Exploring the nausea experience among female patients with breast cancer; A pilot interview study

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Abstract

Introduction: Nausea is a difficult symptom to report and measure in clinical trials. We conducted a pilot interview study to improve our understanding of the nausea experience.

Materials and methods: Female patients with breast cancer that had experienced nausea during radiation therapy and/or chemotherapy underwent semi-structured interviews that focused on patient-defined and standard definitions, preferences for nausea grading scales, and nausea sub-features: intensity, location, timing/duration, character, associated symptoms, precipitating/alleviating factors, impact on quality of life.

Results: 10 patients were interviewed. Patients defined nausea more variably than vomiting and retching/dry heaving. An ordinal grading scale with a 0–10 intensity range was preferred over visual-analogue and qualitative scales. Patients had experienced different intensities of nausea and deemed reporting their worst, average and least intensities feasible. High-intensity episodes were deemed more problematic than low-intensity episodes regardless of their duration. The duration and character of nausea were difficult to describe. A range of associated symptoms, precipitating and alleviating factors were documented. Nausea had a detrimental impact on quality of life.

Conclusions: Nausea has a range of subjective and objective features. Our pilot study provided valuable information that will inform the design of a planned larger survey study. Creating an operational clinical trial definition for nausea appears feasible.

Introduction

Radiation therapy-induced nausea and vomiting (RINV) and chemotherapy-induced nausea and vomiting (CINV) are common and troublesome symptoms among patients with cancer. Rates of vomiting have declined due to decades of antiemetic research; however, similar improvements have not been realized with nausea. Experts and patients agree that new clinical trials must prioritize the control of nausea and incorporate this symptom into their primary outcome measures [1–3].

Unfortunately, nausea is a complicated symptom to measure. Patients experience and report it in different ways, compared to vomiting which is a more easily-recognizable all-or-nothing event [4]. Nausea evokes a range of physical and emotional responses. It can be clustered with other sensations such as bloating, indigestion, taste change, dry retching, anorexia, fatigue, dizziness, and anxiety [5,6]. It can last for minutes with great intensity, or days with mild intensity. Patients can confuse it with other symptoms. Reviews of RINV and CINV trials show great variability in how nausea is defined, measured and reported [3,7–9] and many important open questions remain in the study of this symptom. Do all patients define nausea similarly? Which sub-features are the most bothersome? Are existing grading scales easy to use and representative of the patient experience? What degree of improvement do patients deem meaningful?

A similar challenge was faced previously in the study of pain, but dedicated qualitative work allowed certain populations of patients to guide investigators to measure different pain characteristics and intensities and determine what a clinically-meaningful improvement in pain intensity is [10]. This operationalization of the pain experience allowed for standardization of clinical trial endpoints [11]. We now need the same foundational qualitative work with nausea. Female patients with breast cancer are an ideal population to study; they are particularly prone to nausea due to a combination of patient- and treatment-related factors, and they...
report fearing and being more affected by nausea than vomiting [3,6,12].

We conducted a pilot interview study among female patients with breast cancer that focused chiefly on three aspects of the nausea experience: symptom definitions, nausea grading scales and sub-features. Our aim was to collect data to guide the design of a larger planned survey study that hopes to define ideal patient-informed clinical trial outcome measures for nausea. We hypothesized that patients would define nausea more variably than vomiting, that they would be able to differentiate between different characteristics and intensities of nausea, and that low-intensity long-duration background nausea would be deemed more problematic than high-intensity short-duration nausea.

Materials and methods

This pilot study involved semi-structured interviews. The Ottawa Health Science Network Research Ethics Board approved the study protocol (ID#20180381-01H).

Participants

Patients were eligible if they: were female, >18 years old, understood English, had an Eastern Cooperative Oncology Group (ECOG) performance status ≤3, were undergoing or had previously undergone treatment for breast cancer that included at least one of: high-, moderate-, or low-emetic risk chemotherapy or moderate- or low-emetic risk radiation therapy as defined by the antiemetic guideline from the American Society of Clinical Oncology (ASCO) [1] and had experienced nausea during or shortly after treatment. Potentially eligible patients were identified by their treating radiation- or medical oncologist. A single author [CM] who was not a member of any patient’s circle of care verified eligibility, obtained informed consent, and carried out interviews individually. The following baseline characteristics were captured: age, ECOG status, time from last treatment, histories of prior radiation therapy, chemotherapy, RINV, CINV and anticipatory nausea.

