Delayed Chemotherapy-Induced Nausea in Women Treated for Breast Cancer

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Purpose/Objectives: To describe the experience and intensity of delayed nausea in women undergoing chemotherapy for breast cancer since the advent of the 5-HT_3 antagonists.

Design: Multisite, longitudinal, descriptive.

Setting: 7 outpatient oncology clinics situated in hospitals, 5 outpatient oncology clinics associated with major teaching universities, 27 private outpatient oncology practices, and 1 outpatient clinic located in a county hospital.

Sample: Typical participants (N = 303) were 51.9 years old, Caucasian (79%), married or partnered (65%), born U.S. citizens (92%), heterosexual (96%), living with someone (83%), and high school graduates (82%).

Methods: Baseline and poststudy questionnaires plus a daily diary of nausea through two cycles of chemotherapy (approximately two months) were used to collect data. The Rhodes Inventory of Nausea, Vomiting, and Retching was used to assess the nausea experience.

Main Research Variables: Nausea.

Findings: The worst nausea occurred on the third day after having chemotherapy for breast cancer. The types of oral antiemetics ordered for home use were changed between the two cycles of the study only 8% (n = 24) of the time. Younger, heavier women experienced more delayed nausea. Women who had a history of nausea with stress and women receiving cyclophosphamide experienced more delayed nausea during both time periods.

Conclusions: Delayed nausea is a significant problem for women receiving chemotherapy for breast cancer.

Implications for Nursing: Oncology nurses can use the results from this study to provide anticipatory guidance for patients undergoing chemotherapy for breast cancer.

Key Points . . .

- Delayed nausea is a significant problem for the majority (73%–82%) of women receiving chemotherapy for breast cancer.
- For women who suffer from delayed nausea, days two through four are the worst.
- Older women experience less severe chemotherapy-induced delayed nausea.
- Women diagnosed with breast cancer who have a history of nausea with stress experience more severe chemotherapy-induced delayed nausea.

An estimated 211,300 women will be diagnosed with breast cancer in 2003, 32% of all new cancer cases this year (American Cancer Society, 2003) . Most, if not all, of these patients will receive chemotherapy. Two of the side effects of chemotherapy, nausea and vomiting (N&V), remain a major worry for patients who are undergoing treatment for breast cancer. The positive relationship between survival from breast cancer and the completion of a full course of chemotherapy demonstrates the necessity for compliance with treatment. Some patients experiencing postchemotherapy N&V will withdraw from seemingly beneficial treatment (Fessele, 1996; Osoba et al., 1997). Patients have indicated that nausea contributes to their reluctance to begin chemotherapy and can result in the discontinuation of potentially effective treatment strategies (Rhodes & McDaniel, 1997). Approximately 10%–15% of patients may refuse or delay their chemotherapy treatments because of fears about N&V (Pendergrass, 1998).

Nausea is a protective reflex against the ingestion of toxins and is defined as a subjective phenomenon of an unpleasant sensation in the epigastrium and in the back of the throat that may or may not culminate in vomiting (Rhodes & McDaniel, 1997). Vomiting is the "mechanical result of neurophysiologically induced rhythmic, coordinated, diaphragmatic, chest wall and abdominal muscle action leading to expulsion of gastric contents through the mouth" (Fessele, 1996, p. 1410). N&V during chemotherapy is distinguished as anticipatory, acute, or delayed. Acute N&V occurs within 24 hours of the

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administration of chemotherapy, and delayed N&V occurs after the first 24 hours. Anticipatory N&V occurs not from the stimulus of the chemotherapy, but in anticipation of receiving it. The focus of this article is delayed nausea associated with chemotherapy administration.

Chemotherapy for breast cancer consists of the following standard chemotherapy regimens: cyclophosphamide, methotrexate, and fluorouracil (CMF) and cyclophosphamide and doxorubicin with or without fluorouracil (CA or CAF) and with or without paclitaxel (CAT, CAFT). Although these are considered mildly to moderately emetogenic, significant incidence of N&V occurs with these regimens (Goodman, 1997; Greene, Nail, Fieler, Dudgeon, & Jones, 1994; Stewart, 1996). Delayed chemotherapy-induced nausea particularly is associated with CA (National Comprehensive Care Network [NCCN], 2001).

