



Interview-Based Patient- and Caregiver-Reported Experiences of Hunger and Improved Quality of Life with Setmelanotide Treatment in Bardet-Biedl Syndrome

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ABSTRACT

Introduction: Bardet-Biedl syndrome (BBS) is a rare genetic disease associated with hyperphagia, a pathologic insatiable hunger, due to impaired signaling in the melanocortin-4 receptor (MC4R) pathway. The impact of hyperphagia on the lives of patients with BBS and their families has not been fully characterized.

Methods: Patients with BBS or their caregivers who participated in clinical trials of the MC4R

agonist setmelanotide (NCT03013543 and NCT03746522) were included in this qualitative study. Telephone interviews were conducted using a semistructured interview guide to explore patient experience and caregiver observations of hyperphagia before and during setmelanotide treatment.

Results: Nineteen interviews (8 patients, 11 caregivers) were conducted. The term “hunger” (rather than “hyperphagia”) was used in interviews to ensure common terminology. Before setmelanotide treatment, all participants described their (or their child’s) hunger as all-consuming, leading to an obsessive focus on food. Nine participants recalled intense, continuous hunger, and most participants (5 patients, 10 caregivers) reported lack of control with eating. Negative impacts on patients’ lives included difficulties

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with concentration, emotional and physical manifestations, and impaired relationships. All participants experienced or observed improvements in hunger and health outcomes during treatment, the most meaningful of which included weight loss and decrease in obsessive focus on food and food-seeking behaviors. All participants reported improvements in either physical and/or emotional well-being and being satisfied with setmelanotide.

Conclusions: Hyperphagia and resulting food-seeking behaviors have notable negative impacts on quality of life in patients with BBS and caregivers. Setmelanotide improved hyperphagia, reduced body weight and obsessive focus on food, and facilitated improvements in physical and emotional well-being for both patients and caregivers.

Trial Registration: NCT03013543 and NCT03746522

Keywords: Bardet-Biedl syndrome; Disease burden; Hyperphagia; MC4R pathway; Quality of life; Setmelanotide

Key Summary Points

Hyperphagia and early-onset obesity are hallmark clinical features of Bardet-Biedl syndrome (BBS) and place tremendous burdens on both patients and caregivers; these burdens are not fully characterized.

We conducted in-depth qualitative interviews with a cohort of patients with BBS or caregivers of patients with BBS who received setmelanotide treatment to understand the burden of hyperphagia and obesity in BBS and its modulation by setmelanotide.

Patients with BBS and their caregivers reported experiencing or observing notable hunger and associated consequences (e.g., negative emotions, strained familial relationships, impaired concentration) before setmelanotide treatment.

Interview participants also reported improvements in hunger during setmelanotide treatment that resulted in meaningful improvements in physical and emotional well-being for both patients and caregivers.

INTRODUCTION

Bardet-Biedl syndrome (BBS) is a rare autosomal recessive disease caused by variants in at least 25 genes that impair primary cilia function, resulting in clinical features including visual impairment; polydactyly; hypogonadism; cognitive impairment; genital abnormalities; early-onset, severe obesity; and pathologic insatiable hunger (hyperphagia) [1–7]. Obesity is estimated to occur in 72–92% of patients with BBS and is associated with short- and long-term health deficits, social stigma, and psychological impacts, which affect health-related quality of life (HRQOL) [8–17]. Hyperphagia can also reduce HRQOL and be a source of stress for caregivers and families [18, 19], given that individuals with hyperphagia exhibit excessive hunger and preoccupation with food that may interfere with daily functioning [20, 21].

Despite recognition that obesity and hyperphagia have broad impacts on QOL for patients with BBS and their caregivers, limited direct research in this population exists [19, 22, 23]. Weight management strategies for individuals with BBS have traditionally been similar to those used for general obesity and include lifestyle management, antiobesity medications, and bariatric surgery, none of which specifically target hyperphagia [7, 17, 24].

The hypothalamic melanocortin-4 receptor (MC4R) pathway is a key regulator of hunger, satiety, and energy balance [7, 25]. It is hypothesized that cilia dysfunction in patients with BBS contributes to impaired MC4R pathway signaling, resulting in hyperphagia, decreased energy expenditure, and consequently obesity [25–27]. Setmelanotide is an MC4R agonist approved in the USA and

European Union for rare MC4R pathway diseases of obesity including pro-opiomelanocortin (POMC) deficiency, leptin receptor (LEPR) deficiency, and BBS [28, 29]. Results from a multicenter randomized placebo-controlled phase 3 clinical trial (NCT03746522) showed that setmelanotide was associated with statistically significant body weight and hunger reductions among 32 patients with BBS [30].

In this study, we characterized the impacts of hyperphagia and obesity on HRQOL and their modulation by setmelanotide in patients with BBS and their caregivers. We conducted in-depth qualitative interviews with patients or caregivers of patients with BBS who previously participated in a phase 2 or phase 3 clinical trial of setmelanotide (NCT03013543 or NCT03746522). The primary objectives were to characterize the nature, severity, and effect of hyperphagia on patient and caregiver HRQOL before and during setmelanotide treatment.

