Development of Anticipatory Nausea: A Prospective Analysis

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The development of anticipatory nausea in cancer chemotherapy typically has been viewed in terms of a respondent learning model. Firm support for this etiological model has been precluded by use of retrospective research designs, however. The present study employed a prospective design to identify patient- and treatment-related variables characteristic of patients who subsequently develop anticipatory nausea. Seventy-one chemotherapy outpatients were interviewed before and after each chemotherapy infusion during their first 6 months of treatment. Hierarchical multiple regression analysis revealed that patients who developed anticipatory nausea were characterized by more severe posttreatment nausea, more time-consuming treatment infusions, and greater state anxiety relative to patients without anticipatory nausea. In general, results supported a respondent learning conceptualization of the development of anticipatory nausea. Clinical implications of these findings for the prevention of anticipatory nausea are suggested.

Intravenous cytotoxic chemotherapy is routinely employed in the treatment of many forms of cancer. The toxic side effects of chemotherapy (e.g., immunosuppression, emesis, and hair loss) have been well-documented (see, e.g., Golden, 1975). When severe, they may necessitate reductions in drug dosages or the frequency of treatment infusions. In extreme instances, patients may elect to discontinue treatment (see, e.g., Weddington, 1982).

One of the most distressing side effects of chemotherapy is the nausea or vomiting that some patients may experience prior to their chemotherapy infusions. Typically referred to as anticipatory nausea, this phenomenon is presumed to have nonpharmacological origins. Although alternative models have been

suggested (Redd, Burish, & Andrykowski, 1985), the development of anticipatory nausea typically has been conceptualized in terms of a respondent learning paradigm (Katz, 1982; Nesse, Carli, Curtis, & Kleinman, 1980; Redd & Andrykowski, 1982). According to this view, infusion of cytotoxic drugs (unconditioned stimulus or UCS) results in the occurrence of nausea and/or vomiting (unconditioned response or UCR). Pairing of stimuli (e.g., visual, gustatory, and olfactory) associated with the environment in which patients receive their infusions (conditioned stimulus or CS) may ultimately endow these stimuli with the capability of eliciting anticipatory nausea (conditioned response).

Extensive laboratory investigation of the respondent learning paradigm has identified several factors that might facilitate the acquisition of a conditioned response. These include (a) a greater intensity of both the unconditioned stimulus and unconditioned response (Dragoin, 1971; Nachman & Ashe, 1973), (b) shorter temporal intervals between illness UCR onset and conditioned stimuli (Garcia, Ervin, & Koelling, 1966; Kalat & Rozin, 1971), and (c) an increased number of CS-UCS pairings (MacKintosh, 1974). In addition, it has been suggested that charac-

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teristics such as elevated anxiety (Spence, 1964) and introversion (Eysenck & Levey, 1972) are associated with increased conditionability.

Not all chemotherapy patients develop anticipatory nausea. Thus, a major research focus has been identification of variables that discriminate patients who develop anticipatory nausea from those who do not. Ultimately, the intent of this research is to provide insight into the etiological process underlying the development of anticipatory nausea. If anticipatory nausea can be properly classed as a respondent learning phenomenon, then patients with anticipatory nausea should be characterized by factors that theoretically facilitate the acquisition of a conditioned response. In particular, the likelihood that a patient will develop anticipatory nausea should be a function of certain patient- and treatment-related variables such as magnitude of posttreatment nausea, degree of state anxiety associated with chemotherapy infusions, number of infusions received, and the length of time necessary for drug infusion. Lengthier infusions should facilitate acquisition of the conditioned response (i.e., anticipatory nausea) by reduction of the interstimulus interval between posttreatment nausea and exposure to clinic-related stimuli.

In general, factors that empirically characterize patients with anticipatory nausea or vomiting have been consistent with theoretical predictions. For instance, the development of anticipatory nausea or vomiting has been associated with (a) greater severity of posttreatment nausea and vomiting (Altmaier, Ross, & Moore, 1982; Cohen, Sheehan, Ruckdeschel, & Blanchard, 1982; Fetting et al., 1983; Ingle, Burish, & Wallston, 1984; Morrow, 1982; Nesse et al., 1980; Nicholas, 1982; Wilcox, Fetting, Nettesheim, & Abeloff, 1982), (b) having received a greater number of chemotherapy treatments (Fetting et al., 1983; Nesse et al., 1980), (c) greater trait anxiety (Schulz, 1980), and (d) elevated levels of current state anxiety (Altmaier et al., 1982; Ingle et al., 1984) or "emotional distress" (Nerenz, Leventhal, & Love, 1982, p. 1025). The research also suggests that younger patients are more likely to develop anticipatory nausea (Cohen et al., 1982; Fetting et al., 1983; Ingle et al., 1984; Morrow, 1982),