Patients who experience N&V within the first 24 hours after receiving chemotherapy are significantly more likely to experience delayed N&V. Delayed nausea also is more common in females, patients who drink little or no alcohol, and young patients. Seventy-five percent of those who do not experience N&V in the first 24 hours will not develop delayed N&V. However, this means that 25% of patients will develop delayed N&V despite having no acute symptoms (Italian Group for Antiemetic Research, 2000).

Treating acute N&V is therefore an important component in preventing delayed N&V. Chemotherapy induces acute N&V through direct or indirect stimulation of the chemoreceptor trigger zone (CTZ) and vomiting center. The CTZ is located postrema, on the surface of the brain on the floor of the fourth ventricle. It is located outside of the blood-brain barrier and can be stimulated directly by cytotoxic agents in the blood stream or cerebrospinal fluid (Pendergrass, 1998). The CTZ stimulates the vomiting center, which is located in the lateral reticular formation of the medulla oblongata, through key receptors: serotonin (5-HT_3), dopamine (D_2), and neurokinin (N_1) (Oettle & Reiss, 2001). The CTZ also can be stimulated by enterochromaffin cells on the gastrointestinal mucosa, which release 5-HT_3 when assaulted by cytotoxic agents. The 5-HT_3 binds to 5-HT_3 receptors along the gastrointestinal tract, vagus nerve, and, ultimately, the CTZ, which then sends a signal to the vomiting center (Dicato, 1996; NCCN, 2001). The stimulation of enterochromaffin cells and resultant release of serotonin largely is responsible for acute chemotherapy-induced N&V (Maisano et al., 2000). The understanding of this chain of events and role of neurotransmitters in inducing N&V is an important element of choosing the appropriate treatment regimen.

The most effective medications used to treat chemotherapy-induced acute N&V are aimed at blocking neurotransmitters that ultimately stimulate the vomiting center. These medications include 5-HT_3 antagonists (e.g., ondansetron, granisetron, tropisetron) and dopamine receptor antagonists (e.g., metoclopramide, alizapride) and are most effective when given prior to initiation of treatment. They can be used alone or in combination with a corticosteroid such as dexamethasone, although the mechanism of action is not clearly understood (Oettle & Reiss, 2001; Pendergrass, 1998). The combination of a 5-HT_3 receptor antagonist and a corticosteroid is considered to be the "gold standard" in treating moderately to highly emetogenic doses of cyclophosphamide (Clavel, Soukop, & Greenstreet, 1993; Oettle & Riess; Stewart, 1996). A neuroleptic or benzodiazapine may be used as rescue therapy. Delayed N&V may be reduced somewhat with the use of dexamethasone with or without metoclopramide. For patients who are receiving moderately emetogenic regimens, 5-HT_3 receptor antagonists do not appear to be effective in controlling delayed N&V, resulting in a 22%–89% incidence of delayed N&V (Italian Group for Antiemetic Research, 2000; Uyl-de Groot, Wait, & Buijt, 2000).

Initial studies of 5-HT_3 antagonists, their interpretation by clinicians, and the observation of women as they underwent chemotherapy suggested that acute vomiting almost has been eliminated from the acute side affects associated with chemotherapy administration, with control rates of 75%–90% (Uyl-de Groot et al., 2000). Information about the incidence and intensity of delayed nausea was not clearly delineated during the past decade. Therefore, the purpose of the current study was to describe the delayed nausea experience and intensity in women undergoing chemotherapy for breast cancer since the advent of the 5-HT_3 antagonists.

Methods

Design

The design for this multisite research was a longitudinal, descriptive study during two cycles of chemotherapy. Usually a cycle of chemotherapy for women with breast cancer ranges from 21–28 days.

Sample and Setting

The settings for this study consisted of 40 sites throughout the United States, including 7 outpatient oncology clinics situated in hospitals, 5 outpatient oncology clinics associated with major universities, 27 private outpatient oncology practices, and 1 outpatient clinic located in a county hospital. The sites were located in the western, eastern, and midwestern United States. The sites were a combination of urban and rural. Eligibility criteria included (a) having a confirmed diagnosis of breast cancer, (b) being female, (c) receiving any nausea-inducing chemotherapy regimen, (d) being able to communicate (both verbally and in writing) in English, and (e) being willing to participate in the study. Of the 353 eligible women who were approached to participate, 50 women refused. The most common reason for refusal to participate was that patients complained of feeling overwhelmed.