METHODS

Participant Recruitment

Interview participants were identified from a pool of patients who completed previous phase 2 and 3 clinical trials (NCT03013543 or NCT03746522) of setmelanotide for the treatment of BBS and were provided information about the interview study by mail or email. Patients and caregivers who expressed interest in participating in the interview study were contacted by RTI Health Solutions (RTI-HS), a healthcare consultancy, and screened for eligibility. In addition to completion of a clinical trial of setmelanotide, patient eligibility criteria included age at least 16 years, genetic confirmation or clinical diagnosis per Beales criteria [31] of BBS, and informed consent (i.e., willingness and ability to participate in a 1-h, audio-recorded telephone interview). Study site staff obtained written informed consent for interview participation and for participant contact information to be provided to RTI-HS for scheduling and conducting interviews. Verbal consent was also obtained prior to recording interviews. To ensure patients had sufficient

cognitive function, individuals with BBS were eligible to participate in an interview only if they had self-completed patient-reported hunger items (as opposed to caregivers of patients younger than 12 years of age or those with cognitive impairment completing observer-reported versions of the hunger assessments) during the prior clinical trial. Caregiver eligibility criteria included age at least 18 years, current full-time caregiver status for an individual with genetic confirmation or clinical diagnosis per Beales criteria of BBS aged at least 6 years who had previously participated in a clinical trial of setmelanotide (NCT03013543 or NCT03746522), completion of observer-reported hunger assessments in the clinical trial, and informed consent. Although not required for inclusion, patients and caregivers of patients currently enrolled in the setmelanotide open-label long-term extension study (NCT03651765; prior completion of a phase 2 or 3 trial of setmelanotide required for inclusion) were also eligible for participation.

Compliance with Ethics Guidelines

The method of obtaining and documenting informed consent complied with the International Council on Harmonisation for Good Clinical Practice and all applicable regulatory requirements. Because BBS is a rare disease, qualitative data are reported with limited identifying information to preserve patient confidentiality. This study was conducted in accordance with the Declaration of Helsinki. The institutional review board or independent ethics committee at all trial sites reviewed and approved all appropriate study documentation.

Interview Methods

Eligible participants were contacted by RTI-HS to schedule an interview at a convenient date and time. All interviews were conducted between March and June 2021 in English by members of the RTI-HS project team who have extensive qualitative research experience (CE and LN). During each interview, one researcher led the interview while the other observed and

took field notes. Both patient and caregiver interviews followed semistructured interview guides specific to the type of participant; the caregiver guide was modified following the first few interviews to reduce participant burden (Supplementary Material).

The patient interview guide began with open-ended questions designed to elicit perspectives on experiences of hunger and its effect on the lives of patients before starting setmelanotide treatment. To supplement verbal descriptions and facilitate subsequent discussion about changes in hunger following treatment with setmelanotide, patients were also asked to rate their hunger on a numerical rating scale as was done during the clinical trials from which they were recruited. Caregivers were asked to report their observations related to these issues for the same time period. The term “hunger” was primarily used in interviews (rather than “hyperphagia”) to ensure common terminology. Patients and caregivers were then asked to describe changes in hunger (experienced and observed), weight, and functioning after initiating setmelanotide treatment, as well as the perceived meaningfulness of these changes. Finally, all patients and caregivers were asked about their satisfaction with setmelanotide. Interviews were audio recorded, transcribed, and deidentified.

Analysis

A thematic analysis approach was used to code and analyze the qualitative interview data, which were captured in the form of interview transcripts and Microsoft Excel-based field notes. To facilitate this process, a coding framework based on the content of the interview guide was initially developed; new codes were added throughout the analysis process to allow for emerging concepts. Similar to qualitative interviews conducted in other settings, themes or patterns in participant responses were identified by comparing relevant concepts and predominant trends across interviews [32]. All coding and qualitative analyses, including quality checks, were completed by CE and LN.

RESULTS

Participant Characteristics

Between March and June 2021, 19 telephone interviews were conducted with patients ($n = 8$) and caregivers ($n = 11$). All patients except one were enrolled in the long-term extension study of setmelanotide at the time of their interview. Baseline weight and hunger were previously reported for all patients included in the phase 2 and 3 trial primary analyses [30, 33]. The average age of patient participants was 36 years, and the average age of patients whose caregivers were interviewed was 16 years. Most patient participants were female ($n = 6$; 75.0%) and all caregiver participants were female parents (i.e., the mother). The mean time since the first approximately 1-year clinical trial of setmelanotide was 29 (range 12–48) months for patient participants and 24 (range 8–40) months for patients whose caregivers were interviewed (Table 1). Exemplar quotes are from individual patients with BBS and caregivers of patients with BBS.

