

Identifying Endpoints for Irritable Bowel Syndrome (IBS) Clinical Trials: Incorporating the Patient's Voice

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BACKGROUND

- Historically, primary endpoints in irritable bowel syndrome (IBS) clinical trials have been based on global items assessing the adequacy or extent of relief from IBS symptoms.
- Both the European Medicines Agency (EMA) and the United States Food and Drug Administration (FDA) recommend the involvement of patients in the development and selection of patient-reported outcome (PRO) clinical trial endpoints.
- Qualitative evidence from patients is necessary to identify all symptoms important to the IBS patient population so that these symptoms can be assessed in clinical trials.

OBJECTIVES

- Identify a comprehensive set of symptoms experienced by patients with IBS with constipation (IBS-C)
- Identify the most important symptoms and optimal terminology to assess those symptoms in IBS-C clinical trials
- Achieve concept saturation and provide support for the content validity of the resulting set of endpoints prior to their use in Phase 3 clinical trials of linaclotide

METHODS

- Two iterative sets of interviews were conducted with a total of 27 patients with IBS-C in Raleigh, North Carolina (Round 1, December 2008) and Las Vegas, Nevada (Round 2, January 2009).
- Patients were referred by local gastroenterologists and met modified Rome II criteria for IBS-C.
- Patients recruited were similar (both clinically and demographically) to participants in Phase 2 clinical studies of linaclotide for the treatment of IBS-C (Table 1).

Table 1. Demographic Characteristics of Interview Participants

Demographic Information	N = 27
Gender	
Female	26
Male	1
Age, average (range)	46.5 (20-78)
Race	
White	18
African American/black	8
Hispanic	1
Education	
High school	9
Some college or 2-year degree	10
College graduate	5
Postgraduate	3

- A semistructured interview guide, composed primarily of open-ended questions, was used to ensure consistency within each round of interviews.
- Participants were asked to identify and describe their IBS-C symptoms and the relationships among their symptoms.
 - “What types of symptoms do you experience?”
 - “When you say [symptom], what exactly does that mean to you?”
 - “How do these symptoms relate to each other?”
- Additional rating and ranking methods were used to narrow the full list of IBS-C symptoms and impacts to include only those of greatest importance to the participants. For example:
 - Participants in both sets of interviews were probed to identify their most bothersome IBS-C symptoms.
 - Round 1 participants rated the importance of selected bowel and abdominal symptoms.
 - Round 2 participants identified the five symptoms they would most like improved.

RESULTS

Definition of Constipation

- While somewhat variable, participants' definitions of constipation commonly included infrequent bowel movements (BMs), straining during BMs, and hard stools that were typically difficult or uncomfortable to pass. Sample descriptions included:
 - “I think two things, really hard stools and having to really strain. And I guess underlying all of that is the fact that you're not going very often. And so constipation, for me, constipation is the frequency, and straining, and completeness.”
 - “Constipation is when you can't use the bathroom.”
 - “Like I have a bowel movement maybe two or three times a week. They're always hard. They're usually like hard or clumpy, [requiring] straining.”
 - “It means that your bowel movement won't pass. I don't care what you do. You can just strain, cry, kick, scream and it just won't work.”
 - “Well you can't use the bathroom. You know you need to, but it doesn't come out. And when it...it's very difficult for it to come out. It hurts and then sometimes...it just won't come out by itself.”

Spontaneous Symptom Reports

- When asked to report their IBS-C symptoms, participants spontaneously reported 54 potentially distinct concepts: 8 abdominal symptoms, 12 bowel symptoms, 31 additional physical symptoms, and 3 mental or emotional issues.
- Although participants generally described a similar constellation of bowel and abdominal symptoms, there was variability in their choice of descriptors.
- Additional symptoms were generally regarded by participants as the consequence of severe bowel or abdominal symptoms:
 - Participants reported rectal pain, hemorrhoids, and rectal bleeding secondary to straining and hard stools.
 - Extremely infrequent BMs were associated with additional gastrointestinal (GI) problems such as nausea, vomiting, and early satiety, as well as non-GI issues such as fatigue and irritability.
- A complete list of symptoms spontaneously reported by at least 2 participants is provided in Table 2.