Interview guide and interviews

An interview guide was developed to address three main areas: symptom definitions, nausea grading scales and sub-features (Appendix A). We incorporated into its design, material from previous CINV interview guides [3,5], a systematic review of endpoints and outcome measures in randomized trials of RINV [7], and other antiemetic questionnaires commonly used in oncology [13-17]. Interviews were semi-structured with discrete-choice and open-ended questions. Scripted probe questions promoted discussion if necessary. Patients defined in their own words vomiting, retching/dry heaving and nausea, then indicated on a 5-point Likert-type scale how much they agreed with the definitions for those symptoms provided by the Multinational Association of Supportive Care in Cancer (MASCC) [16]. If they strongly disagreed, disagreed or neither agreed nor disagreed they were asked what would improve the definition. Next, patients were shown five common nausea grading systems used in antiemetic clinical trials: the scale from the Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0 manual, a visual analogue scale (VAS) with anchors of 0 and 100 on a horizontal line, an ordinal scale with numbers from 0 to 10 equally spaced on a horizontal line, a short qualitative scale with four options (none, mild, moderate, severe), and a long qualitative scale with five descriptive options (Appendix A) [3,7,13,17]. Patients indicated on a 5-point Likert-type scale how much they agreed with the scales being easy to understand and use. If they strongly disagreed, disagreed or neither agreed nor disagreed they were asked what would improve the scale. Then they chose the scale they preferred and indicated which scale would give their doctor a better understanding of their experience of nausea compared to the others. Lastly, using the MASCC definition as reference, the following nausea sub-features were explored with scripted questions and open-ended discussion (questions paraphrased here): intensity (e.g. did you always experience nausea of the same intensity or were some episodes worse than others?), location (e.g. in what part of your body did you feel nausea?), timing (e.g. how long after treatment did you begin to experience nausea?), duration (e.g. for how long did your nausea typically last?), character (e.g. use words like stabbing, dull, achy, radiating and throbbing to describe pain – are there certain words that describe your nausea?), associated symptoms (e.g. which of the following symptoms do you consider associated with nausea - appetite change, heartburn, bloating, taste change, fatigue), precipitating factors (e.g. did anything make your nausea worse?), alleviating factors (e.g. was there anything you could do to reduce your nausea and help you feel better?), and impact on quality of life (e.g. how did nausea impact your quality of life?) (Appendix A).

Face validity and ease of use were refined after testing the guide with the Simple Measure of Gobbledygook (SMOG) Readability Formula [18], as well as pilot interviews with a radiation oncologist, a radiation therapist and an undergraduate health sciences student. Outpatient interviews coincided with previously booked appointments and took place in private clinic rooms. Inpatient interviews took place at bedside.

Statistical and analytic methods

Interviews were digitally recorded and transcribed using Microsoft Word. No dedicated qualitative data analysis software was used. No formal coding of text was performed, but the transcripts allowed for some early content analysis of patients’ responses to open-ended questions. Descriptive statistics summarized demographics and results from discrete choice questions. We planned to stop enrolment after we reached thematic saturation with patient definitions for vomiting, retching/dry heaving and nausea. In qualitative studies it is common to deem saturation to have occurred after three subsequent interviews with no novel concepts or themes emerging [19].

Results

Patients

Fifteen patients were approached between Feb 27th 2018 and March 9th 2018 and 10 agreed to be interviewed. Each interview took less than 10 minutes. Saturation was reached after the 10th patient’s data was analyzed, and enrolment was stopped. See Table 1 for baseline characteristics of the interviewed patients. Their median age was 62 years, half had received both radiation therapy and chemotherapy and half were actively undergoing treatment.

Symptom definitions

All patients suggested definitions of vomiting and retching/dry heaving that closely matched the provided definitions, and all patients either strongly agreed or agreed with the provided definitions (Table 2). Definitions of nausea suggested by patients were more variable (Table 3), for example: “feeling sick to your stomach, wanting to vomit, not being able to... feeling dizzy and sick” and
“the feeling of queasiness...and unsettledness...in my stomach”. Seven of ten patients strongly agreed or agreed with the provided definition of nausea. Of the three patients that disagreed, one stated: “I don’t feel necessarily that I’m going to vomit...I feel the queasiness...that won’t go away” while another stated: “sometimes you are just not hungry because you are nauseous, but it’s not enough to lose your breakfast...you just don’t feel like you are going to eat, so I guess there’s different levels”.