Table 1 Baseline patient characteristics

	Self-reported patients ($n = 8$)	Caregiver-reported patients ($n = 11$)
Age, mean (range), years	36 (17–65)	16 (7–36)
Sex of patient, n (%)		
Female	6 (75)	6 (55)
Male	2 (25)	5 (45)
Sex of caregiver, n (%)		
Female	NA	11 (100)
Male	NA	0 (0)
Time since first clinical trial, mean (range), months	29 (12–48)	24 (8–40)

NA not applicable

Table 2 Patient- and caregiver-reported experiences of hunger, eating habits, and effect of hyperphagia before treatment with setmelanotide in clinical trials

Feelings of hunger	Eating habits	Effect of hyperphagia on patients	Effect of hyperphagia on caregivers
<p>“I was always hungry. And if I didn’t eat when I needed to, I would be very unhappy. Couldn’t wait to eat.”</p> <p>—Patient with BBS</p>	<p>“I was eating pretty much whatever, whenever and wasn’t able to stop myself from eating or sneaking food in the middle of the night.”</p> <p>—Patient with BBS</p>	<p>“I felt very agitated and very sad a lot of the time... I just really didn’t have many friends, really even many friends to hang out with and...I don’t know. I just kind of felt alone in a sense.”</p> <p>—Patient with BBS</p>	<p>“I have baseline anxiety and depression. And his hyperphagia combined with his vision loss and his epilepsy were affecting me so much so that I became suicidal, or having suicidal thoughts, or thoughts of harming myself on a daily basis.”</p> <p>—Caregiver of patient with BBS</p>
<p>“She was hungry all the time, and it was a relentless hunger. She would eat everything on her plate and everything on my plate, and anything she could find.”</p> <p>—Caregiver of patient with BBS</p>	<p>“He would eat until he was physically hurting. And then in the same breath, tell us that he was hurting and asked for a snack or something to eat. He’d sneak food.”</p> <p>—Caregiver of patient with BBS</p>	<p>“I’d feel crappy and crabby because maybe I ate sweets and stuff I really shouldn’t have had but I wanted... It made me mad after I ate it because I know I did want it, but then I thought, ‘Should I have really eaten that even though I really wanted it?’”</p> <p>—Patient with BBS</p>	<p>“Yeah, we didn’t like to go places. And if you go to somebody’s house, trying to keep them away from the chips and dip is so hard, it’s easier to just not go.”</p> <p>—Caregiver of patient with BBS</p>
<p>“His whole world revolved around food. Seems like he was always thinking about it, always asking about it. He just never seemed satisfied with a meal.”</p> <p>—Caregiver of patient with BBS</p>	<p>“If there was somewhere that it was reachable, she’d get a stool and try and reach it. We had put locks on the fridge at one point to kind of keep her from eating cheeses.”</p> <p>—Caregiver of patient with BBS</p>	<p>“She couldn’t do as well in school because she was thinking about what was in her lunchbox or what she was going to get at lunch or when she could eat it or how soon to lunch. It really did, it was very obsessive the amount of thoughts about the timing of food.”</p> <p>—Caregiver of patient with BBS</p>	<p>“It mostly affected me emotionally because I constantly felt like I was failing. It was like a no-win situation because if I did not give her extra food, then I felt terrible for denying her that when I knew she felt like she was starving, and if I did give it to her, I felt like I was slowly killing her and causing her health problems.”</p> <p>—Caregiver of patient with BBS</p>

Table 2 continued

Feelings of hunger	Eating habits	Effect of hyperphagia on patients	Effect of hyperphagia on caregivers
<p>“She was very hungry all the time and just really based her life around food if that makes any sense. When she would write in her journal, she would write everything that she ate during the day, when she told anyone about anything that was happening in life, it was always based around food.”</p> <p>—Caregiver of patient with BBS</p>	<p>“She always wanted to drink and eat. She would often even sneak food. I would find wrappers in her bags or in her drawers or bedside table.”</p> <p>—Caregiver of patient with BBS</p>	<p>“Looking back at it now, I think it affected his concentration a lot, especially at school. Before the trial, at school, he’d spend a lot of time out of the classroom. He’d be crying, he’d be upset about something. Most times, he wouldn’t be able to tell them why he was upset. And I just always think that it was because he was hungry. But of course, we didn’t know that at the time.”</p> <p>—Caregiver of patient with BBS</p>	<p>“And it’s really hard. Like, you’d go to the doctor and they’d say, ‘Look how heavy she is. And you should feed her less; go see the dietician.’ And then the dietician would say, ‘You should try feeding her less.’ That’s a great idea. And then I’d have to pull her away because she’s eating the fake food on the food triangle that the dietician has in her office. And every time we’d go in, we’d have to look at the cheese with the teeth marks in it because my kid did it, just trying to eat your fake cheese right now.”</p> <p>—Caregiver of patient with BBS</p>

Each cell represents a single individual’s response. Responses from 4 patients and 7 caregivers are included
BBS Bardet-Biedl syndrome

Symptoms and Behaviors Associated with Hyperphagia

Feelings of Hunger and Pursuit/Consumption of Food

While all 19 participants described experiences of uncontrollable hunger that were consistent with hyperphagia, none spontaneously used the term “hyperphagia” (Table 2). All participants characterized hyperphagia as all-consuming and extreme, which caused an obsessive focus on and a relentless pursuit and consumption of food. Hyperphagia was continuous, with nearly half of participants ($n = 9$) reporting hunger that was intense throughout the day; the

remaining participants reported hunger that varied in relation to the time of day. Caregivers indicated that hyperphagia prompted incessant food-seeking behaviors from patients including queries about the next meal or constantly wanting more food.

