Examining Clinical Trial Results with Single-Subject Analysis: An Example Involving Behavioral and Nutrition Treatment for Young Children with Cystic Fibrosis

Scott W. Powers,[1,2] PhD, ABPP, Carrie Piazza-Waggoner,[1] PhD, Julie S. Jones,[3] PsyD, Kathleen S. Ferguson,[1,2] PhD, Cori Daines,[2,4] MD, and James D. Acton,[2,4] MD

[1]Division of Behavioral Medicine and Clinical Psychology, Cincinnati Children's Hospital Medical Center, [2]Department of Pediatrics, University of Cincinnati College of Medicine, [3]Division of Developmental and Behavioral Pediatrics, Greenville Hospital System Children's Hospital, and [4]Cystic Fibrosis Center, Cincinnati Children's Hospital Medical Center

Objective To examine the process of change in a clinical trial of behavioral and nutrition treatment for children age 18–48 months with cystic fibrosis (CF) using single-subject analysis. **Methods** The 5-week treatment included nutrition counseling and child behavioral management training for parents and was designed to increase energy intake measured by diet diaries 600–800 calories per day. **Results** Energy intake changed at each meal, only when treatment was introduced (week 1: snacks, 420 to 691; week 2: breakfast, 325 to 443; week 4: lunch, 350 to 443; and week 5: dinner, 373 to 460 calories per day). Total daily intake increased in a systematic fashion that exceeded the criterion set each week during treatment. **Conclusions** Toddlers and preschoolers with CF meet energy intake recommendations as a result of behavioral intervention. Single-subject research designs are important methodologies for advancing clinical investigation in pediatric psychology.

Key words changing criterion design; multiple baseline design; parenting; pediatrics; single case experimental designs.

The consensus recommendation of the United States Cystic Fibrosis Foundation is that children with cystic fibrosis (CF) should eat a diet that has 120–150% of the recommended dietary allowance (RDA) for energy per day (Borowitz, Baker, & Stallings, 2002; Ramsey, Farrell, & Pencharz, 1992). This level of energy intake is suggested so that children can meet the clinical care goal of normal growth (Borowitz et al., 2002). Recent studies have shown that improved growth in young children with CF is positively predictive of better lung function (Konstan et al., 2003; Peterson, Jacobs, & Milla, 2003). Yet, based upon current practice, young children with CF are not meeting the energy intake recommendations (Powers et al., 2002; Stark et al., 1995) or the goal of normal growth (Cystic Fibrosis Foundation, 2004). For the nutritional care of young children with CF to advance, better treatments must be developed (Powers, Jones, Patton, & Janicke, 2003; Stark, Mackner, Patton, & Acton, 2003). Such treatments could significantly improve the long-term health of these children (Konstan et al., 2003; Peterson et al., 2003).

A behavioral and nutrition treatment to increase energy intake has been developed for toddlers and preschoolers with CF (Powers, 2003; Powers, Byars, et al., 2003). In a recent randomized clinical trial (Powers et al., 2004; Powers et al., in press), this intervention was found to produce superior energy intake compared with current practice, and 100% of the children who received the

All correspondence concerning this article should be addressed to Scott W. Powers, PhD, ABPP, Division of Behavioral Medicine and Clinical Psychology, Center for Child Behavior and Nutrition Research, MLC: D-3015, 3333 Burnet Avenue, Cincinnati, Ohio 45229-3039. E-mail: scott.powers@cchmc.org.

Journal of Pediatric Psychology 31(6) pp. 574–581, 2006
doi:10.1093/jpepsy/jsj049
Advance Access publication July 13, 2005

treatment met the consensus conference recommendation of greater than 120% RDA energy intake per day. Children who received this treatment exhibited weight and height velocities over a 12-month period that met the clinical goal of normal growth. A between-group research design focused on the average treatment effect in the two groups (behavioral and nutrition treatment compared with usual medical care) was used to determine whether statistically and clinically significant outcomes were obtained in this clinical trial. Although such a design can include measures of the process through which treatment objectives were accomplished, single-subject analysis provides another mechanism for analyzing the process of change. Moreover, single-subject research designs are unique in their ability to illustrate changes (or the lack thereof) for each individual that participated in the treatment (Allen, Friman, & Sanger, 1992; Madsen, & Bytzer, 2002).