Nausea grading scales

The ordinal scale with numbers from 0 to 10 spaced on a horizontal line was the highest scoring scale with nine of ten patients strongly agreeing or agreeing that it was easy to understand and use (Table 4). The long qualitative scale was the next highest-scoring with seven of ten. The CTCAE scale scored the lowest.

The most preferred scale, and the scale patients believed would help their doctor understand their nausea experience best was the ordinal scale (by six of ten patients), followed by the long qualitative scale (by four of ten). Patients deemed the ordinal scale “easier”, “very straightforward”, better than the visual analogue scale “because it’s got a grading system”, “simpler”, and better than the short qualitative scale because “those words mean different things to different people”.

Nausea Sub-Features

Intensity

Seven of ten patients said the intensity of their nausea would vary. All patients believed that talking about the intensity of their nausea at its worst, its average and its least would be feasible in clinic. High-intensity nausea was deemed more problematic than low-intensity nausea by all patients, even when the duration of the episodes was short.

Location

Patients experienced nausea in many body locations: the upper abdomen (seven of ten), the throat and upper esophagus (six of ten), the chest, the head, behind the ears, and over their entire body.

Table 1
Baseline characteristics of interviewed patients (n = 10).

| Age (in years) | n | % |
|---------------|---|---|
| Median = 60 Range = 46–86 | | |
| 3 | 4 | 40% |
| 2 | 3 | 30% |
| 1 | 1 | 10% |
| 0 | 2 | 20% |

| ECOG status | n | % |
|-------------|---|---|
| Radiation therapy | 3 | 30% |
| Chemotherapy | 2 | 20% |
| Both | 5 | 50% |
| On treatment | 5 | 50% |
| <1 month | 2 | 20% |
| 1–6 months | 2 | 20% |
| >2 years | 1 | 10% |

| Prior treatment | n | % |
|----------------|---|---|
| Radiation therapy | 3 | 30% |
| Chemotherapy | 2 | 20% |
| Both | 5 | 50% |
| Time from last treatment | n | % |
| On treatment | 5 | 50% |
| <1 month | 2 | 20% |
| 1–6 months | 2 | 20% |
| >2 years | 1 | 10% |

Table 2
Number of patients agreeing or disagreeing with standard symptom definitions (n = 10).

| Definition | Strongly agree | Agree | Neither agree nor disagree | Disagree | Strongly disagree |
|-----------|---------------|-------|---------------------------|----------|------------------|
| Nausea: the feeling that you might vomit | 4 (40%) | 3 (30%) | 0 | 3 (30%) | 0 |
| the bringing up of stomach contents | 6 (60%) | 4 (40%) | 0 | 0 | 0 |
| Retching/dry heaving: the attempt to bring up stomach contents without actually doing so | 4 (40%) | 6 (60%) | 0 | 0 | 0 |

Timing and duration

Four of ten patients reliably had nausea during the hours after treatments. The other six had nausea at random times. The duration of nausea episodes varied from five minutes to several weeks. Patients described short-duration episodes when the intensity of their nausea was at its worst. It was easier to estimate the duration of these episodes than it was the duration of lower intensity background nausea that patients referred to as “constant” and “unrelenting”. Overall, however, patients found duration a more difficult sub-feature to describe than intensity and location, with most stating that the duration would be different every time.

Character

Patients described the character of their nausea similarly, without many descriptors beyond what they used in their own definitions. They suggested words like queasy, unsettled, gross, groggy, dizzy, heaviness, and whirlpool to further describe the character of their nausea. Overall, they did not seem to think that nausea is suited to sub-feature characterization in the same way that pain is.

Associated symptoms

Nine of ten patients said that nausea was associated with appetite change, eight said taste change, seven said both fatigue and anxiety, four said both heartburn and bloating, three said retching/dry heaving, and two said dizziness.