“I was always hungry. And if I didn’t eat when I needed to, I would be very unhappy. Couldn’t wait to eat.” —Patient

“She was hungry all the time, and it was a relentless hunger. She would eat everything on her plate and everything on my plate, and anything she could find.” —Caregiver

Patients were also asked to recall the highest level of hunger they experienced before starting the clinical trial using a numerical rating scale where 0 = “not hungry at all” and 10 = “the hungriest possible.” Pretreatment peak hunger ratings ranged from 8 to 10, and peak hunger was associated with physical and emotional manifestations including fatigue, pain, frustration, irritability, and a hyperfocus on obtaining food. When caregivers were asked what behaviors signified their child was experiencing the most intense level of hunger, they reported severe tantrums, irritability, and hyperfocus on obtaining food.

“If she didn’t get food, she was just a terror.... She’d have a fit, everything except for self-harming. That’s the only thing she didn’t do.”
—Caregiver

While patients consistently reported some level of satisfaction after eating, many noted the sensation was short-lived, only achieved with a large meal, and resembled fullness or satiation rather than a feeling of positive emotional valence. Conversely, most caregivers ($n = 9$; 81.8%) reported that their child never seemed to be full or satisfied after eating.

Eating Habits and Engagement in Food-Seeking Behaviors

All participants reported that hyperphagia influenced what and/or how much was consumed (Table 2), with carbohydrates and/or sugary foods being the most sought during periods of extreme hunger. Further, most participants (15 of 19 overall [78.9%]; 5 of 8 patients [62.5%] and 10 of 11 caregivers [90.9%]) described a lack of control with eating, and caregivers frequently remarked that their child would not stop eating without outside influence (Table 2). Food-seeking behaviors were reported by most caregivers and included begging, bargaining, and/or attempting to bribe others for food. Although hiding and stealing food is considered a hyperphagic behavior [6, 21], only 25.0% of patients reported doing this, but more than half of caregivers ($n = 6$; 54.5%) reported observing these behaviors.

“I was eating pretty much whatever, whenever and wasn’t able to stop myself from eating or sneaking food in the middle of the night.” —Patient

“He would eat until he was physically hurting. And then in the same breath, tell us that he was hurting and asked for a snack or something to eat. He’d sneak food.... It seemed like he was just hungry all the time.” —Caregiver

Multifactorial Consequences of Hyperphagia on Patients and Caregivers

Emotional Consequences of Hyperphagia

Participants were asked about the effects of hyperphagia experienced before beginning setmelanotide treatment. Overall, most patients ($n = 7$; 87.5%) and caregivers ($n = 10$; 90.9%) experienced negative effects directly related to hyperphagia; one patient and one caregiver attributed negative effects to increased weight instead. The most commonly reported effect pertained to patients’ emotional states (Table 2). Both patients and caregivers reported emotional effects of hyperphagia including sadness, frustration, irritability, anxiety, and guilt. These feelings often centered around food and were related to either the desire to eat (e.g., irritability, anxiety) or the patients’ inability to control their hunger or eating habits (e.g., frustration, guilt).

“I felt very agitated and very sad a lot of the time.... I just really didn’t have many friends, really even many friends to hang out with and...I don’t know. I just kind of felt alone in a sense.” —Patient

“I’d feel crappy and crabby because maybe I ate sweets and stuff I really shouldn’t have had but I wanted.... It made me mad after I ate it because I know I did want it, but then I thought, ‘Should I have really eaten that even though I really wanted it?’” —Patient

Impacts of Hyperphagia on Family Dynamics

Hyperphagia had broad negative impacts on family dynamics including impaired relationships with siblings and tensions between caregivers and patients (Table 2). For example, one caregiver described decreased interactions

between siblings because the siblings “didn’t know how to handle” the consistent emotional distress of the patient. Caregivers also experienced strains on spousal and familial relationships due to regulation of food intake.

“It affected my relationship with my husband...he is a lot better at saying no than I am. And sometimes it would be so hard for me because he was just so black-and-white about it and would just say, ‘No, get out of the kitchen,’ and then I would feel bad and cry and be mad at him. I would think he was being mean to her when really, he was doing what was best for her.”—Caregiver

Caregivers experienced diminished emotional and psychological well-being due to their child’s hyperphagia, reporting feeling burdened by the need to constantly monitor eating behaviors, guilt related to their child’s health, and fear of judgment from others. For more than half of caregivers ($n = 6$; 54.5%), hyperphagia negatively impacted social participation because of required hypervigilance in situations involving food and reluctance to leave their child in the care of another individual.

“Yeah, we didn’t like to go places. And if you go to somebody’s house, trying to keep them away from the chips and dip is so hard, it’s easier to just not go.”—Caregiver

Productivity at Work and School

Participants reported impaired concentration and focus as a consequence of hyperphagia (2 of 8 patients [25.0%]; 8 of 11 caregivers [72.7%]). For children, this translated into challenges at school because of an obsessive focus on food.

“Looking back at it now, I think it affected his concentration a lot, especially at school. Before the trial, at school, he’d spend a lot of time out of the classroom. He’d be crying, he’d be upset about something. Most times, he wouldn’t be able to tell them why he was upset. And I just always think that it was because he was hungry. But of course, we didn’t know that at the time.”—Caregiver

A subset of caregivers ($n = 2$; 18.2%) also experienced reduced productivity and ability to

complete tasks as a result of their child’s hyperphagic behaviors and the attendant need to plan and prepare meals.