In the randomized clinical trial, i.e., the focus of this report, the behavioral and nutrition treatment was designed to address energy intake goals one meal at a time over a 5-week period. As such, the process of change in energy intake during this treatment should be a systematic and gradual increase in total energy intake per day over the course of the 5 weeks of intervention. Using single-subject analysis, this process can be examined at the group (i.e., dependent variable is the average daily energy intake across subjects) and the individual subject (i.e., dependent variable is the daily energy intake for a single child) levels. Therefore, this report has two objectives. First, using the group's average energy intake per day, the results of the randomized clinical trial were examined with single-case research designs (such as multiple baseline and changing criterion designs; Barlow & Hersen, 1984). The aim was to empirically demonstrate that the planned process/mechanism of change occurred for the group of subjects that received the behavioral and nutrition treatment. It was hypothesized that energy intake would increase only when snacks or a meal were targeted during the intervention (multiple baseline across meals) and that average total energy intake per day would increase in a systematic, stepwise fashion over the course of the 5-week treatment (changing criterion). Second, single-subject analysis was used to examine how individual participant's daily energy intake responded to the treatment. The aim was to determine which subjects in the trial were actually affected by the intervention and to illustrate a typical subject's response using a multiple baseline across meals design. It was hypothesized that the child's energy intake would increase only when snacks or a meal were targeted during the intervention.

Methods

Participants

Between February and August, 2003, 14 children with CF and pancreatic insufficiency ages 18–48 months from the CF Center of a major children's hospital in the Midwestern United States met criteria for enrollment. Ten of the 14 families who met the inclusion criteria were enrolled and randomized (71% of eligible families), with four assigned to the behavioral and nutrition intervention and six assigned to the usual care control condition. Two families did not regularly attend clinic and could not be reached by phone. Two families, although expressing interest in helping their child improve his/her nutritional status, declined to participate due to an inability to commit the time needed to regularly attend the weekly treatment sessions. Following the completion of the clinical trial, families in the control group were offered the opportunity to receive the behavioral intervention, and five of the six families chose to receive the treatment. Families who received the behavioral and nutrition treatment are currently being regularly assessed as part of a 4-year follow-up study. To date, the 12-month follow-up has been completed. The study was approved by the institutional review board of the children's hospital, and the child's parent provided written informed consent. All nine families who completed the behavioral and nutrition intervention arm of the study are included in this analyses. Participants included six males and three females. All participants were Caucasian. Marital status was married for seven and single for two families. The mean age of participants was 31.5 months (SD = 6.2 months; range = 22–43 months), mean weight for age z-score was −0.19 (SD = 0.85; range = −1.41 to 1.15), and mean height for age z-score was −0.19 (SD = 1.01; range = −1.31 to 2.03). Based upon the consensus conference guidelines of the CF foundation, seven of the nine participants were in the at-risk range for nutritional status (78% of the sample). The other two participants were in the acceptable range (Borowitz et al., 2002).

Measures

Children's energy intake was measured using 7-day diet diaries (Willett, 1990). At an initial study visit, all families were provided with a food scale as well as measuring cups and spoons. They were taught how to measure food and complete the diet diary via written instructions, modeling, and active practice at this study visit. Families were instructed to record information on the diet diaries after each snack and meal. At each intervention session, the diet diaries were examined for completeness,

and the instructions for completion were reviewed. Diaries were completed 1 week before intervention and then weekly throughout the behavioral and nutrition intervention (a total of 6 weeks). To date, diet diaries have also been collected at a 3-month follow-up (with 4-day records using the approach described above) and a 12-month follow-up (with 3-day records using a 24 h recall method; Willett, 1990). All diet diaries were analyzed by trained research assistants supervised by a registered dietitian utilizing the Food Processor Program, version 8.0 (ESHA, 2002). Information was obtained on energy intake per snack/meal per day and total energy intake per day.

