orally at post-treatment (baseline % kilocalories oral = 26.93 ± 16.31; post = 100.00 ± 0.00; $t = -16.16$, $P < .001$). Body mass index percentile decreased across the entire sample from pre

(45.11 ± 30.63) to post (27.86 ± 30.52; $t = 2.73$, $P = .017$). Pain decreased from pre (12.85 ± 12.37) to post (8.0 ± 14.27; $t = 1.85$, $P = .006$). Nonstatistically significant changes from pre to post included decreases in total cost of care (in US dollars; pre = 643.54 ± 1495.98; post = 115.29 ± 149.19; z = 1.51; $P = .13$). **Table IV** (available at www.jpeds.com) shows quality of life changes. There were no between group (placebo/amitriptyline) differences for change from pre to posttreatment for any of the measures (**Table V**).

Aim 2, the role of pain in the efficacy of the protocol (regardless of group assignment), was difficult to assess as all of the children who completed the study were taking all of their calories orally at the end of the study, meaning that there were ceiling effects in terms of protocol effectiveness. The correlation between change in % kilocalories obtained orally and change in total NCCPC-R score was not significant (Pearson correlation = −0.35, $P = .27$).

There were no serious adverse events reported during the current study that were determined to be associated with the protocol. Reported symptoms that patients experienced during the study period included irritability, vomiting, choking, constipation, cough, Crohn's disease exacerbation, elbow injury, fever, gum sensitivity/teething, infectious pneumonia, postnasal drip, restless sleep, watery eyes, and low cortisol levels. The low morning serum cortisol levels were associated with the 6 weeks of megesterol. Based upon these findings in the initial subjects, we changed the protocol to include megesterol for only 4 weeks, instead of the planned 6 weeks, which avoided the adrenal hypofunction. There were no side effects or ECG changes associated with the amitriptyline. Details of the effects of amitriptyline on ECGs can be found in a separate publication.[22]

Discussion

The current study assessed the efficacy of amitriptyline in a 24-week outpatient multidisciplinary protocol for transitioning infants and toddlers from tube to oral feeding. Of the 21 patients who were randomized, 2 did not complete baseline paperwork, and 5 more withdrew during the protocol. The rate of drop out after starting treatment (24%) is consistent with previous research of this nature (30%; 12). Of all patients enrolled in the study (including completers and noncompleters), 87.5% transitioned to oral feeding regardless of group assignment, demonstrating that amitriptyline was not necessary in transitioning children to oral eating. The only other study of an outpatient clinic based protocol for moving children off of their feeding tubes found a 47% success rate for their behavioral therapy intervention (and a 0% success rate for their nutritional intervention).[13] A study of weaning children through hunger provocation during a day-treatment program[23] attained an 86% success rate in the 2-week program. Thus, the success rate of the current protocol appears to be an improvement over both clinic based programs and day-treatment programs.

Table V. Change scores from pre to post on key variables by group

	Amitriptyline	Placebo
% Kilocalories obtained orally	68.62 (17.29)	76.89 (15.68)
BMI percentile	−25.06 (29.47)	−9.44 (14.25)
NCCPC-R	−2.5 (19.85)	−6.86 (8.65)
ITQOL-Behavior	−20.63 (38.25)	−16.58 (42.53)
Cost of care	−61.67 (89.34)	−994.83 (1884.78)

BMI, body mass index.
Note: differences not statistically significant.

The current study used an appetite stimulant, which could have contributed to the success of participants. The precise mechanism of action that leads to increased appetite and weight gain is unknown, but is likely related to megestrol's glucocorticoid effect.[24] There are several pediatric trials examining megesterol therapy for anorexia or malnutrition[25-27]; however, safety and efficacy in children like those studied here remain to be defined. Studies of megestrol and other appetite stimulants used in the pediatric population are warranted, with a focus on their use in facilitating tube weaning.