Changes with Setmelanotide Treatment

Improvements in Hyperphagia, Food-Seeking Behaviors, and Weight with Setmelanotide Treatment

Table 3 shows the proportion of participants who reported improvements in hyperphagia and associated outcomes with setmelanotide treatment. All participants ($N = 19$) reported substantial improvements in hyperphagia and satiety within 2 months of initiating setmelanotide treatment. Decreases in peak hunger scores ranged from 2 to 6 points. Notably, a previous psychometric evaluation estimated that within-patient decreases in hunger score of

Table 3 Proportion of participants who reported improvements in hyperphagia and associated consequences with setmelanotide treatment

	Self-reported patients ($n = 8$)	Caregiver-reported patients ($n = 11$)
Improved family dynamics/ relationships related to improved hyperphagia, n (%)	4 (50.0)	6 (54.5)
Improved social life/ friendships related to improved hyperphagia, n (%)	2 (25.0)	3 (27.3)
Increased ability to focus related to improved hyperphagia, n (%)	8 (100)	11 (100)
Improved task performance due to improved focus related to improved hyperphagia, n (%)	2 (25.0)	7 (63.6)

1–2 points are sufficient to yield improvements in clinical status and perceived meaningfulness of hunger reduction [30]. Similarly, caregivers consistently observed changes in food-seeking and eating behaviors.

“I feel great. I feel satisfied. I feel full when I’m done eating. Sometimes, I won’t eat everything that’s on my plate.” —Patient

“After we started this setmelanotide trial, she told me for the first time that she had no idea what it was not to be hungry. So that was really sad. So before the trial, I guess, according to her, she had never experienced not being hungry before....” —Caregiver

Consistent with improved hunger, all participants reported a large reduction in food consumption, greater control over how much food was consumed, and consumption of or requests for healthier foods (Table 4).

“I feel like I’ve had a lot more willpower since I’ve been on the medication, and I feel like I haven’t really been tempted to grab really anything during meals, which has felt good.” —Patient

Patients and caregivers also reported fewer hyperphagic behaviors (e.g., eating in secrecy, eating foods that others would find undesirable) after treatment initiation. None of the participants who reported these behaviors before setmelanotide (2 of 8 patients [25.0%] and 6 of 11 caregivers [54.5%]) experienced or observed them after initiating setmelanotide treatment. Additionally, all 11 caregivers noted the ability to give their child greater autonomy around food choices and consumption and a reduced need to monitor their child’s food intake.

“I’ll let her eat what she wants. I guess that’s the biggest deal is that. Do you want to eat more brussels sprouts? Eat more brussels sprouts because I know you’re not going to eat 10 servings of macaroni and cheese or a whole jar of peanut butter today.” —Caregiver

In addition to improvements in hyperphagia and related behaviors, all participants reported weight loss following setmelanotide treatment

initiation. While patients self-reported an average weight loss of 52 pounds (range 25–130 pounds; $n = 8$), three reported regaining some weight, which they attributed to the coronavirus disease 2019 (COVID-19) pandemic (e.g., constant access to food, lack of physical activity). Caregivers reported that patients lost an average of 36 pounds (range 5–100 pounds; $n = 11$), which underestimates reductions in body mass index, because many noted that their child’s height had also increased (range 2–12 inches).

Emotional and Physical Impacts of Improved Hyperphagia in Patients and Caregivers

Most patients ($n = 7$; 87.5%) reported improvements in how they felt physically while receiving setmelanotide (e.g., had more energy, could be more active). Caregivers also observed physical improvements, frequently noting that their child was more readily able to participate in recreational activities and sports. Participants consistently reported significant improvements in patients’ moods or emotions with treatment; improvements in hunger led to decreased anxiety, stress, and irritability, as well as increased happiness, self-esteem, and confidence (Table 4). Caregivers also reported reduced stress, worry, and/or anxiety stemming from the need to monitor and control their child’s food intake after their child initiated setmelanotide treatment.

“It made me more positive and more peppy, my voice and thinking and wanting to be out more with people.” —Patient

Improvements in Family and Social Dynamics with Setmelanotide Treatment

Both patients ($n = 4$; 50.0%) and caregivers ($n = 6$; 54.5%) noted that improvements in hunger had benefited family dynamics including better sibling interactions, and some participants (2 of 8 patients [25.0%]; 3 of 11 caregivers [27.3%]) noted their (or their child’s) social life and friendships improved because of improved hunger (Table 3). Further, for some caregivers, reduced stress and worry led to improved family relationships, better sleep, and a more positive outlook.