Instruments

The **Patient Information Questionnaire (PIQ)** was used to collect demographic information, including age, education, partnership status, ethnicity, employment status, and income. This tool has been used successfully to collect demographic data in previous studies.

The **Disease and Treatment Questionnaire (DTQ)** documented information from patients' medical records, including diagnosis date, surgical treatment, type of breast cancer, treatment regimens, chemotherapy dosages, and antiemetics ordered for IV chemotherapy and home use. Developed by the principal investigator of the current study, versions of this tool have been used for more than 15 years.

The **daily log** consisted of the three-item nausea experience subscale from the Rhodes Index of Nausea, Vomiting, and Retching (INVR). These items measured the amount of time (in hours) that women experienced nausea, the distress that the nausea produced, and the number of times per day nausea occurred. This scale has established reliability and validity (Rhodes, Watson, & Johnson, 1984; Rhodes, Watson, Johnson,

Madsen, & Beck, 1987). Items from this subscale were summed. The subscale score could range from 0–12, with a higher number reflecting a more severe nausea experience. In addition, the log provided a place for patients to record any interventions they used for N&V control. Ratings were entered on a daily basis prior to bedtime.

Procedures

Institutional review board approval of the protocol was obtained for each institution participating in this study. Nurses at each site participated in training about the conduct of the study either in person or via telephone. The training was conducted by the project director, who did not release data packets to the sites until this training was successfully completed. Research assistants in the waiting room, physicians, or nurses approached potential participants about the study. After consenting to take part in the study, participants completed the baseline data collection and were taught how to complete the daily logs. All women received their usual antiemetics as prescribed by their physicians and recorded their usage on a daily basis. Participants recorded in their daily logs for two cycles of chemotherapy. Women who were receiving chemotherapy on a weekly basis were asked to complete their logs for three weeks per log. In addition, nurses reviewed patients' medical records to obtain information about their cancer diagnosis, antiemetic prescriptions, and current, previous, and known future treatment modalities. The project director reviewed the completed data packets to ensure the integrity and completeness of the data. All participants who completed the study were paid $10 to thank them for their time, and all sites received $90 per completed study patient to defray the costs of participating in the study.

Data Analysis

The SPSS® statistical software package version 11 (SPSS, Inc., Chicago, IL) as well as SAS® version 8.2 (SAS Institute Inc., Cary, NC) were used for data analysis. Data were double entered into SPSS, and discrepancies between the files were resolved to ensure accuracy of the data entered. Descriptive statistics were generated related to sample characteristics and other variables of interest. Repeated measures analysis of variance was used to determine the change in nausea over time. In this analysis strategy, participants serve as their own controls so that the variability resulting from individual differences is eliminated from the error term (Dawson-Saunders & Trapp, 1994). This analysis technique is quite robust with small sample sizes and statistical assumption violations. In addition, a delayed nausea scale (DNS) was created by summing the nausea subscale of the INVR for days 2–11 after chemotherapy administration. Scores on the DNS could range from 0–120. Because of the small sample size, researchers did not attempt to explore differences resulting from setting or types of treatment. Other statistical tests utilized were t tests, paired t tests, chi-square, McNemar's test, and analysis of variance.

Results

Typical participants (N = 303) were 51.9 years old (SD = 11.0), Caucasian (79%), married or partnered (65%), not on disability (86%), unemployed (52%), born U.S. citizens (93%), heterosexual (96%), not living alone (84%), and had annual personal incomes of more than $20,000 (58%). The average education for these participants was 13.9 years (SD = 2.9), and 56% had more than a high school education. The average body mass index (BMI, a ratio of weight to height) for these women was 28.3 kg/m^2 (SD = 6.1 kg/m^2); 30% of the women had a BMI between 25–30, which reflects being overweight, and 35% of the women had a BMI of greater than 30, which indicates obesity. Most (68%) of the women had experienced morning sickness with a pregnancy, 24% had a history of seasickness, 20% had a history of being carsick, and 22% had a history of nausea with stress (see Table 1).