Precipitating and alleviating factors

Five of ten said that riding in vehicles precipitated nausea, four said fatty foods brought it on, while a few patients described precipitating factors such as rotating their body, twisting, lying flat, ingesting caffeine, and strong smells. Beyond pharmacological therapy, factors that alleviated nausea included food smell and sight avoidance, using a cool cloth on the forehead, eating starchy foods, walking for fresh air, social support, and taking a hot bath.

Table 3
Patient-suggested definitions of nausea.

| Definition | n |
|-----------|---|
| a feeling of...sickness...a feeling of suddenly throwing up feeling generally sick...head-achy...dizzy...lack of appetite feeling sick to your stomach, wanting to vomit, not being able to...feeling dizzy and sick a twisting or turning of stuff in your stomach...like a heaviness...like the food is heavy in your stomach you just feel gross...like something is terribly wrong but it’s not happening, something needs to happen and it’s not happening unrelenting...feeling of sickness of your stomach being upset but not knowing how to settle it...if you’re feeling nauseated you want to vomit to feel better the feeling of nausea...and unsettledness...in my stomach the feeling of not being able to control...like you are going to lose whatever is in your stomach like...when you eat something, sometimes you drink, it won’t go down properly a queasiness in your stomach throwing up |

Table 4
Nausea grading scales

| Scale | n | % |
|-------|---|---|
| Ordinal scale | 9 | 90% |
| Qualitative scale (long) | 7 | 70% |
| Qualitative scale (short) | 5 | 50% |
| CTCAE scale | 2 | 20% |
Quality of life impact

The impact of nausea on patients’ quality of life ranged from “inconvenience” to “making life absolutely miserable”. Patients indicated that higher intensity nausea had a greater impact: “I would literally just go from the cancer centre home…I wouldn't do anything else. Nothing, unless I had to go and see the doctor. So, I just stayed at home. I had no quality of life. I was just…getting through it”. Another stated: “Your interest in doing anything is gone because you don't know if you're going to vomit. You don't go anywhere; you don't do anything. You just wait for it to be over”. A different patient stated: “I could not focus on anything else. And at times it was so bad, just overwhelming I would just sit in a chair. I couldn't do anything else. I was totally incapacitated”.

Discussion

This pilot interview study of female patients with breast cancer has provided us with valuable information that will inform the design of a larger planned survey on the nausea experience.

We hypothesized correctly that patient-suggested definitions of nausea would vary more than those for vomiting and retching. This is in line with previous findings [4] and it reinforces the need to provide a clear operational definition for nausea in future studies. Unfortunately, this is not always done. A systematic review of 34 phase III RINV trials showed that no trials reported their operational definition of nausea [7]. Most of our patients strongly agreed or agreed with the provided MASCC definition of nausea so it seems reasonable to use this moving forward. Using the adjective ‘queasy’ may also be helpful, given how commonly patients suggested it. It was also used in a recent RINV cohort study [20] and is found in the CTCAE guide definition [17].

We also hypothesized correctly that patients could appreciate different intensities of their nausea and that a classification of worst, average and least nausea could be used in future studies. This conveniently aligns with pain scales such as the Brief Pain Inventory that is widely used in clinical and research settings and differentiates between worst, average and least pain [21].

Linking these descriptors to numbers on a 0–10 scale, such as the ordinal scale that was the most preferred by our patients would also allow investigators to structure future trials in RINV and CINV like trials of palliative radiotherapy for the relief of pain from bone metastases. These studies measure worst pain on a 0–10 ordinal scale, as recommended by a long-standing international consensus working group on outcomes measures in this setting [11]. Patients might also be able to clarify what degree of improvement on a 0–10 nausea scale would be deemed clinically meaningful. This information could be incorporated into trial outcome measures.

Although it is more common to see qualitative grading scales for nausea in antiemetic clinical trials [7], our patients preferred an ordinal scale. It may be that they were influenced by their familiarity with this type of scale, however. Patients seen at any cancer centre in the Canadian province of Ontario have regular symptom screening with the 0–10 ordinal Edmonton Symptom Assessment System [22]. Given the popularity and successful use of ordinal scales in the study of pain, however, we believe patients will prefer them in our upcoming confirmatory qualitative study as well.