Table 4 Patient- and caregiver-reported experiences of hunger, eating habits, and effect of hyperphagia during and after treatment with setmelanotide in clinical trials

Feelings of hunger	Eating habits	Effect of hyperphagia on patients	Effect of hyperphagia on caregivers
<p>"I don't feel like I'm hungry or craving in the evening to the extent that I was before I started the medication."</p> <p>—Patient with BBS</p>	<p>"I feel like I've had a lot more willpower since I've been on the medication, and I feel like I haven't really been tempted to grab really anything during meals, which has felt good."</p> <p>—Patient with BBS</p>	<p>"I feel better.... I'm feeling healthier. I think that's probably a pretty good thing. It's a physical reaction. You have more energy. Your blood pressure is lower. Level across all the other criteria. They're just better."</p> <p>—Patient with BBS</p>	<p>"Well, it's just a lot easier because I don't have to be the food police anymore.... It's like everything in the house is more laid back instead of being on edge about food."</p> <p>—Caregiver of patient with BBS</p>
<p>"I feel great. I feel satisfied. I feel full when I'm done eating. Sometimes, I won't eat everything that's on my plate."</p> <p>—Patient with BBS</p>	<p>"Let's see. I would say more normal portions. Say if I were to go to Golden Corral before I was on the medicine, I'd probably eat at least 3 to 4 plates. But now I'd probably want a plate or 2."</p> <p>—Patient with BBS</p>	<p>"It made me more positive and more peppy—my voice and thinking and wanting to be out more with people."</p> <p>—Patient with BBS</p>	<p>"I was so worried. He was so heavy and he was prediabetic. And then I was worried his kidneys were going to get worse. I don't worry about all that stuff so much anymore."</p> <p>—Caregiver of patient with BBS</p>
<p>"After we started this setmelanotide trial, she told me for the first time that she had no idea what it was not to be hungry. So that was really sad. So before the trial, I guess, according to her, she had never experienced not being hungry before...."</p> <p>—Caregiver of patient with BBS</p>	<p>"I haven't noticed her getting anything out of the trash."</p> <p>—Caregiver of patient with BBS</p>	<p>"And he has friends this year. He's never really had friends, probably because he was always crying.... So, yeah, he's got some buddies this year."</p> <p>—Caregiver of patient with BBS</p>	<p>"I think I sleep better now, just not having that, that stress or not having to wake up, make sure he's not in the kitchen."</p> <p>—Caregiver of patient with BBS</p>

Table 4 continued

Feelings of hunger	Eating habits	Effect of hyperphagia on patients	Effect of hyperphagia on caregivers
<p>“She will push food away when she’s full. And she will literally say, ‘I’ve had enough. I’m full. And I don’t want to eat this.’ She seems to know how much is enough.”</p> <p>—Caregiver of patient with BBS</p>	<p>“She decided last year, one of her cousins was going without sugar. This is dessert and candy. And one of her cousins was going without, for a year, just trying an experiment that, and she decided to join her and she did it for a whole year. And I think there’s not a chance in the world that she would’ve been able to do that before.”</p> <p>—Caregiver of patient with BBS</p>	<p>“I think it has helped. Not that he had a mood problem but I think he is happy that he knows he can control things himself, that this has empowered him to make life choices and they’re the good choices. I’m sure that’s given him some confidence.”</p> <p>—Caregiver of patient with BBS</p>	<p>“It just affected us so much. Obviously, as a parent, you worry so much about your kids and when something like that drastic changes, it’s pretty freeing and pretty amazing. Even my husband and I, our relationship together, because we were always so worried about it. It really helped us to be able to calm down and not be so stressed out.”</p> <p>—Caregiver of patient with BBS</p>
<p>“He’d tell me his stomach hurt after he ate. And then we finally figured out that it...I think he was full. What that feeling was, he didn’t know what to call it. He didn’t know what that was. That’s what I think, anyway. I think he was feeling full and that was a new feeling for him, and he didn’t quite know how to describe it.”</p> <p>—Caregiver of patient with BBS</p>	<p>“I find that she makes a lot of better choices since she’s been on setmelanotide, willingly. I don’t have to...she packs her lunch and she knows my rules. You have to have a veggie, fruits, and then a yogurt. But often she would try...before, she would try to sneak other things in there or put more. But now she makes her own lunch and when I look in it, it’s all healthy.”</p> <p>—Caregiver of patient with BBS</p>	<p>“She’s more confident. She’s, yes, more happy, more confident. I think her self-esteem is better. I do remember before this clinical trial...she just had a breakdown. ‘I hate this. I never asked for it.’ It was horrible. And I was in tears watching her.... And to just see where that episode was and where we are now, it’s like, ‘Thank God.’”</p> <p>—Caregiver of patient with BBS</p>	<p>“We go out regularly now. So we try to go out once a week and are comfortable with taking them to the sitter now, because.... Yeah. You’re going to make me cry. Yeah, that was a big change. Huge, huge.... Yeah, we’re just...I keep saying happier. We’re just happier.”</p> <p>—Caregiver of patient with BBS</p>

Each cell represents a single individual’s response. Responses from 4 patients and 6 caregivers are included
BBS Bardet-Biedl syndrome

Table 5 Most important improvement to patients in clinical trials with setmelanotide

	Patient reported (<i>n</i> = 8), <i>n</i>	Caregiver reported (<i>n</i> = 11), <i>n</i>	Total (<i>N</i> = 19), <i>n</i> ^a
Weight (able to eat less) and general health	5	6	11
Decrease in obsessive focus on food/hunger	3	5	8
Increase in energy	1	2	3
More social/interactions with friends/family	3	–	3
Physical ability	–	2	2
Better mood/happier	–	2	2
Greater control over food	1	–	1

^aSome patients and caregivers reported > 1 most important improvement; therefore, the total number included is > 19

“And he has friends this year. He’s never really had friends, probably because he was always crying.... So, yeah, he’s got some buddies this year.” —Caregiver

“Well, it’s just a lot easier because I don’t have to be the food police anymore.... It’s like everything in the house is more laid back instead of being on edge about food.” —Caregiver

Improvements in Concentration and Productivity at School and Home with Setmelanotide Treatment

All participants reported improved focus and concentration related to reductions in obsessive behaviors associated with food. A subset of participants (2 of 8 patients [25.0%]; 7 of 11 caregivers [63.6%]) noted that this increased ability to focus resulted in improved task performance at school or home (Table 3).