Table 1. Demographic Characteristics of Participants

Characteristic	n	%
Age (years)		
$\bar{X}$ (SD) = 51.9 (11.0)	–	–
Range = 28–86	–	–
Education (years)		
$\bar{X}$ (SD) = 13.9 (2.9)	–	–
Range = 7–23	–	–
Body mass index (kg/m^2)		
$\bar{X}$ (SD) = 28.3 (6.1)	–	–
Range = 15.5–40.4	–	–
Ethnicity		
Caucasian	239	79
Other	62	21
Sexual orientation		
Heterosexual	272	96
Other	12	4
Employed		
Yes	145	48
No	155	52
Born a U.S. citizen		
Yes	281	93
No	22	7
Retired		
Yes	66	22
No	234	78
Disabled		
Yes	41	14
No	259	86
Personal income		
< $20,000	106	42
$20,000–39,999	79	32
≥ $40,000	65	26
Relationship status		
Married or partnered	196	65
Other	105	35
Living alone		
Yes	48	16
No	253	84
History of car sickness		
Yes	61	20
No	240	80
History of seasickness		
Yes	71	24
No	220	76
History of nausea with stress		
Yes	66	22
No	233	78
History of morning sickness		
Yes	181	68
No	86	32

N = 303

Note. Because some data are missing for some variables, the n values may not equal the total N.

The average time since diagnosis for these women was 79.2 days (SD = 278.5). Included in these statistics were two women who had recurrent disease. Excluding those two women resulted in an average time since diagnosis for the sample of 57.8 days (SD = 56.11) or approximately two months. Participants typically had surgical biopsy (64%) to determine that they had infiltrating ductal breast cancer (80%). Most (62%) of the women did not have a mastectomy. Multiple lymph nodes were examined in 241 women (80%), and 12% of the women had a sentinel node biopsy. Positive nodes were reported in 46% of the participants. Radiation therapy had been completed or concurrent with their chemotherapy in 7% of the sample, and 61% were planning to undergo radiation therapy after finishing their chemotherapy (see Table 2).

Most (76%) of the women were receiving CA as their chemotherapy regimen. The average dose of doxorubicin was 103 mg, and the average dose of cyclophosphamide was 993 mg. The dosages of chemotherapy were reduced between the two cycles of the study only 5% of the time. The most common IV antiemetics given during the administration of chemotherapy were dexamethasone (80%), ondansetron (49%), granisetron (24%), and tropisetron (17%). The types of IV antiemetics were changed between the two cycles of the study only 6% of the time. The most common antiemetic ordered for home use was prochlorperazine (70%). The types of oral antiemetics ordered for home use were changed between the two cycles of the study only 8% of the time (see Table 3).

The pattern of delayed nausea as measured by the nausea subscale of the INVR can be observed in Figure 1. The worst nausea occurred on the third day after having chemotherapy for breast cancer. Included in those statistics were those who did not experience nausea on a particular day. Figure 2 details the percentage of participants who described any nausea as measured by the nausea subscale of the INVR on a particular day. More than half of the participants experienced nausea during both cycles of chemotherapy on days two, three, and

Table 2. Participants' Diagnostics and Surgical Treatments

Characteristic	n	%
Time since diagnosis[a] (months)		
$\bar{X}$ (SD) = 1.93 (1.87)	–	–
Range = 0.07–19.4	–	–
Surgical biopsy		
Yes	193	64
No	108	36
Lumpectomy		
Yes	145	48
No	156	52
Mastectomy		
Yes	113	38
No	188	62
Lymph node dissection		
Yes	241	80
No	60	20
Sentinel node biopsy		
Yes	37	12
No	264	88
Positive nodes		
Yes	123	46
No	142	54
Type of breast cancer		
Infiltrating ductal	238	80
Infiltrating lobular	25	8
Other	24	12
Radiation therapy		
Yes	19	7
No	92	33
Planned after chemotherapy	171	61

N = 303

[a] Excludes two patients who had recurrence.

Note. Because some data are missing for some variables, the n values may not equal the total N. Because of rounding, percentages may not total 100.