Table 2. Spontaneously Reported IBS-C Symptoms in Rounds 1 and 2

	Round 1 (n = 15)	Round 2 (n = 12)	Total (%) (N = 27)
Abdominal symptoms, n			
Bloating	13	10	23 (85.2%)
Abdominal pain	13	6	19 (70.4%)
Abdominal discomfort (uncomfortable)	8	6	14 (51.2%)
Abdominal cramping	3	8	11 (40.7%)
Stomach pain/ache	4	6	10 (37.0%)
Feeling of fullness/full feeling	6	2	8 (29.6%)
Distention	6	0	6 (22.2%)
Churning/rumbling and/or gurgling in stomach	2	3	5 (18.5%)
Bowel symptoms, n			
Infrequent BMs	14	11	25 (92.6%)
Hard (or lumpy) stool	12	7	19 (70.4%)
Constipation	12	6	18 (66.7%)
Gas (trapped gas, flatulence)	8	8	16 (59.3%)
Unsuccessful attempts for BMs	10	4	14 (51.2%)
Straining	7	7	14 (51.2%)
Incomplete BMs	5	7	12 (44.4%)
Stools too small (or too large)	4	8	12 (44.4%)
Passing mucus with stool	1	1	2 (7.4%)
Rectal consequences, n			
Rectal pain	5	8	13 (48.1%)
Hemorrhoids	5	3	8 (29.6%)
Rectal bleeding	5	3	8 (29.6%)
Rectal tearing	3	2	5 (18.5%)
Other physical symptoms or consequences, n			
Nausea/queasy	6	3	9 (33.3%)
Feeling backed up	4	4	8 (29.6%)
Back pain	3	5	8 (29.6%)
Headaches	2	6	8 (29.6%)
Loss of appetite/don't want to eat/early satiety	4	3	7 (25.9%)
Bad breath	0	4	4 (14.8%)
Vomiting	3	0	3 (11.1%)
Swelling (e.g., in legs, face, hands, lips)	2	1	3 (11.1%)
Exhausted/weak from straining	2	1	3 (11.1%)
Feeling of twisting, squeezing (lower stomach and back)	0	3	3 (11.1%)
Acid reflux	2	0	2 (7.4%)
Indigestion	2	0	2 (7.4%)
Weight gain	1	1	2 (7.4%)
Burping/belching	1	1	2 (7.4%)
Strong odor of gas	0	2	2 (7.4%)
Lightheaded after BM	0	2	2 (7.4%)
Skin issues/breakouts	0	2	2 (7.4%)
Mental or emotional impacts of IBS-C, n			
Moodiness, mood swings, irritability	3	6	9 (33.3%)
Fatigue/tiredness	4	4	8 (29.6%)

Note: Includes only symptoms reported by at least 2 participants.

Most Bothersome Symptoms

- When asked to describe the most bothersome symptom(s) of IBS-C, participants mentioned abdominal and bowel symptoms with similar frequency; rectal consequences of hard stools and straining were also reported.
- Across all 27 participants, the symptoms most frequently identified as most bothersome included bloating; abdominal discomfort; abdominal pain; and infrequent, incomplete, and unsuccessful BMs (being unable to have a BM when needed or desired). Sample responses included:
 - “The bloating. I think because it, well I know it's caused from the bowels, but it still, it's very uncomfortable.”
 - “I think the pain, the uncomfortable feeling, and the bloating.”
 - “The constant discomfort. Yeah. I would say that.”
 - “The scariest and the most bothersome is when it starts hurting and you can't defecate, I guess.”
 - “Not feeling empty. I mean I'd say having this infrequent bowel movement, you know, and the bloating too.”
 - “When you leave the bathroom and you know you're not through, but you can't do anything about it.”
 - “Well that feeling that you have to go, but you can't—or that you went but you didn't think you finished.”

Rating and Ranking Exercises

- When asked to rate the eight core symptoms of IBS-C shown in Table 3, Round 1 participants generally rated both bowel and abdominal symptoms as very important.

Table 3. Summary of Importance Ratings for Core Symptoms (Round 1; N = 15)

Symptom, n	0	1	2	3	Mean
BM frequency				15	3.0
Constipation (overall)			1	14	2.9
Straining			2	13	2.9
Abdominal pain			3	12	2.8
BM completeness		2	1	12	2.7
Stool consistency			4	11	2.7
Bloating ^a	1	1	2	11	2.7
Abdominal discomfort ^b			5	8	2.6