Perceived Meaningfulness and Overall Satisfaction with Treatment

Participants were asked to identify the most important changes attributable to improvements in their (or their child’s) hunger (open-ended question; Table 5). The most frequently reported changes (5 of 8 patients [62.5%]; 6 of 11 caregivers [54.5%]) were weight loss and associated health benefits (e.g., reduced blood pressure) and reduced obsessive focus on food (3 of 8 patients [37.5%]; 5 of 11 caregivers [45.5%])

and associated life impact. Patients and caregivers commonly described the improvements in hyperphagia as “very meaningful” and “life changing” (Table 6).

“Oh, totally meaningful. This is who he gets to be for the rest of his life. Somebody who’s conscious of what food does to your body and be healthy and not die young. This is everything.” —Caregiver

All but one participant reported that they were “very satisfied” with setmelanotide (Table 6). Similar to perceived meaningfulness, participant satisfaction was attributed to improvements in hyperphagia and associated behavioral changes, as well as weight loss and associated health benefits. Participants also commonly reported feeling less worry about their (or their child’s) health in the future as a result of treatment. The patient who indicated being less than very satisfied with setmelanotide noted being satisfied with the improvement in hunger, but was disappointed with weight regain during the COVID-19 pandemic.

At the conclusion of each interview, participants were asked to describe how they would feel if patients could no longer take setmelanotide (Table 6). Patients commonly used the terms “very upset,” “disappointed,” and “distracted.” Caregivers used more dramatic language such as “terrifying,” “devastating,” and “a death sentence.”

Table 6 Patient- and caregiver-reported meaningfulness of improvements in hunger, overall satisfaction of treatment, and feelings if treatment were discontinued

Meaningfulness	Overall satisfaction	Discontinuing setmelanotide
<p>“I feel way much better now with this. Like I say, it’s a miracle drug to me, even though you have to inject it into your stomach with a needle.... It’s very important to me because I see that the medication is working and will work, and I would never be able to lose as much weight with this syndrome if this medication wasn’t available.”</p> <p>—Patient with BBS</p>	<p>“I’m very satisfied with the medication because it has helped me be more aware of food and what I’m eating or what the medication is telling my brain or helping me lose weight.”</p> <p>—Patient with BBS</p>	<p>“I would be very upset and mad and I would fight to voice my opinion and fight to have me keep taking it because I know how powerful it is for me and people with this syndrome.”</p> <p>—Patient with BBS</p>
<p>“It seemed like even when I smelled food, I would gain weight. And I’ve been able to lose some weight, which has been very, very nice, but I’ve also had the activity. My activities have been a lot better. I’ve had more energy and I’ve been able to do more and that has been very nice. I think that’s probably the best improvement.”</p> <p>—Patient with BBS</p>	<p>“The drug is doing exactly what it’s supposed to do.”</p> <p>—Caregiver of patient with BBS</p>	<p>“Oh, I would feel very distraught and very disappointed and just not myself...because I’ve lost so much weight, and people have recognized how hard I’ve been trying to work on that. And I also have a therapist who I’ve also been working on some mental stuff. And I think it’s just...I think it would affect all of it.”</p> <p>—Patient with BBS</p>
<p>“Oh gosh. Well, I feel like I’ve had more positive interactions with people not revolving around the weight.... I think just, whether it was family or friends, whoever, realizing that this actually was working and that it was making an impact on my life.”</p> <p>—Patient with BBS</p>	<p>“I’m going to go with ‘very’ [satisfied]. If there’s something higher than that, I’ll take that, too.... I would never have expected to be this satisfied with it.”</p> <p>—Caregiver of patient with BBS</p>	<p>“I would be devastated. And that’s one of my biggest fears. Because I feel like it would be taking away all our hope. Before we started this trial, I literally felt hopeless, like there was nothing I can do, like it was completely out of my control.... And if it was taken away, I would feel like it would literally be a death sentence.”</p> <p>—Caregiver of patient with BBS</p>