Intervention

The behavioral and nutrition treatment combined individualized nutritional counseling that targeted increasing energy intake in one meal each week and parent training of effective child behavior management skills (Powers, 2003; Powers et al., 2004; Powers, Byars, et al., 2003; Powers et al., in press). The treatment focused on three areas: first, increasing calorie and fat intake, with a goal of meeting 120–150% RDA for energy and 35–40% of calories derived from fat; second, ensuring appropriate dosage and timing of pancreatic enzyme replacements plus regular meal schedule; and third, teaching effective parent management skills (such as differential attention using systematic praising and ignoring and age-appropriate limit setting using contingency management) to address common behavioral challenges of toddlers and preschoolers at mealtime. Individualized goals were set using data from each child's pretreatment diet record. Meals were targeted in the order of snacks (week 1), breakfast (week 2), lunch (week 4), and dinner (week 5). The general guideline involved increases of approximately 200 calories for snacks (individual snack goals were note set of evaluated) and 175 for each meal, with a total goal of 600–800 calories per day change pre- to posttreatment. Individual sessions were conducted by a PhD level therapist in an outpatient clinic setting. The therapist was trained to use the intervention manual and supervised during the trial by the principal investigator. The usual care control condition involved scheduled clinic visits every 3 months. During the clinic visits, weight and height checks were obtained, and families saw their CF physician. The CF dietitian was consulted when diet and growth issues and/or pancreatic enzyme replacement dosage changes were identified. This control condition was consistent with the 2001 CF Foundation Consensus Conference guidelines for pediatric nutrition in CF (Borowitz et al., 2002).

Results

Findings at the Group Level of Analysis

Figure 1 illustrates, using a multiple baseline across meals format, the change in average daily energy intake of the nine subjects by snacks and each of the three meals for the 1 week of pretreatment and the 5 weeks of intervention. Of note, there was no change in energy intake for a specific meal or snacks until that meal or snacks were targeted for change by the intervention. When targeted, energy intake at a meal or snacks increased and remained at a level greater than baseline for that meal or snacks throughout the treatment. These results demonstrate experimental control and show that the changes were not due to the passage of time.

Figure 2 illustrates, using a changing criterion format, the average total energy intake per day of the nine subjects for the 1 week of pretreatment and the 5 weeks of intervention. Total energy intake of the nine subjects at the 3- and 12-month follow-up assessments is also included in the figure. Of note, the average total energy intake per day increased in a stepwise fashion consistent with the changing criterion approach of the intervention. Although the criterion goal for snacks was set as 200 calories above baseline (M = 1,395 calories per day), the group far exceeded this by reaching an intake of approximately 400 calories above baseline following the first intervention session (M = 1,767 calories per day). Following the next session, which targeted breakfast, the group average only increased about 20 calories (M = 1,794 calories per day). An examination of Fig. 1 shows that after learning how to increase energy intake at breakfast, participants balanced the overall goal of 375-calorie increase from baseline between snacks and breakfast and thereby exceeded the criterion set for total daily energy intake during the 2-week period following the intervention session focused on breakfast. Following the session focused on lunch (week 4), the group again exceeded the criterion set for total daily energy intake at that point in the intervention (M = 2,021 calories per day). Finally, after the session focused on dinner (week 5), the group exceeded the set criterion and exceeded the overall intervention goal of a 600- to 800-calorie increase in total energy intake per day (actual change of 900 calories per day; M = 2,295 calories per day). At the 3-month follow-up, the group decreased to an average energy intake of 1,960 calories per day (or 565 calories per day more than pretreatment). Although less than the intake achieved at posttreatment, this level of intake corresponds with 151% RDA, exceeding the upper end of the recommendation of 120–150% RDA for energy intake. At the 12-month follow-up, the participants were again