Our primary measure of body mass, body mass index percentile, decreased regardless of group assignment, but remained in the "normal" range. Hartdorff et al found a mean weight loss of 8.8% in their hunger provocation day-treatment study, less than the rate of weight loss found here. Across both our study and the Hartdorff study, a few parents withdrew children because of parent concerns about weight loss. Unfortunately, neither study assessed for parent stress using a validated measure, which would help to further delineate the relationship between parent stress and tube weaning. Another possibility regarding the weight loss seen in children undergoing the transition from tube to oral feeding may be that tube-fed children are actually overfed.[28]

We hypothesized that pain plays an important role in feeding refusal in children,[29] which is why we included a pain treatment medication (amitriptyline) and jejunal feedings in our protocol. The current results do not support amitriptyline as a key component, but it is possible that pain (or, parent perception of pain) may play a role. Pain, as measured by parent report, decreased from pre to post for the entire sample, with no differences by group, and there was no relationship between change in % kilocalories oral and change in pain scores. All patients in our study received continuous overnight feedings for 10 weeks prior to the initiation of tube weaning. Continuous overnight feedings avoid the gastric distension associated with bolus feeding, which can be perceived as a noxious stimulus in a patient with visceral hypersensitivity. Lack of pediatric-specific literature comparing the use of continuous vs bolus feeds highlights the existence of a knowledge gap that, if studied, may help us to understand how pain may be related to weaning in tube fed children.

Baseline and poststudy scores for quality of life were generally low (poor). Others reported children with functional abdominal pain and burns[30] had quality of life scores that were, on average, at least 10 points higher than the scores

found in this tube feeding sample. Our data do suggest that tube feeding may negatively impact child quality of life, and that transitioning to oral feeding may improve child quality of life, but that it still may remain negatively impacted even after the transition to oral feeding. Thus, there may be a need for continued work with the family to improve quality of life even after the transition has taken place, which is not currently part of routine interdisciplinary clinical care.[31] The current results suggest that quality of life improves, as measured by some subscales, as a child transitions from tube to oral eating. The subscales of Growth and Development; Behavior; General Health Perceptions; Parental Impact: Emotional; and Parental Impact: Time improved significantly on the ITQOL from pre- to posttreatment. Therefore, any work on quality of life after the transition to oral feeding may want to focus on Physical Abilities; Discomfort/Pain; Temperament and Moods; and General Behavior as these were the subscales that did not see statistically significant improvements from pre- to posttreatment.

The average cost of care decreased as the child transitioned from tube feeding to oral feeding, but this change was not statistically significant because of the large variations in reported cost, regardless of group assignment. Future studies would overcome these weaknesses by using a larger sample size, or by using a more highly structured measure of cost, perhaps one that also asked if the previous 7 days was representative of the previous weeks or asked about a representative week, as possibly there was also variability on a week by week basis that was not captured by our current measure.

The current study had several weaknesses, primarily our small sample size. The small sample size was directly due to problems with recruitment, which occurred uniformly across the 4 participating sites. The primary reason for refusal was that parents did not want to be randomly assigned to the amitriptyline/placebo; they either wanted the drug or did not, but refused to leave that decision to chance. Despite the lack of ability to recruit our target, however, we did achieve statistically significant results for the effectiveness of our protocol, indicating that our power calculations may have overestimated our needs. It is also possible, however, that had we recruited a larger sample, some of our secondary measures, such as cost, may have achieved statistically significant results. Further research with larger samples will be necessary to determine if and how amitriptyline may affect the relationship between pain and oral intake in these medically complicated children. Future research will also need to assess how our protocol works for specific age groups and developmental ranges, as these ranges for the current study were rather broad.

In terms of future directions, we need a better understanding of which remaining parts of the protocol are key to successful weaning, particularly focusing on whether or not megesterol impacts the transition to oral feeding. Other important components of the protocol that need further investigation include the use of continuous jejunal feedings, the 10-day nature of the tube wean, and the impact of the amount of time a child has been tube fed on this weaning process. Outside of protocol efficacy, the results here have suggested a need for future research regarding whether or not tube fed children are overfed, and what role parent stress plays in the weaning process. For example, it may be possible that amitriptyline could be useful for specific groups of children, such as those from families where parent stress plays a very large role, or for children with a significant pain history.

