Development of the Hyperphagia Questionnaire for Use in Prader-Willi Syndrome Clinical Trials

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BACKGROUND

- Beloranib, a methionine aminopeptidase 2 inhibitor, is in development for the treatment of hyperphagia-related behaviors and obesity in individuals with Prader-Willi syndrome (PWS). PWS is a complex rare genetic disorder with multiple systemic effects, including neurologic, cognitive, and behavioral issues; endocrine deficits; and metabolic abnormalities.
- The hallmark of PWS is an incessant feeling of insatiable hunger, regardless of food intake (hyperphagia), and patients typically also have problems with growth and development, intellectual disabilities, maladaptive and compulsive behaviors, and often, severe obesity. The characteristics of PWS have a profound effect on the daily lives of both the individuals with this rare genetic disorder and their caregivers.
- Because of the intellectual limitations associated with PWS, patients are unable to reliably report the severity of their hyperphagia. As a result, a caregiver-reported measure focused on food-seeking behaviors is needed to support pharmaceutical product development and labeling claims related to hyperphagia in this patient population.
- The Hyperphagia Questionnaire (HQ), a 13-item caregiver-reported measure of food-seeking behaviors observed among individuals with PWS, was developed and validated using rigorous methods and is considered the gold standard for the assessment of hyperphagia among clinicians specializing in PWS.[1] However, this questionnaire has limitations when compared with industry guidance and standards for the support of product labeling claims (e.g., Food and Drug Administration [FDA], 2009[2]).

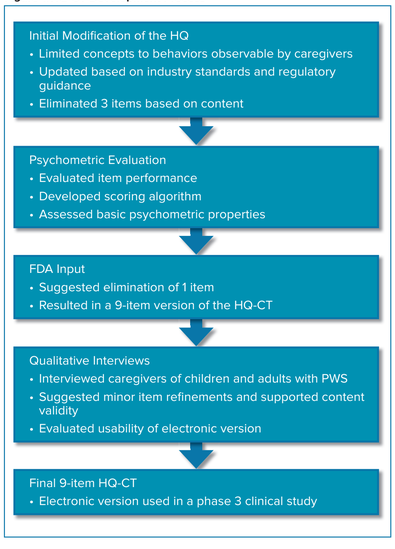
OBJECTIVE

- The goal of this research was to develop and psychometrically evaluate a modified version of the HQ for use in PWS clinical trials, the HQ for Clinical Trials (HQ-CT).

METHODS

Figure 1 summarizes the process used to develop the HQ-CT.

Figure 1. HQ-CT Development Process



Initial Modification of the HQ

- The developers of the HQ and additional experts in the development and validation of clinical outcome assessments modified the HQ with the following objectives:
  - Limit the concepts of measurement to behaviors that are observable by caregivers (without inference) and that have the potential to change during the course of a clinical trial
  - Incorporate industry guidance related to patient- and caregiver-reported outcome measures, including recommendations in the FDA PRO guidance.[2]

Psychometric Evaluation

- The preliminary version of the HQ-CT was administered in the context of a phase 2 clinical trial of beloranib in patients with PWS to evaluate the performance of each item, develop a scoring algorithm, and evaluate psychometric properties such as reliability and validity.

Trial Design

- The phase 2 clinical trial was a single-center, randomized, double-blind, placebo-controlled study involving overweight and obese adult patients with PWS.
- The 17 subjects, residents in a group home dedicated to patients with PWS, were randomized to one of three dosing arms, including placebo and two doses of beloranib.
- Data collected during clinic visits at the beginning of the placebo lead-in period (week 1), the beginning of randomized treatment (week 3), and the end of randomized treatment (week 7) were used in the psychometric evaluation.
- In addition to the preliminary version of the HQ-CT, the following measures were used in the evaluation:
  - Weight in kilograms
  - Food-Related Problem Questionnaire (FRPQ): A 16-item measure developed to assess preoccupation with food, satiety impairment, and food-related negative behaviors in patients with PWS.[3]
  - Food intake/behavior daily journal (FIB-DJ): A daily caregiver observations (i.e., counts) diary of several aberrant or food-related observable behaviors, such as stealing food and aggression.

HQ-CT Analyses

- Item-response frequencies were tabulated to assess the use and appropriateness of the response scales and to identify possible floor and ceiling effects.
- Item-level standard descriptive statistics (mean, standard deviation [SD], median, range, and percentage missing) were computed to assess the distribution of HQ-CT scores across time.
- Item-total correlations and inter-item correlations for the HQ-CT were computed to inform the HQ-CT scoring algorithm.
- Cronbach's coefficient alpha[4] was computed to investigate the internal consistency of candidate composite HQ-CT scores.
- To evaluate construct validity, correlations (Spearman) were conducted among the HQ-CT items, candidate HQ-CT composite(s), weight, FRPQ items and subscales, and weekly counts of FIB-DJ behaviors.
- Preliminary estimates of responsiveness were evaluated by computing responsiveness effect size estimates for each HQ-CT item.
- Due to small sample sizes, Cohen's general rule of thumb[5] was applied to characterize effect size estimates in change scores (i.e., 0.20, small; 0.50, moderate; 0.80, large).