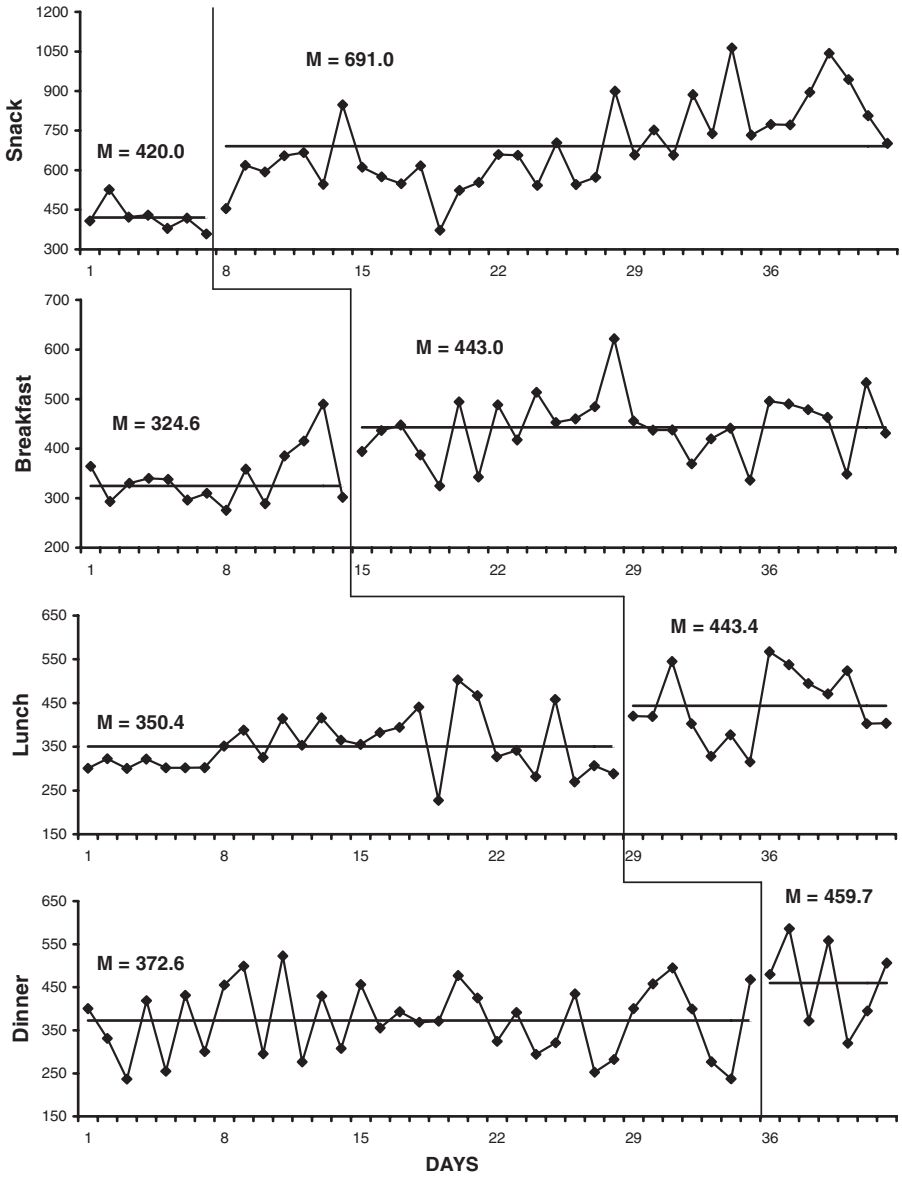

Figure 1. Multiple baseline design illustrating change in daily energy intake across meals ($n = 9$).

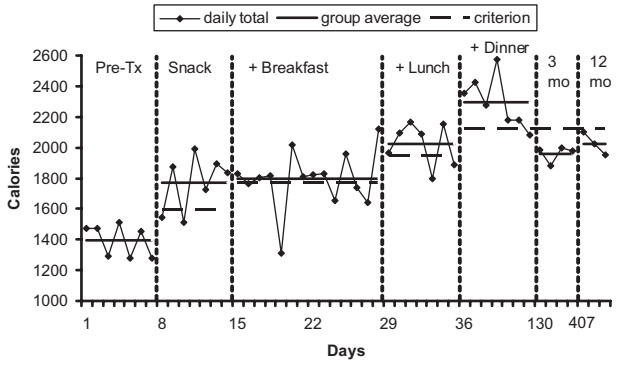

Figure 2. Changing criterion design illustrating change in average energy intake per day ($n = 9$).

found to be exceeding the goal of at least 600 calories per day above baseline, averaging 2,026 calories per day (or 631 calories per day more than pretreatment). Although slightly less than the intake achieved at posttreatment, this level of energy intake corresponds with 156% RDA, again exceeding the upper end of the recommendation of 120–150% RDA for energy intake.