Table 6 continued

Meaningfulness	Overall satisfaction	Discontinuing setmelanotide
<p>“It gives me the hope for the future that he’s going to be a secure, independent person, even if he lives with his sister or if he lives with a caretaker. He’s going to be healthy and he’s going to live longer, for sure.”</p> <p>—Caregiver of patient with BBS</p>	<p>“Because I literally feel like it’s saved her life or going to save her life because...I don’t know. I feel eternally grateful to have been able to get her in this and for everything that they’ve done for her and the medicine. Absolutely very thankful.”</p> <p>—Caregiver of patient with BBS</p>	<p>“His ophthalmologist is working on gene therapy that could stop his...prevent his vision from getting any worse, even though he’s already legally blind. But I asked him, I said, ‘If you could only have one of the medications, and if they could reverse your blindness entirely and you could see completely fine, but you wouldn’t have access, you wouldn’t be able to have setmelanotide, which one would you choose?’ And then he’s—no hesitation—the setmelanotide. He says, ‘I just...I can think about other things.’ And for someone to give up blindness for hunger, choosing blindness, I think, speaks incredible volumes.”</p> <p>—Caregiver of patient with BBS</p>

Each cell represents a single individual’s response. Responses from 3 patients and 5 caregivers are included
BBS Bardet-Biedl syndrome

DISCUSSION

Hyperphagia and obesity are salient clinical features associated with BBS [1, 6]. The present study adds to existing evidence and highlights the considerable burden that hyperphagia and obesity impose on patients with BBS and their families. Further, these interviews exemplify the usefulness of “patient experience data,” as recommended by the US Food and Drug Administration for patient-centered drug development, given that such data elucidate how setmelanotide treatment is important to patients with BBS and could potentially aid in the development of robust HRQOL measures in this patient population [34]. Currently available patient-reported outcome measures used to assess hyperphagia focus on the severity of hyperphagia and associated behaviors but do not address their impacts on the lives of

patients and caregivers [20, 21]. Our results suggest that improving hyperphagia through pharmacologic intervention can minimize its negative impact on productivity, family dynamics, overall patient health, and emotional well-being.

The results across the interviews were highly consistent, with all participants describing very similar experiences of hyperphagia. To our knowledge, these are the first detailed descriptions of hyperphagia and related effects provided by both patients with BBS and their caregivers. These results complement findings from the phase 3 trial of setmelanotide in BBS, where patients experienced improved hunger, reduced weight, and improvements in HRQOL following 1 year of setmelanotide treatment [35, 36]. Specifically, 85% of patients reported clinically meaningful improvements (i.e., change in Impact of Weight on Quality of Life

Questionnaire-Lite (IWQOL-Lite) or Pediatric Quality of Life Inventory (PedsQL) scores of 7.7–12 or more than 4.4 points, respectively) in HRQOL or preserving their nonimpaired HRQOL status after 1 year of setmelanotide treatment [36].

No new themes or concepts important to participants (i.e., regarding symptoms and impacts associated with hyperphagia) were reported while the interviews progressed, supporting concept saturation [37]. In addition, the overall sample size herein is supported by previously conducted research [38]. Nonetheless, this study has several limitations. Participants were patients and mothers of patients who chose to continue treatment, which may reflect bias toward setmelanotide. Further, no fathers or other caregivers were included in the sample. No sex- or gender-specific analyses for patients or caregivers were performed because of these limitations. Another limitation is the variable duration of time that patients were treated with setmelanotide and length of time since the first clinical trial, which may have contributed to baseline recall bias and potentially accounted for some differences between patient and caregiver reports. This point is highlighted by varying perceptions of hyperphagia severity and associated behaviors between patients and caregivers. Patients may not have realized the extent of their condition because of the time elapsed since and/or their age before they initiated treatment, whereas these factors may not have impacted caregiver perceptions. Further, it is possible that patients had never conceptualized what life without hyperphagia was like before participating in the clinical trial and may have not believed it was abnormal or particularly uncomfortable because this was their personal usual state. One additional consideration when interpreting the results is that patients were interviewed during the COVID-19 pandemic, during which three participants reported patient weight gain.

CONCLUSIONS

This study confirms that hyperphagia imposes a substantial burden on patients with BBS and

their families. Additionally, this study provides insights into less obvious consequences of living with insatiable hunger such as the inability to focus on tasks or build relationships. Treatment with setmelanotide facilitated improvements in hunger and promoted beneficial changes in patient and caregiver experiences. Thus, the impact of setmelanotide treatment in patients with BBS extends beyond clinically beneficial outcomes (e.g., weight reduction) and includes HRQOL improvements that are deeply meaningful to patients and their families. These findings are consistent with previous results from similar interviews of patients with POMC or LEPR deficiency who showed substantial QOL improvements following setmelanotide treatment [39]. Our results support further research on the long-term consequences of hyperphagia and obesity and treatment interventions that can alleviate their impact on HRQOL in patients with BBS.

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Compliance With Ethics Guidelines. Informed consent was obtained for participation in the clinical trials of setmelanotide (NCT03013543 and NCT03746522); the trials were conducted in accordance with International Council on Harmonisation for Good Clinical Practice and the Declaration of Helsinki with institutional review board or independent ethics committee approval obtained at all trial sites. Study site staff obtained written informed consent for interview participation and for participant contact information to be provided to RTI Health Solutions for scheduling and conducting interviews. Verbal consent was also obtained prior to recording interviews. All patients provided informed consent for data to be reported in aggregate and anonymously.

Data Availability. The data sets generated and/or analyzed during the current study are not publicly available. Public data sharing was

not included in the study consent as the rarity of this condition prohibits (or greatly reduces) the ability to ensure participant anonymity.

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