although the theoretical relation between this factor and the respondent learning paradigm is unclear. It has been suggested that this relation is a spurious consequence of the possibility that younger patients are more likely to receive highly emetogenic chemotherapy regimens and/or respond to their infusions with greater elevations in state anxiety (Redd et al., 1985).

Despite the consistency of these results with the respondent learning paradigm, firm support for the heuristic value of this model for understanding the etiology of anticipatory nausea is lacking. All of the studies previously cited employed a retrospective research design. Although patients who reported anticipatory nausea also tended to report greater current levels of state anxiety and posttreatment nausea, it is impossible to determine whether these conditions were present prior to the development of anticipatory nausea. Logically, a cause must precede an effect, and it is possible that state anxiety and posttreatment nausea were elevated as a consequence of a patient's experience of anticipatory nausea. A prospective research design potentially enables separation of causal versus reactive effects in the development of anticipatory nausea.

The present study attempted to provide support for the respondent learning conceptualization of the etiology of anticipatory nausea. A prospective research design was employed to enable identification of factors that were associated with the subsequent development of anticipatory nausea. In accordance with a respondent learning model, it was hypothesized that patients who developed anticipatory nausea would be characterized by (a) more severe posttreatment nausea, (b) lengthier treatment infusions, (c) greater state anxiety in association with their chemotherapy infusions, and (d) greater trait anxiety and introversion.

Method

Patients

Participants were outpatient chemotherapy patients at a community-based cancer center in the midwest. Eligible patients (a) were at least 18 years of age, (b) never received intravenous cytotoxic chemotherapy before, and (c) were scheduled to receive their chemotherapy treatments as outpatients. Ninety-eight patients in a sequential

Table 1

Primary Cancer Diagnoses and Intravenous (IV) Drugs Received in the Total Sample (N = 80)

Primary diagnosis	No. of patients	IV drug	No. of patients ^a
Breast	26	fluorouracil	42
Lung	16	doxorubicin	31
Colon	10	methotrexate	30
Lymphoma	8	cyclophosphamide	26
Multiple myeloma	6	vincristine	16
Prostate	3	carmustine (BCNU)	8
Pancreas	2	vinblastine	3
Leiomyosarcoma	2	mitomycin-c	3
Miscellaneous diagnoses	7	cisplatin	2
		miscellaneous agents	5

Note. Forty-six of 80 patients received oral chemotherapy agents as follows: prednisone ($n = 23$), cyclophosphamide ($n = 23$), lomustine ($n = 6$), and procarbazine ($n = 5$).

^a Totals add up to more than 80 because most patients received multiple oral and IV agents.

series were asked to participate in the present study, and 80 patients agreed to participate (82%). Comparison of those patients who agreed to participate with those who declined revealed no significant differences with respect to age, sex, primary diagnosis, or drugs received.

The initial participant sample consisted of 41 women and 39 men with a mean age of 59.8 years ($SD = 11.2$ years). The diagnoses and drugs represented in the sample are shown in Table 1.¹ Nine patients received their initial chemotherapy infusion as hospitalized inpatients. These patients did not significantly differ from the remainder of the sample with respect to drugs received or diagnoses. Except for those receiving only fluorouracil, all patients were hydrated intravenously during and following infusion of their chemotherapy drugs. Antiemetics, primarily prochlorperazine in oral and suppository form, were routinely prescribed for all patients at the beginning of their course of treatment. In addition, 21 patients received intramuscular injections of prochlorperazine either immediately before or after each of their chemotherapy infusions.