Table 3. Participants' Chemotherapy Treatments

Characteristic	n	%
Chemotherapy regimen		
Cyclophosphamide/doxorubicin	228	76
Cyclophosphamide/methotrexate/fluorouracil	34	11
Cyclophosphamide/doxorubicin/fluoruracil	5	2
Doxorubicin/cyclophosphamide/paclitaxel	7	2
Other	28	9
Weekly chemotherapy		
Yes	23	7
No	277	93
Dosage of cyclophosphamide (mg) (n = 273)		
$\bar{X}$ (SD) = 993.2 (267.7)	–	–
Range = 90–1,888	–	–
Dosage of 5-fluorouracil (mg) (n = 41)		
$\bar{X}$ (SD) = 920.6 (232.2)	–	–
Range = 60–1,200	–	–
Dosage of doxorubicin (mg) (n = 258)		
$\bar{X}$ (SD) = 102.7 (16.9)	–	–
Range = 30–145	–	–
Dosage of chemotherapy decreased with next cycle		
Yes	14	5
No	285	95
IV antiemetics given		
Dexamethasone	241	80
Ondansetron	148	49
Granisetron	72	24
Tropisetron	51	17
Lorazepam	20	7
Prochlorperazine	12	4
Diphenhydramine	7	2
IV antiemetics changed with subsequent chemotherapy		
Yes	18	6
No	282	94
Oral antiemetics ordered		
Prochlorperazine	211	70
Ondansetron	113	38
Dexamethasone	68	23
Lorazepam	59	20
Granisetron	36	12
Phenergan	15	5
Diphenhydramine	15	5
Oral antiemetics changed with subsequent chemotherapy		
Yes	24	8
No	273	92

N = 303

Note. Because some data are missing for some variables and some patients received more than one antiemetic treatment, the n values may not equal the total N and percentages may not total 100.

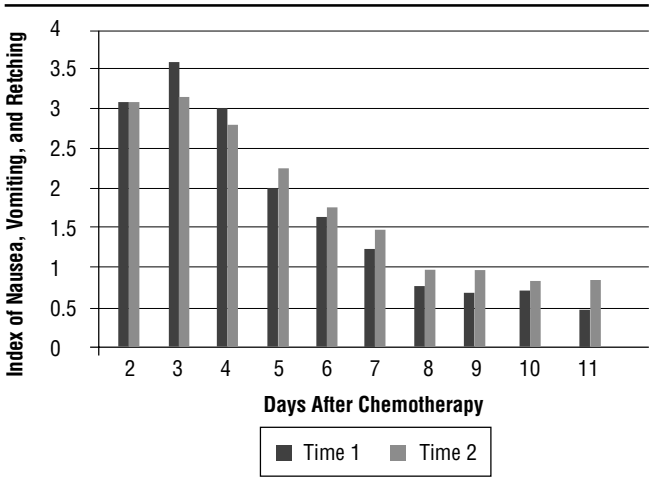

Figure 1. Delayed Nausea Over Time

N = 253

four. If the women who did not experience nausea on a particular day are eliminated from the analyses, nausea clearly is a significant problem for those who have it (see Figure 3).

The mean DNS score for the women during the first data collection period was 17.1 (SD = 16.9, range = 0–101, n = 265), and the mean DNS for the women during the second data collection period was 18.0 (SD = 20.6, range = 0–111, n = 252). These values were compared using a paired t test, and no significant differences existed in delayed nausea between the two time periods (t = 0.616, p = 0.539, n = 242). In exploring the percentage of women who experienced absolutely no delayed nausea, 18% of women during the first data collection period and 27% of the women during the second were found to be free from delayed nausea. Using McNemar's test, researchers found significant (p = 0.001) differences in the percent of women with delayed nausea from the first to second data collection periods. Most (67%) experienced delayed nausea during both time periods, but 14% had no delayed nausea during both time periods (n = 243). Of the 45 women without delayed nausea at the first data collection