We incorrectly hypothesized that low-intensity long-duration nausea would be deemed the most problematic. As with pain, patients were clear that high-intensity nausea episodes were worse, even those episodes that lasted just a short time. Control of this aspect of the nausea experience is what future trial designs could prioritize. Patients would undoubtedly prefer to have no nausea at all [3], and trials should have endpoints that capture this ideal outcome, but given how difficult nausea is control it seems prudent to develop multiple endpoints that would allow for prioritized step-wise improvements.

Many sensations were associated with nausea, and these will need to be measured and addressed in future studies as well. Eliminating nausea altogether will likely require solutions to other symptoms such as appetite and taste changes, bloating, heartburn, fatigue, anxiety and vomiting. Indeed, nausea seems to be part of an integrated cluster of symptoms [5–6].

It is unlikely that future trials will be able to accurately measure the duration and timing of nausea episodes. Our patients stated that episodes of varying intensities would last for unpredictable amounts of time. Similarly, there do not seem to be characteristic types of nausea as there are different types of pain (e.g. dull, sharp, searing).

Other groups have surveyed and interviewed patients about their nausea experiences and their preferred endpoints for future trials [3,5]. We believe our study is the first to include patients having had RINV, however. It also seems that these studies did not first ask patients to define what they meant by nausea before engaging in other questions about the experience. Given the variability in nausea definitions documented by our group and others, we felt it necessary to establish definitions first.

Our study was small, and our next investigations will examine a more diverse patient population. For example, patients with breast cancer might experience and report nausea differently than patients with gastrointestinal or central nervous system cancers due to the modulating effects of these tumors and their treatments. We intend on surveying and equally sampling larger groups of both male and female patients who have previously received and/or are actively receiving each of: high-, moderate- and low-emetogenic risk chemotherapy, moderate- and low-emetogenic risk radiation therapy, and concurrent radiation therapy and chemotherapy.

In summary, we explored the experience of nausea during semi-structured interviews with female patients with breast cancer. We gained insight into how they defined symptoms, which grading systems they preferred, and which sub-features of nausea they could detect. Patients defined nausea more variably than vomiting or retching. Most patients agreed with ‘standard’ symptom definitions after prompting. An ordinal scale with a 0–10 intensity range was preferred over other grading scale designs. High-intensity episodes of nausea seemed more problematic than low-intensity

Table 4

| Scale                  | Strongly agree | Agree | Neither agree nor disagree | Disagree | Strongly disagree |
|------------------------|----------------|-------|---------------------------|----------|------------------|
| A: CTCAE scale         | 1 (10%)        | 2 (20%) | 0                         | 3 (30%)  | 7 (70%)          |
| B: visual analogue scale | 1 (10%)        | 4 (40%) | 0                         | 3 (30%)  | 2 (20%)          |
| C: ordinal scale       | 6 (60%)        | 3 (30%) | 0                         | 1 (10%)  | 0                |
| D: short qualitative scale | 1 (10%)        | 4 (40%) | 0                         | 3 (30%)  | 2 (30%)          |
| E: long qualitative scale | 3 (30%)        | 4 (40%) | 0                         | 3 (30%)  | 0                |
episodes regardless of the duration of those episodes. Nausea had a detrimental impact on quality of life. Our results will inform the design of a larger planned survey that will explore the nausea experience further and help define components of ideal patient-informed clinical trial outcome measures for nausea.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Interview guide

Patient ID number:
Study staff completing interview:
Date of completion:

Symptom definitions

How would you define the word vomiting?
How much do you agree or disagree with the following definition of vomiting: “The bringing up of stomach contents”?

• strongly agree/agree/neither agree nor disagree/disagree/strongly disagree
• [if neither agree nor disagree/disagree/strongly disagree]: How would you recommend improving the definition?

How would you define the words retching/dry heaving?
How much do you agree or disagree with the following definition of retching/dry heaving: “The attempt to bring up stomach contents without actually doing so”?

• strongly agree/agree/neither agree nor disagree/disagree/strongly disagree
• [if neither agree nor disagree/disagree/strongly disagree]: How would you recommend improving the definition?

How would you define the word nausea?
How much do you agree or disagree with the following definition of nausea: “The feeling that you might vomit”?

• strongly agree/agree/neither agree nor disagree/disagree/strongly disagree
• [if neither agree nor disagree/disagree/strongly disagree]: How would you recommend improving the definition?