Because energy intake, although collected in a systematic and carefully monitored fashion by families, is almost always measured in a self-report format within clinical nutrition studies, the examination of whether the reported changes in energy intake were associated with child growth can add confidence to the assumption that the dietary data were reliably and accurately measured. Hence, although not a primary endpoint for the

pre- to posttreatment comparisons of the clinical trial, weight and height assessments were collected at baseline, posttreatment, and at the 3- and 12-month follow-up for all nine subjects. Using pretreatment and 3-month follow-up data, weight and height velocities for 6 months were calculated. Clinical benchmarks were based upon the 2000 Centers for Disease Control and Prevention (CDC) growth charts for a same-aged child who was growing at the 50th percentile (1 kg/6 months and 3.5–4.5 cm/6 months, respectively). The average weight velocity was 1.4 kg (*SD* = 0.33). Seven of the nine participants (78%) met the weight velocity benchmark. However, the two who did not obtain the goal of 1 kg per 6 months were less than one-tenth of a kg from this goal. The average height velocity was 5.1 cm (*SD* = 0.77). All nine participants (100%) met the minimum benchmark for height velocity; five of them exceeded the upper end of the range expected across 6 months. Using posttreatment and 12-month follow-up data, weight and height velocities for 12 months were calculated. Clinical benchmarks were based upon the 2000 CDC growth charts for a same-aged child who was growing at the 50th percentile (2 kg/12 months and 7–9 cm/12 months, respectively). The average weight velocity was 2.5 kg (*SD* = 0.96). Seven of the nine participants (78%) met the weight velocity benchmark. The two children who did not obtain the goal of 2 kg per 12 months were within 0.6 and 0.3 kg from this goal. The average height velocity was 8.3 cm (*SD* = 1.2). All nine participants (100%) met the minimum benchmark for height velocity. These data support the hypothesis that children were meeting the recommended energy intake levels of 120–150% (as was reported via the diet records) thought to be needed for individuals with CF to meet the goal of normal growth.

Findings at the Individual Subject Level of Analysis

Each child who received the treatment met the consensus conference recommendation of greater than 120% RDA energy intake per day, and the examination of single-subject analyses for each child showed that changes occurred via the process described under the group analysis section (data not shown for each subject due to space limitations). To illustrate the use of single-subject analysis at the individual subject level, Fig. 3 presents a multiple baseline across meals design for a subject who showed a change in daily energy intake of 607 calories per day from pretreatment to posttreatment. This case was chosen because the change achieved was at the low end of the targeted change of 600–800 calories per day, and the subject was considered an example of an average responder to the intervention (baseline = 1,441 calories per day or 111% RDA; posttreatment = 2,057 calories per day or 158% RDA). As with Fig. 1, there was no change in energy intake for a specific meal or snacks until that meal or snacks were targeted for change by the intervention. When targeted, energy intake at a meal or snacks increased and remained at a level greater than baseline for that meal or snacks throughout the treatment. These results demonstrate experimental control and show that the changes were not due to the passage of time. Multiple baseline across meals analysis of an individual subject also allows for the examination of where the changes in total intake occurred for a particular child. In this case, the goal of a 200-calorie increase for snacks was achieved (235 calorie increase), whereas for breakfast, lunch, and dinner the increases were less than the goal of 175 calories per meal but consistently between 100 and 150 calorie increases (breakfast = 117 calorie increase, lunch = 107 calorie increase, and dinner = 148 calorie increase). Single case analysis is unique in its ability to illustrate which subjects in a clinical trial were actually affected by the independent variable (i.e., manualized behavioral and nutrition intervention in this example).