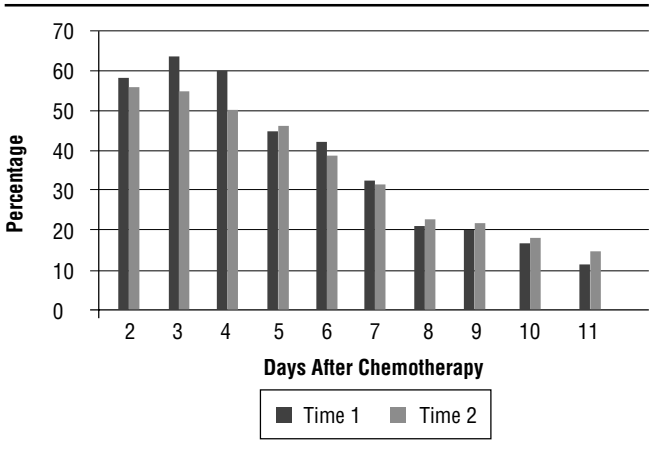

Figure 2. Percentage of Sample With Delayed Nausea Over Time

N = 253

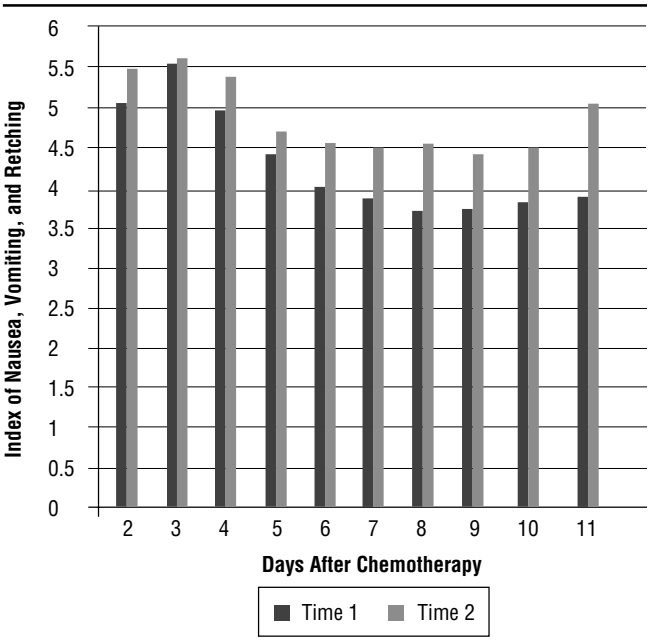

Figure 3. Intensity of Delayed Nausea Over Time

Note. Only patients who reported experiencing nausea are included.

period, 12 (27%) developed delayed nausea during their next cycle of chemotherapy. Of the 198 women with delayed nausea at the first data collection period, 35 (18%) did not experience delayed nausea with their next cycle.

Next, the researchers explored information about the women who experienced the most intense delayed nausea, defined as those with a DNS score of 30 or greater. At time one, this represented 18% of the sample and increased to 23% of the sample at time two. Demographic factors associated with a higher DNS score at time one included age (r = –0.21, p = 0.001) and weight (r = 0.17, p = 0.005); younger, heavier women experienced more delayed nausea. These significant relationships did not continue during the second time period. Education was not associated with DNS score at either time period. No significant differences existed in DNS scores by ethnicity, relationship status, or living circumstance. Significant differences did exist in DNS scores by history of nausea with stress; those who had nausea with stress had more severe delayed nausea during both time periods (see Table 4). Although the DNS scores were higher for those with a history of seasickness, car sickness, or morning sickness, these differences during either time period were not significant. Those receiving their chemotherapy on a weekly basis reported experiencing less delayed nausea during the second time period than those on a more traditional 21- or 28-day cycle. Women who received IV ondansetron with their chemotherapy had higher DNS scores during both time periods; however, the scores during the second time period were significantly higher (p = 0.03). Differences in DNS scores were not significant by any other IV antiemetic usage. Those who had their IV antiemetic changed had significantly higher DNS scores during the first time period (p = 0.034) but not during the second (p = 0.596).

Women who received oral prochlorperazine for home use had significantly lower DNS scores than those who did not during the first time period (p = 0.023) but not during the