In sum, the current study does not support amitriptyline as a component of our protocol for weaning children from tube to oral feeding. Future research, as outlined above, is needed in order to determine the optimal methods for moving medically fragile children from tube to oral feeding. ■

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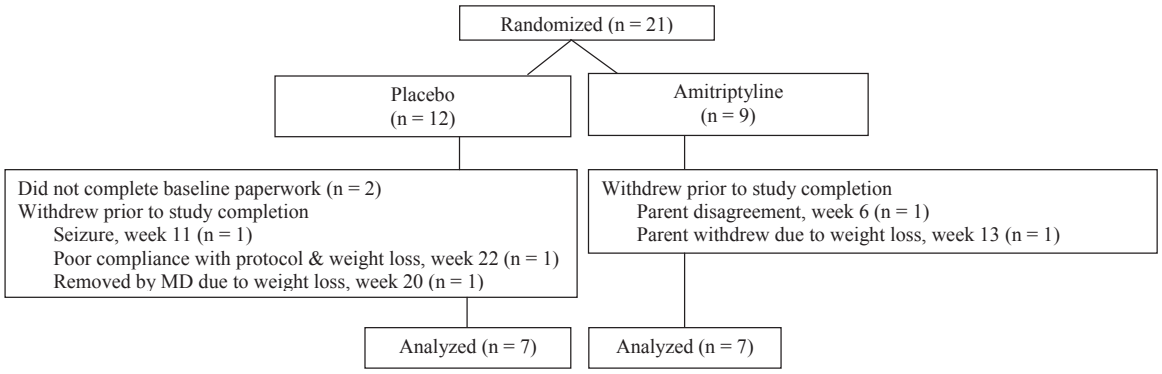

Figure 2. CONSORT diagram. *MD*, physician.

Table II. Pre-existing diagnoses at time of enrollment*

Age, y	Sex	Diagnoses
3	F	Spastic quadriplegia, strabismus
2	F	Abnormal facies, hypotonia, developmental delay
4	M	None†
4	F	Cow milk protein allergy
2	M	Abnormal facies, developmental delay
6	F	Abnormal facies, low muscle mass, hypotonia, developmental delay
2	M	Developmental delay, GERD, asthma, allergies
3	F	Autosomal deletion syndrome, webbed toes, GERD, constipation
4	M	Developmental delay, constipation
3	F	Asthma
4	M	Constipation, sinusitis, GERD
4	F	Asthma, constipation
3	M	Attention deficit hyperactivity disorder, GERD
3	F	Respiratory failure (vent dependent), vomiting, constipation, asthma, GERD
7	F	GERD, recurrent ear infections, developmental delay
3	M	Developmental delay
4	F	Crohn's disease, reactive airway disease, colostomy, scoliosis
4	M	Constipation, seizure disorder, short stature, developmental delay, cerebral palsy, GERD
6	M	Bronchopulmonary dysplasia, necrotizing enterocolitis, postfundoplication, vomiting, constipation, attention deficit hyperactivity disorder, patent ductus arteriosus postligation
4	M	Reactive airway disease, GERD, hepatitis

F, female; *GERD*, gastro-esophageal reflux disease; *M*, male.
*For 1 patient who was consented, not enrolled, this information was not available, so they are not listed below.
†All patients had pre-existing diagnoses of feeding problems or failure to thrive prior to initiation of tube feedings.

Table III. Baseline demographics for total sample, and by group

	Total sample	Amitriptyline	Placebo
N	21	9	12
Sex (% female)	52.63	44.44	60.00
Age, mean (SD)	3.73 (1.99)	3.54 (2.25)	3.89 (1.84)
% Caucasian	80.95	100.00	66.67

Note: differences not statistically significant.

Table IV. Results of the ITQOL

Subscale	No. of items	Baseline mean (SD)	Post mean (SD)	*t*
Physical abilities	10	71.11 (30.95)	72.59 (17.19)	−.280
Growth and development	10	61.25 (13.51)	70.83 (12.85)	−2.285*
Discomfort/pain	3	70.83 (26.71)	79.86 (16.07)	−1.817
Temperament and moods	18	71.53 (11.28)	74.31 (13.26)	−.665
General behavior	12	63.37 (14.50)	66.67 (17.04)	−1.012
Behavior	15	62.22 (9.44)	69.31 (9.81)	−2.376*
General health perceptions	11	39.39 (13.41)	49.43 (20.42)	−2.717*
Parental impact: emotional	7	63.09 (12.86)	70.24 (11.02)	−2.232*
Parental impact: time	7	66.27 (22.47)	82.94 (20.55)	−3.718†

Only multi-item scales were included in the current study.
*$P < .05$.
†$P < .005$.