Discussion

Using single-subject analysis, the process of change in energy intake produced by a behavioral and nutritional treatment for toddlers and preschoolers with CF who participated in a randomized clinical trial was demonstrated. The intervention was designed to produce increases in energy intake one meal at a time over a 5-week period, with the result being a stepwise increase each week in total energy intake per day. As predicted, energy intake increased only when snacks or a meal was targeted during the intervention (multiple baseline across meals design), and total energy intake per day increased in a systematic, stepwise fashion over the course of the 5-week treatment (changing criterion design). The planned outcome was an increase in energy intake per day of 600–800 calories, meeting the recommended goal of 120–150% RDA for energy per day. This outcome was achieved and maintained at the 3-and 12-month follow-up assessments. Growth velocity (weight and height) over 6 and 12 months indicated that the changes in energy intake were associated with a pattern of normal growth. Families did not have contact with the research team during the follow-up. They received usual care from the CF Center team. Because energy intake was found to decease slightly from posttreatment to 3- and 12-month follow-ups, booster treatment sessions may be needed to assist with maintenance of

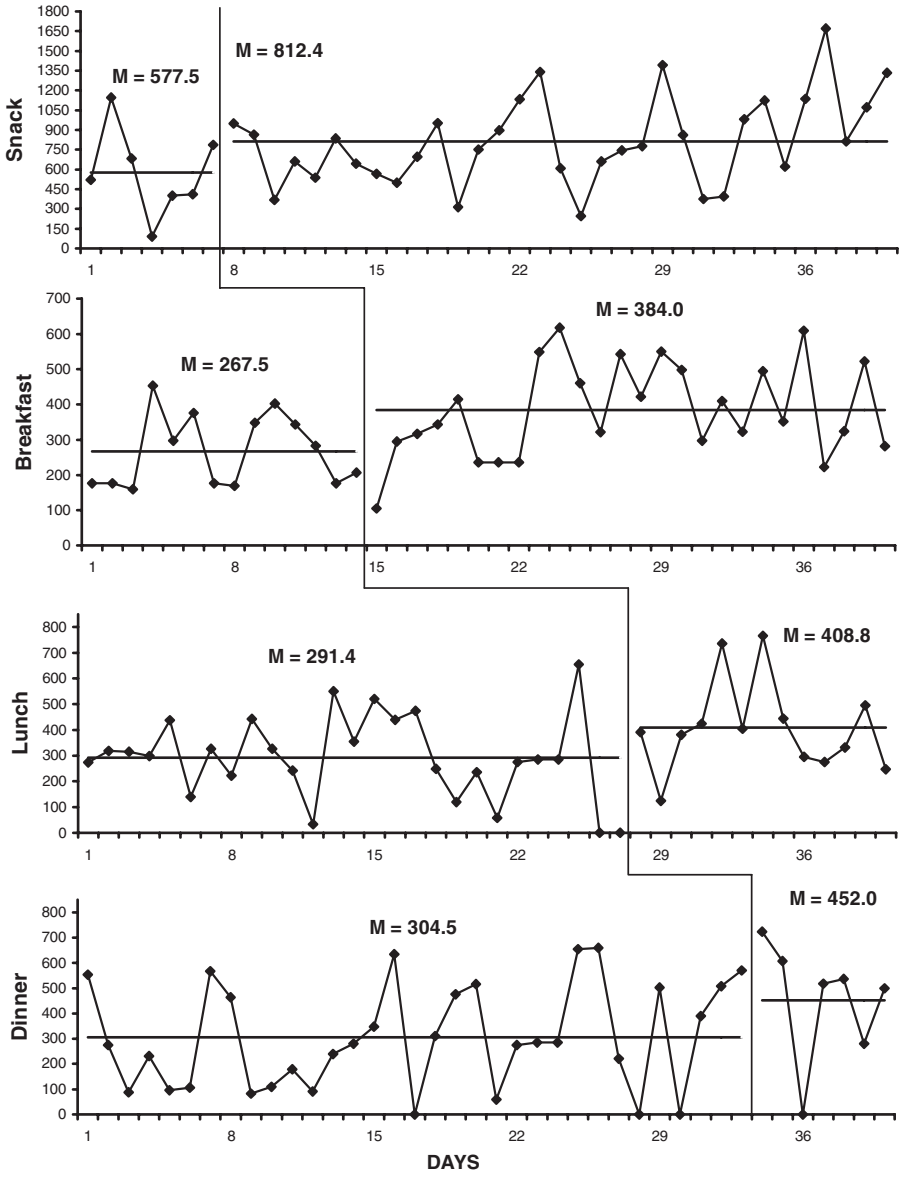

Figure 3. Multiple baseline design illustrating change in daily energy intake across meals for an individual subject ($n = 1$).