FDA Input

- During an end-of-phase 2 meeting, the FDA recommended removal of an item (Item 3 in Table 1) they deemed less than ideal for several reasons.

Qualitative Interviews

- In-depth interviews were conducted with 6 caregivers of children or adults with PWS at a regional conference for a PWS patient support organization. Inclusion criteria for the caregivers were as follows:
  - Primary caregiver of an individual with PWS, aged 13 to 65 years
  - If PWS patient is an adult, must have a body mass index (BMI) of ≥ 30
  - If PWS patient is a child, must have a BMI ≥ 95th percentile for age and sex, per the National Health and Nutrition Examination Survey (NHANES)
- Interviews were conducted using a semistructured interview guide and included both a concept elicitation exercise and cognitive debriefing of an electronic version of the HQ-CT to meet the following objectives:
  - Inform any further refinements to facilitate ease of item comprehension and response by caregivers
  - Provide additional support for content validity
  - Optimize the usability of the electronic data capture device

RESULTS

Initial Modification of the HQ

- Initial modifications included reducing the recall period to 2 weeks, revising the response scales to match the recall period, and modifying the wording of several items to be more objective and observable (e.g., replaced "to what extent" with "how often," removed "food-related thoughts" and maintained "food-related talk or behavior").
- Three items were removed, because they did not address observable behaviors or were not expected to change with a reduction in hyperphagia (i.e., child's age of increased interest in food, variability of the preoccupation or interest in food, being clever or fast to obtain food).
- Based on the initial modifications of the HQ, a preliminary 10-item version of the HQ-CT was created.

Psychometric Evaluation

- Overall, results of the psychometric evaluation supported the use of a single HQ-CT composite score in future trials, as well as the reliability and validity of this measure.
  - All average item scores improved (decreased) either from week 1 to week 3 or from week 3 to week 7.
    - The magnitude of change was small, most likely given the controlled environments in which the trial participants resided (i.e., a PWS group home).
  - All inter-item correlations were positive at each time point, and the majority of correlations were moderate to strong in magnitude.
  - Alpha estimates ranged from 0.85 (week 3) to 0.92 (week 1), suggesting a set of items that is strongly related and capable of supporting a unidimensional scoring structure, but is not redundant.
  - With a maximum total score (10-item sum) of 40, the average total HQ-CT score was relatively low (10.0 at week 1), but there was a trend toward improvement on average (7.53 by week 7).
  - While correlations between changes in HQ-CT item scores and changes in weight were low, there were several instances of strong correlations between HQ-CT items and FRPQ items addressing similar concepts. Responses to HQ-CT item 8 ("…how often did the person try to steal food"?) were also correlated with FIB-DJ food stealing counts.
- The HQ-CT total score was able to demonstrate improvements in hyperphagia-related behavior between placebo and pooled treatment groups as shown in Table 1.

Table 1. HQ-CT Item-Level Responsiveness: Changes From Week 3 to Week 7 by Treatment (N = 17)

	HQ-CT Item	Mean (SD)		Effect Size
		Placebo (n = 6)	Treatment (n = 11)	
1.	Upset when denied food	–0.17 (1.2)	0.09 (1.4)	0.22
2.	Try to bargain or manipulate	–0.17 (0.4)	0.18 (1.7)	0.85
3.	Effort required to redirect	0.50 (1.0)	–0.27 (0.8)	–0.74
4.	Forage through trash for food	0.33 (0.8)	–0.27 (0.9)	–0.74
5.	Get up at night to food seek	–0.17 (0.4)	–0.18 (0.6)	–0.04
6.	Persistence after being told no more	–0.33 (1.4)	–0.09 (0.8)	0.18
7.	Time spent talking about food	0.00 (1.7)	–0.91 (1.3)	–0.54
8.	Try to steal food	0.33 (0.5)	–0.36 (1.1)	–1.35
9.	Distress when told to stop food-related talk	0.00 (1.1)	–0.36 (1.2)	–0.33
10.	Interference with daily activities from food-related talk or behavior	–0.33 (1.0)	–0.09 (1.0)	0.23
Total: 10-item sum		0.00 (5.8)	–2.27 (4.3)	–0.39

SD = standard deviation.