Nausea grading scales

Grading scales allow investigators and healthcare providers to learn about the intensity of nausea and its impact on patients. For each of the following nausea grading systems we are interested in whether or not you believe they are easy understand and use, and whether or not you believe they would allow investigators and your healthcare providers to understand the intensity and impact of your nausea.

| Scale A |
|---------|
| 1       | 2         | 3 |
| loss of appetite without alteration in eating habits | oral intake decreased without significant weight loss, dehydration or malnutrition | inadequate oral caloric or fluid intake; tube feeding, TPN, or hospitalization indicated |

How much do you agree or disagree with this grading scale being easy to understand and use?

• strongly agree/agree/neither agree nor disagree/disagree/strongly disagree
• [if neither agree nor disagree/disagree/strongly disagree]: How would you recommend improving the scale?

Scale B

| 0 | 10 |
|---|----|
| 0 = no nausea | 10 = nausea as bad as it could be |

How much do you agree or disagree with this grading scale being easy to understand and use?

• strongly agree/agree/neither agree nor disagree/disagree/strongly disagree
• [if neither agree nor disagree/disagree/strongly disagree]: How would you recommend improving the scale?

Scale C

| 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 |
|---|---|---|---|---|---|---|---|---|---|----|
| 0 = no nausea | 10 = nausea as bad as it could be |

How much do you agree or disagree with this grading scale being easy to understand and use?

• strongly agree/agree/neither agree nor disagree/disagree/strongly disagree
• [if neither agree nor disagree/disagree/strongly disagree]: How would you recommend improving the scale?

Scale D

| none | mild | moderate | severe |
|------|------|----------|--------|

How much do you agree or disagree with this grading scale being easy to understand and use?

• strongly agree/agree/neither agree nor disagree/disagree/strongly disagree
• [if neither agree nor disagree/disagree/strongly disagree]: How would you recommend improving the scale?
Scale E

| I did not have nausea | I had nausea but I could still eat as I normally do | I had nausea and had to change my diet/food less than I would normally | I had nausea and was unable to eat | I had nausea, was unable to eat and had to have intravenous fluids/be hospitalized |
|-----------------------|-----------------------------------------------|------------------------------------------------|--------------------------------|---------------------------------|

How much do you agree or disagree with this grading scale being easy to understand and use?

- strongly agree/agree/neither agree nor disagree/disagree/strongly disagree
- [if neither agree nor disagree/disagree/strongly disagree]: How would you recommend improving the scale?

Which of the above grading scales do you prefer?

Which of the above grading scales do you believe would give your doctor a better understanding of your experience of nausea compared to the others?

**Nausea sub-features**

**Intensity**
Did you always experience nausea of the same intensity or were some episodes worse than others?

- [probe if different intensities]: What was most bothersome to you – mild background nausea or intermittent waves of severe nausea?

**Location**
In what part of your body did you feel nausea?

- [probe]: stomach, belly, throat, head, all over

**Timing**
How long after treatment did you begin to experience nausea? Was it predictable or different every time?

**Duration**
For how long did your nausea typically last? Minutes or hours? Was this variable?

- [probe]: Would you have different intensities of nausea that would last different amounts of time? Did you experience long-duration background mild nausea? Did you experience shorter-duration intermittent waves of severe nausea? What was most bothersome to you?

**Character**
How would you describe the nausea you experienced while undergoing treatment?

- [probe]: We use words like stabbing, dull, achy, radiation, throbbing to describe sub-features of pain. Are there certain words that describe sub-features of your nausea?

**Associated symptoms**
Which of the following symptoms do you consider associated with the experience of nausea: retching/dry heaving, appetite change, heartburn, bloating taste change, fatigue, anxiety? Please add any that are missing.

**Precipitating factors**
Did anything reliably bring on your nausea? Did anything make it worse?

- [probe]: Did certain smells or taste or motion bring on nausea?

**Alleviating factors**
Was there anything you could do to reduce your nausea and help you feel better?

**Impact on quality of life**
How did your nausea impact your quality of life?

- [probe]: did it affect your appetite, the types of food you ate, or when you ate?
- [probe]: did your nausea cause you to stay at home or in bed?

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