change for some families. However, the growth velocity outcomes and the fact that average total energy intake per day continued to exceed the upper end of the current recommendations of 120–150% RDA per day suggest that the intake achieved up to 1 year posttreatment may be at a level that allows for clinically meaningful outcomes with only usual clinical care at an accredited CF center.

This study shows how single case research designs can be used to illustrate what led to changes and when changes occurred during the course of treatment conducted within a randomized clinical trial. From both a group level (average energy intake across nine subjects) and an individual subject level (daily energy intake by a particular child), the results illustrate that the intervention worked as it was designed and add further confirmation that behavioral and nutrition treatment to improve energy intake in young children with CF is efficacious. Behavioral and nutrition therapy may fill an important gap regarding early, evidence-based nutritional interventions in CF and lead to advances in the nutritional care of young children with CF and pancreatic insufficiency (Powers et al., 2004; Powers et al., in press). Future studies need to focus on two complementary objectives: first, confirmation of the efficacy of this treatment in a large, multicenter, randomized clinical trial that includes an attention control group and is designed to evaluate energy intake, growth, and lung health outcomes in toddlers and preschoolers with CF; and second, development and testing of the effectiveness of this type of therapy under real world conditions. In addition to illustrating the process of change in a clinical trial, single case research designs may be particularly useful in the initial

testing of treatments under real world conditions (Barlow & Hersen, 1984; Drotar & Lemanek, 2001).

As many authors have suggested (e.g., Aeschleman, 1991; Allen et al., 1992; Backman & Harris, 1999; Barlow & Hersen, 1984; Drotar & Lemanek, 2001; Elder, 1997; Kinugasa, Cerin, & Hooper, 2004; Madsen, & Bytzer, 2002; Marvel & Amodei, 1992; Zhan & Ottenbacher, 2001), single-subject research methodology offers many advantages for advancing clinical investigation in pediatric behavioral medicine, as well as in many other health care fields. Especially in pediatrics, where at a single institution a relatively small population of children may be affected by a particular disease or condition, the rigorous use of single-subject analysis could result in important pilot study results for new interventions and, in and of themselves, the findings from studies that use these valid research designs could lead to significant scientific and clinical care advances for the field. Indeed, some areas of clinical research that have had a notable impact on society, such as applied behavioral analysis, were established on the basis of these research methodologies. Barlow and Hersen (1984) as well as Allen et al. (1992) are two of some excellent works that extensively detail the strengths, weaknesses, and use of single case experimental designs. Aeschleman (1991) is also an excellent reference that highlights how some basic misconceptions about these designs may have limited more widespread use of these empirical strategies. The use of single-subject analysis in this report will hopefully stimulate further application and dissemination of these research designs in clinical investigations conducted within the field of pediatric psychology.

Acknowledgments

Supported by the NIH/NIDDK (Grants #R01 DK54915 & K24 DK59973 to SWP) and General Clinical Research Center at Cincinnati Children's (NCRR Grant #M01 RR08084).

Received December 30, 2004; revisions received May 6, 2005; accepted June 22, 2005

References

Aeschleman, S. (1991). Single-subject research designs: Some misconceptions. *Rehabilitation Psychology, 36*, 43–49.

Allen, K., Friman, P. C., & Sanger, W. (1992). Single subject design in reproductive toxicology. *Reproductive Toxicology, 6*, 115–121.

Backman, C., & Harris, S. (1999). Case studies, single-subject research, and N of 1 randomized trials: Comparisons and contrasts. *American Journal of Physical Medicine and Rehabilitation, 78*, 1701–1176.

Barlow, D. H., & Hersen, M. (1984). *Single case experimental designs: Strategies for studying behavior change* (2nd ed.) Boston, MA: Allyn and Bacon.