Table 4. Comparison of Differences in Delayed Nausea by Various Factors

	Time 1 (N = 265)				Time 2 (N = 252)			
Variable	**n**	**$\bar{X}$**	**SD**	**p**	**n**	**$\bar{X}$**	**SD**	**p**
Reported history of car sickness	59	18.7	17.0	0.397	57	19.1	23.4	0.653
No history of car sickness	205	16.6	16.9	–	194	17.7	19.8	–
Reported history of seasickness	69	18.9	15.9	0.350	62	19.4	21.1	0.554
No history of seasickness	194	16.5	17.3	–	188	17.6	20.5	–
Reported history of nausea with stress	57	21.4	18.0	0.029	55	24.1	25.4	0.037
No history of nausea with stress	207	15.9	16.4	–	196	16.3	18.8	–
Reported history of morning sickness	151	18.4	16.6	0.397	146	19.6	20.7	0.653
No history of morning sickness	113	15.2	17.2	–	105	15.8	20.4	–
Receiving weekly chemotherapy	23	12.1	13.8	0.144	22	9.3	12.9	0.004
Not receiving weekly chemotherapy	239	17.5	17.2	–	228	18.9	21.0	–
Receiving IV ondansetron	128	18.2	17.9	0.317	123	21.0	22.2	0.030
Not receiving IV ondansetron	134	16.1	15.9	–	127	15.3	18.7	–
Receiving IV dexamethasone	211	17.1	17.0	0.974	202	18.7	21.4	0.350
Not receiving IV dexamethasone	52	17.0	16.9	–	48	15.6	17.1	–
Receiving IV lorazepam	19	18.8	14.9	0.640	17	26.2	18.2	0.092
Not receiving IV lorazepam	244	17.0	17.1	–	233	17.5	20.7	–
Receiving IV diphenhydramine	6	5.7	7.8	0.095	7	11.6	20.5	0.397
Not receiving IV diphenhydramine	257	17.0	17.0	–	243	18.3	20.6	–
Receiving IV granisetron	63	16.3	15.5	0.692	60	17.6	20.2	0.844
Not receiving IV granisetron	200	17.3	17.4	–	190	18.2	20.8	–
Receiving IV tropisetron	44	17.0	17.5	0.955	46	14.3	18.5	0.168
Not receiving IV tropisetron	219	17.1	16.9	–	204	18.9	21.0	–
Changed IV antiemetic	15	26.1	15.1	0.034	16	20.6	19.1	0.596
Did not change IV antiemetic	247	16.5	16.9	–	233	17.8	20.7	–
Receiving oral prochlorperazine	190	15.6	16.0	0.023	179	16.7	19.2	0.169
Not receiving oral prochlorperazine	72	20.9	18.8	–	70	21.1	23.7	–
Receiving oral lorazepam	52	19.4	15.1	0.262	48	17.3	16.6	0.797
Not receiving oral lorazepam	210	16.5	17.4	–	201	18.1	21.5	–
Receiving oral phenergan	12	20.5	20.4	0.473	12	11.3	17.9	0.253
Not receiving oral phenergan	250	16.9	16.8	–	237	18.3	20.7	–
Receiving oral dephenhydramine	13	16.0	18.7	0.818	13	14.6	18.9	0.546
Not receiving oral dephenhydramine	249	17.1	16.9	–	236	18.2	20.7	–
Receiving oral granisetron	31	21.0	17.9	0.172	29	16.2	16.7	0.630
Not receiving oral granisetron	231	16.5	16.8	–	220	18.2	21.1	–
Receiving oral ondansetron	98	18.7	17.3	0.234	99	21.1	20.1	0.048
Not receiving oral ondansetron	164	16.1	16.7	–	150	15.9	20.5	–
Receiving oral dexamethasone	65	17.0	17.5	0.942	63	14.9	20.3	0.175
Not receiving oral dexamethasone	197	17.1	16.8	–	186	19.0	20.7	–
Receiving cyclophosphamide	239	17.8	17.2	0.004	227	19.0	21.0	0.004
Not receiving cyclophosphamide	26	10.1	11.7	–	25	9.3	14.2	–
Receiving 5-fluorouracil	37	13.5	13.3	0.163	33	12.4	15.2	0.097
Not receiving 5-fluorouracil	228	17.7	17.3	–	219	18.8	21.2	–
Receiving doxorubicin	227	17.7	17.3	0.135	218	18.9	21.2	0.064
Not receiving doxorubicin	38	13.3	13.4	–	34	11.9	15.0	–
Chemotherapy regimen								
Cyclophosphamide/doxorubicin	195	18.8	17.7	0.303	186	20.2	21.5	0.270
Cyclophosphamide/methotrexate/ 5-fluorouracil	31	15.4	15.9	–	28	15.5	18.8	–

Note. Because some data are missing for some variables, the n values may not equal the total N.

second (p = 0.169). Differences in DNS scores were not significant with any other oral antiemetic regimen except ondansetron. Those women who received ondansetron during the second time period had significantly higher delayed nausea scores (p = 0.048). Those who were taking cyclophosphamide had significantly higher DNS scores for both time periods (p = 0.004, p = 0.004). Although the DNS scores were higher for patients receiving doxorubicin during both time periods, no significant difference existed during either time period. Lastly, no statistically significant difference existed in delayed nausea by chemotherapy regimen (CA/AC versus CMF) during either time period.