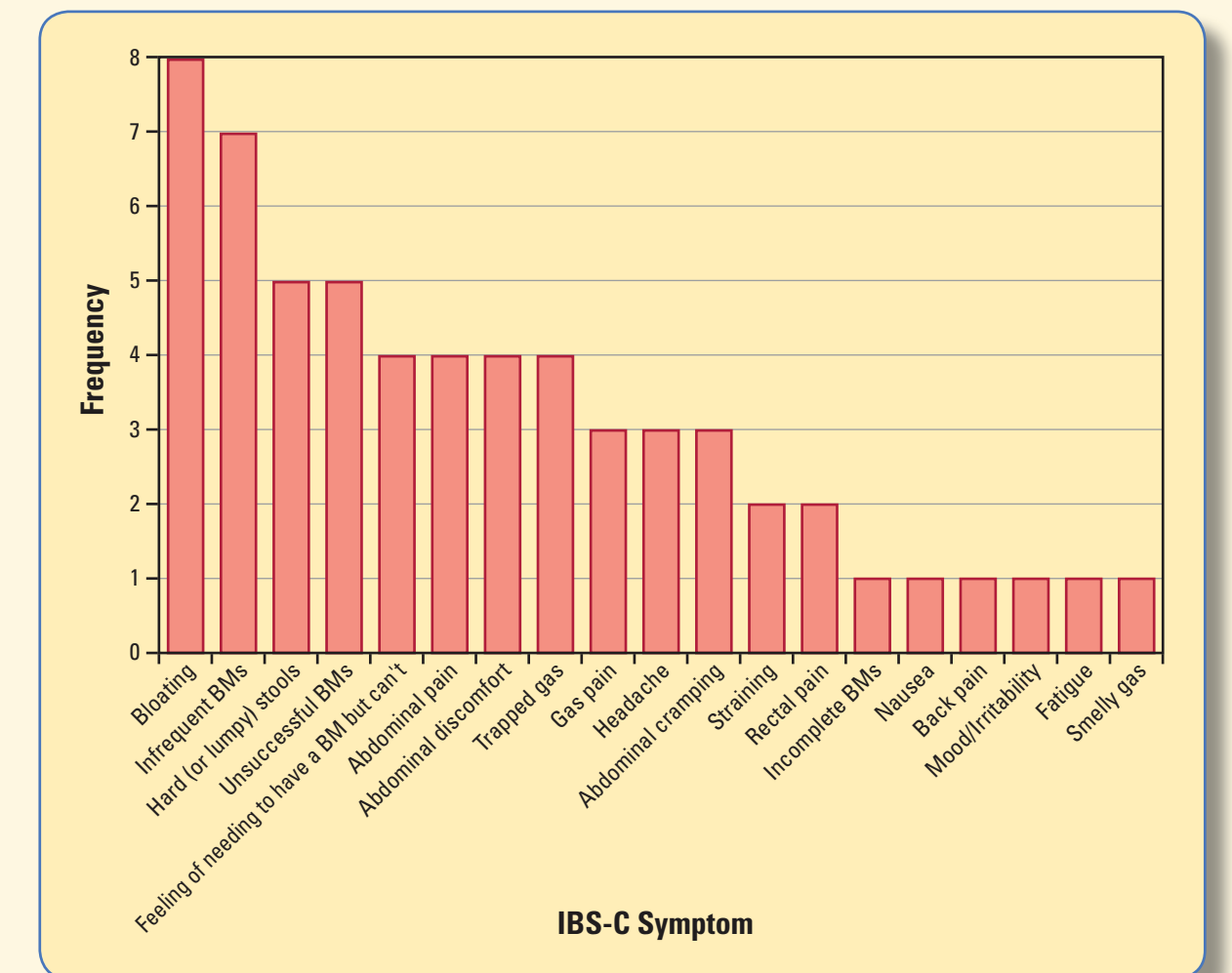
Note: Importance ratings: 0 = totally irrelevant; 1 = relevant but not important; 2 = moderately important; 3 = very important.

^a One participant assigned a rating of “0” to the bloating item because she thought this symptom was fully assessed in the abdominal discomfort item.

^b Two participants who equated bloating with abdominal discomfort did not provide a rating for the latter. The results for abdominal discomfort, therefore, represent the ratings of 13 rather than the full 15 participants.

- Figure 1 summarizes the “top 5” symptoms identified by Round 2 participants as those they wished to see improve with treatment.
- All 12 participants included both bowel and abdominal symptoms in their list.

Figure 1. Frequency of Symptoms Included in Participants' “Top 5” List (Round 2; N = 12)



SUMMARY AND CONCLUSIONS

- Participants identified a wide variety of IBS-C symptoms and impacts; however, symptom assessment in a clinical trial should focus on the most relevant symptoms reported by patients.
- Within and across the two separate rounds of interviews, participants consistently reported the importance of abdominal pain, abdominal discomfort, bloating, stool frequency, stool consistency, straining, and incomplete evacuation, demonstrating concept saturation with respect to these symptoms. Further, according to participants, improvements in these symptoms would constitute an improvement in IBS-C overall.
- A conceptual framework depicting the abdominal and bowel symptoms, as well as presenting the broader concepts of constipation and overall IBS-C symptom severity assessed in clinical trials of linaclotide for the treatment of IBS-C, is shown in Figure 2.

Figure 2. Conceptual Framework: Assessment of IBS-C Symptom Severity