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

Cystic Fibrosis Foundation. (2004). *Patient registry 2003: Annual data report*. Bethesda, MD: Cystic Fibrosis Foundation.

Drotar, D., & Lemanek, K. (2001). Steps toward a clinically relevant science of interventions in pediatric settings: Introduction to the special issue. *Journal of Pediatric Psychology, 26*, 385–394.

Elder, J. (1997). Single subject experimentation for psychiatric nursing. *Archives of Psychiatric Nursing, 11*, 133–138.

ESHA. (2002). The food processor nutrition analysis and fitness software (Version 8.0). Retrieved July 7, 2005 from http://www.esha.com/products/

Kinugasa, T., Cerin, E., & Hooper, S. (2004). Single-subject research designs and data analyses for assessing elite athlete's conditioning. *Sports Medicine, 34*, 1035–1050.

Konstan, M., Butler, S., Wohl, M., Stoddard, M., Matousek, R., Wagener, J., et al. (2003). Growth and nutritional indexes in early life predict pulmonary function in cystic fibrosis. *Journal of Pediatrics, 142*, 624–630.

Madsen, L., & Bytzer, P. (2002). Review article: Single subject trials as a research instrument in gastrointestinal pharmacology. *Alimentary Pharmacologic Therapeutics, 16*, 189–196.

Marvel, M., & Amodei, N. (1992). Single-subject experimental designs: A practical research alternative for practicing physicians. *Family Practice and Research Journal, 12*, 109–121.

Peterson, M., Jacobs, D. J., & Milla, C. (2003). Longitudinal changes in growth parameters are correlated with changes in pulmonary function in children with cystic fibrosis. *Pediatrics, 112*, 588–592.

Powers, S. W. (2003). Nutrition in early childhood: Focus on parent interaction. *Pediatric Pulmonology, S25*, 138–139.

Powers, S. W., Byars, K. C., Mitchell, M. J., Patton, S. R., Schindler, T., & Zeller, M. H. (2003). A randomized pilot study of behavioral treatment to increase

calorie intake in toddlers with cystic fibrosis. *Children's Health Care, 32*, 297–311.

Powers, S. W., Jones, J. S., Ferguson, K. S., Heidemann, M. L., Henry, R., Piazza-Waggoner, C., et al. (2004). Behavioral treatment for toddlers and preschoolers with cystic fibrosis produces recommended energy intake and normal rates of growth. *Pediatric Pulmonology, S27*, 361.

Powers, S. W., Jones, J. S., Ferguson, K. S., Piazza-Waggoner, C., Daines, C., & Acton, J. D. (in press). Randomized clinical trial of behavioral and nutrition treatment to improve energy intake and growth in toddlers and preschoolers with cystic fibrosis. *Pediatrics*.

Powers, S. W., Jones, J. S., Patton, S. R., & Janicke, D. M. (2003). Nutritional recommendations for children with cystic fibrosis. *Italian Journal of Pediatrics, 29*, 44–50.

Powers, S., Patton, S., Byars, K., Mitchell, M., Jelalian, E., Mulvihill, M., et al. (2002). Caloric intake and eating behavior in infants and toddlers with cystic fibrosis. *Pediatrics, 109*, 75–80.

Ramsey, B., Farrell, P., & Pencharz, P. (1992). Nutritional assessment and management in cystic fibrosis: A consensus report. The Consensus Committee. *American Journal of Clinical Nutrition, 55*, 108–116.

Stark, L., Jelalian, E., Mulvihill, M., Powers, S., Bowen, A., Spieth, L., et al. (1995). Eating in preschool children with cystic fibrosis and healthy peers: Behavioral analysis. *Pediatrics, 95*, 210–215.

Stark, L. J., Mackner, L. M., Patton, S. R., & Acton, J. D. (2003). Cystic fibrosis. In M. C. Roberts (Ed.), *Handbook of pediatric psychology* (3rd ed., pp. 286–303). New York: Guilford Press.

Willett, W. (1990). *Nutritional epidemiology*. New York: Oxford University Press.

Zhan, S., & Ottenbacher, K. (2001). Single subject research designs in disability research. *Disability Rehabilitation, 23*, 1–8.