Discussion

The results of this study indicated that despite the emergence of 5-HT_3 antagonists (considered the "gold standard" for acute chemotherapy-induced N&V), delayed nausea continues to be a significant problem for patients with breast cancer. Of particular interest is the degree to which delayed nausea prevalence increases or persists despite treatment with multiple antiemetics, potentially contributing to the withdrawal by patients of this lifesaving treatment. This illustrates the need for better medications or therapeutic techniques for patients to use while receiving chemotherapy for breast cancer. A myth exists that women no longer suffer from chemotherapy-related nausea. Time and again when the current study's researchers asked oncology practices to participate in nausea studies, they were told, "nausea is no longer a problem for our patients." The new medications certainly have contributed to fewer women suffering from these side effects in the office, but the current study's research clearly demonstrates that a significant number of women continue to suffer from delayed nausea despite these medications. Although healthcare professionals have come to a consensus on which medications to give for acute nausea, no such consensus exists for delayed nausea (Gandara et al., 1998; Gralla et al., 1999). Healthcare professionals still do not know the best pharmacologic or nonpharmacologic treatments to assist women who are suffering from chemotherapy-induced delayed nausea.

The National Institutes of Health (NIH) Consensus Conference, which met in 1998 to evaluate existing medical literature and discuss the use and effectiveness of acupuncture in treating various conditions, stated that acupuncture is a beneficial treatment for chemotherapy-induced nausea (NIH Consensus Development Panel on Acupuncture, 1998). However, acupuncture requires the skill of a trained professional. An effective, alternative technique to deal with chemotherapy-induced delayed nausea may be acupressure, which follows the same principles and pressure points as acupuncture but differs in that it is the application of finger pressure instead of inserting a needle. Women can be taught to perform this treatment for themselves.

From the current study's data, the researchers know that women who experience nausea in stressful situations have a significantly higher rate of delayed nausea. Perhaps relaxation training may be useful for these women. Relaxation training has been shown to effectively help patients deal with the side effects of chemotherapy treatment (Luebbert, Dahme, & Hasenbring, 2001). A pilot study of Chinese patients with breast cancer using progressive muscle relation therapy demonstrated that this therapy also is an effective adjuvant method to decrease nausea (Molassiotis, Yung, Yam, Chan, & Mok, 2002). The results from this study indicated that the usual historical nausea indicators (seasickness, car sickness, or morning sickness) were not associated with the delayed nausea experience. Therefore, oncology nurses can tell patients that no association exists between delayed nausea and women's historical experiences, except nausea under stress.

The relationship of BMI with delayed nausea is interesting. Chemotherapy doses are determined by taking into account body weight, yet antiemetics are not administered using those guidelines. Another explanation might be that the clearance of chemotherapy from the bodies of women with higher BMI is delayed, resulting in more delayed nausea. The relationship between BMI and delayed nausea needs to be confirmed in a future study. If a relationship is established, then the mechanisms involved in delayed nausea need to be explored in future research efforts.

Delayed nausea clearly is at its worst on the third day after chemotherapy administration. Perhaps a nursing intervention would be to call patients on this day to see how they are feeling and whether they need to change their antiemetic medications, or to suggest other potentially useful interventions. Again, this project would need to be tested in a future research study.

This study has a number of limitations. First, the sites that were used may have been those where nausea was a particular problem. The physicians who indicated that their patients did not experience any nausea may have been right and this article is demonstrating the experience of those women who are not properly treated for this side effect. Second, participants in the current study primarily were Caucasian, thus limiting the generalizability of this study to all racial and ethnic groups. For instance, the researchers do not know if those with African heritage experience delayed nausea differently than those of Scandinavian heritage. Third, the women were not followed for their entire chemotherapy experience; thus, the researchers do not know how many women eventually stopped treatment or if the nausea got better or worse with subsequent cycles.

Summary

Oncology nurses must recognize that delayed nausea is an issue at some time for most (82%) women undergoing chemotherapy for breast cancer. This study provides a detailed examination of the phenomenon of chemotherapy-induced delayed nausea in women being treated for breast cancer. Future research should explore the relationship among delayed nausea, anxiety, stress, BMI, and age, as well as specific antiemetic regimens. The current study demonstrates that new medications or other treatments must be developed and tested because delayed nausea continues to be a problem for women since the advent of the 5-HT_3 antagonists.

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