Item Reduction

- FDA reviewers noted the following concerns about the content of item 3 ("…once the person started talking about food, how much effort did it take to get him/her to stop talking about food and on to other things?"):
  - Similar to that of another item (item 6, "…how persistent was the person in asking or looking for food after being told 'no' or 'no more'?")
  - Focused more on interactions between the caregiver and patient than on the patient's behavior per se
- Following discussion of this recommendation, developers agreed that removal of this item would not compromise the content validity of the measure. Thus, item 3 of the preliminary 10-item HQ-CT was eliminated, resulting in a 9-item version of the HQ-CT for further evaluation during the qualitative interviews.

Qualitative Interviews

- Characteristics for the 6 caregivers and the individuals under their care are provided in Table 2.

Table 2. Characteristics of Qualitative Interview Participants

Characteristic	PWS Caregivers (N = 6)
Caregiver	
Sex, female, n (%)	4 (66.7)
Relationship to person under care, parent, n (%)	6 (100.0)
Race/ethnicity, white, n (%)	6 (100.0)
Education, n (%)	
High school	1 (16.7)
College degree	2 (33.3)
Postgraduate coursework/advanced degree	3 (50.0)
Person under care	
Age in years, mean (range)	32.7 (22.0-44.0)
BMI, mean (range)	34.6 (30.5-46.6)
Living situation (≥ 50% of the time), n (%)	
Home/private residence	3 (50.0)
Group home for patients with PWS[a]	3 (50.0)

[a] Patients were required to spend time at their parents'/caregivers' homes where the caregivers were directly involved in their care.

- The 9 HQ-CT items were generally deemed clear and easy to understand by the interview participants; caregivers also indicated that the 2-week recall period was appropriate and easy to reference.
- All concepts were deemed relevant by the interview participants. When asked if any food-related behaviors or concepts were missing, all 6 caregivers reported that the most important concepts were already addressed in the HQ-CT.
- Based on the results of the qualitative interviews, minor wording changes were made to several HQ-CT items.
- The electronic handheld device was deemed easy to use by all interview participants.
- The final HQ-CT used in the ongoing phase 3 study is shown in Figure 2.

Figure 2. Final HQ-CT

Hyperphagia Questionnaire for Clinical Trials (HQ-CT)

Instructions: The following items refer to the person in your care and assessment of his/her food-related behavior during the past 2 weeks.

(1) During the past 2 weeks, how upset did the person generally become when denied a desired food?
- ☐ Not at all upset
- ☐ A little upset
- ☐ Moderately upset
- ☐ Very upset
- ☐ Extremely upset

(2) During the past 2 weeks, how often did the person try to bargain or manipulate to get more food at meals?
- ☐ Never
- ☐ Up to 2 times a week
- ☐ 3 to 6 times a week
- ☐ Every day
- ☐ Several times a day

(3) During the past 2 weeks, how often did the person forage through trash for food?
- ☐ Never
- ☐ 1 time
- ☐ 2 times
- ☐ 3 times
- ☐ 4 or more times

(4) During the past 2 weeks, how often did the person get up at night to food seek?
- ☐ Never
- ☐ 1 time
- ☐ 2 times
- ☐ 3 times
- ☐ 4 or more times

(5) During the past 2 weeks, how persistent was the person in asking or looking for food after being told "no" or "no more"?
- ☐ Not at all persistent
- ☐ A little persistent
- ☐ Moderately persistent
- ☐ Very persistent
- ☐ Extremely persistent

(6) During the past 2 weeks, outside of normal meal times, how much time did the person generally spend asking or talking about food?
- ☐ Less than 5 minutes a day
- ☐ 5 to 15 minutes a day
- ☐ 15 to 30 minutes a day
- ☐ 30 minutes to 1 hour a day
- ☐ More than 1 hour a day

(7) During the past 2 weeks, how often did the person try to sneak or steal food (that you are aware of)?
- ☐ Never
- ☐ 1 time
- ☐ 2 times
- ☐ 3 times
- ☐ 4 or more times

(8) During the past 2 weeks, when others tried to stop the person from asking about food, how distressed did he or she generally appear?
- ☐ Not at all distressed
- ☐ A little distressed
- ☐ Moderately distressed
- ☐ Very distressed
- ☐ Extremely distressed

(9) During the past 2 weeks, how often did food-related behavior interfere with the person's normal daily activities, such as self-care, recreation, school, or work?
- ☐ Never
- ☐ Up to 2 times a week
- ☐ 3 to 6 times a week
- ☐ Every day
- ☐ Several times a day

Note: The HQ-CT total score is created by summing the 9 item-level responses (which range from 0 to 4) for a maximum score of 36.

CONCLUSIONS

- Qualitative and quantitative evidence provide support for use of the 9-item HQ-CT total score for the assessment of food-seeking behaviors in PWS clinical trials.
- While the existing evidence strongly supports use of the HQ-CT to assess hyperphagia in PWS clinical trials, a psychometric evaluation of the HQ-CT using data from the ongoing phase 3 beloranib trial is planned to confirm and extend the previous findings.

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