Procedure

Potential participants were approached immediately prior to their initial chemotherapy infusion by the senior author or one of several research assistants. The nature of the present research was explained to the patients, and their participation was requested. All patients who agreed to participate were interviewed immediately before and after each of their subsequent chemotherapy infusions. Patients were interviewed for a period of no less than 6 months or until they no longer were receiving outpatient chemotherapy infusions. Two patients declined further research participation after their initial chemotherapy infusion, and complete data were missing for 7 patients, 3 of whom never received a second chemotherapy infusion. These 9 patients were omitted from all subsequent analyses. The remaining 71 patients were interviewed for a total of 709 infusions ($M = 10.0$, $SD = 7.1$) across a mean of 6.6 cycles of chemotherapy ($SD = 4.0$). All interviews were conducted by the senior author or by

one of several undergraduate research assistants. All patients were interviewed and treated in the clinic chemotherapy treatment room, a large room approximately 20 ft $\times$ 50 ft (6.11 m $\times$ 15.2 m) with straight back and recliner chairs located along the walls.

Patient Response Measures

All patients completed the Spielberger Trait Anxiety Inventory (STAI; Spielberger, Gorsuch, & Lushene, 1970) and the Eysenck Personality Inventory (EPI; Eysenck, 1963). The STAI was completed prior to a patient's initial chemotherapy infusion, whereas the EPI was completed prior to the patient's second infusion.

Immediately before each of their chemotherapy infusions the following information was obtained from each patient: (a) severity of posttreatment nausea following their preceding chemotherapy infusion, (b) severity of pretreatment state anxiety, (c) presence or absence of various physical symptoms during the preceding 24 hr, and (d) severity of pretreatment nausea, if present. Severity of posttreatment nausea was assessed using a 10-cm

¹ Chemotherapy regimens for most patients involved a combination of oral and intravenous drugs. Drugs were given in repeating cycles consisting of one to five separate treatment infusions. Sixty-five of the 80 patients received the same intravenous drugs for all infusions throughout the course of their chemotherapy treatment. Chemotherapy regimens for the remaining 15 patients involved administration of different drugs or drug combinations for the individual infusions within each cycle of treatment. Initial drug dosages for each patient were determined on the basis of squared meters of body surface. Drug dosages for 57 of the 80 patients were constant throughout their course of treatment. Twenty patients subsequently had their dosages reduced for one or more infusions, whereas 3 patients had their dosages increased. Readers unfamiliar with the rationale and procedures involved in cytotoxic chemotherapy are referred to general texts on this topic such as Rosenthal and Bennett (1981) and Becker (1981).

Table 2

Frequency of Anticipatory Nausea (AN) for Various Drug Regimens (N = 71)

Drugs	No. of patients	No. of patients with AN
Cyclophosphamide (po), methotrexate, fluorouracil, and prednisone (po)	10	3
Cyclophosphamide (po), methotrexate, and fluorouracil	9	2
Fluorouracil (5 consecutive days)	9	1
Fluorouracil (weekly)	5	1
Cyclophosphamide, doxorubicin, vincristine, and prednisone (po)	5	4
Cyclophosphamide, doxorubicin, and vincristine	4	1
Cyclophosphamide (po), doxorubicin, and fluorouracil	4	3
Cyclophosphamide, vincristine, carmustine, and prednisone (po)	3	1
Mitomycin-C, doxorubicin, and fluorouracil	3	1
Cyclophosphamide, doxorubicin, methotrexate, and procarbazine (po)	2	1
Cyclophosphamide, doxorubicin, methotrexate, and prednisone (po)	2	0
Cyclophosphamide, vinblastine, carmustine, prednisone (po), and procarbazine (po)	2	2
Doxorubicin	2	1
Miscellaneous regimens*	11	5

Note. Oral chemotherapy agents indicated by (po).

* All regimens received by only 1 patient.

visual analogue scale (VAS; see, e.g., Fetting, Grochow, Folstein, Ettinger, & Colvin, 1982; Redd, Andresen, & Minagawa, 1982). Pretreatment state anxiety was also assessed using a VAS. For each infusion, separate state anxiety ratings were obtained for four points in time: (a) last evening; (b) that morning, before coming to the clinic; (c) while in the waiting room; and (d) now, immediately prior to infusion. An 8-item Physical Symptom Checklist (PSC) was used to obtain indications of the presence or absence of various physical symptoms during the preceding 24 hr. Patients indicated with a yes or no whether they had experienced any of eight symptoms (headaches, loss of appetite, fatigue, dry mouth, sleep problems, dizziness, vomiting, or nausea) in the preceding 24 hr. Ratings of the severity of pretreatment nausea experienced were obtained only from those patients who indicated on the PSC that they had experienced nausea within the preceding 24 hr. Using a VAS, separate pretreatment nausea ratings were obtained for four different points in time: (a) last evening; (b) that morning, before coming to the clinic; (c) while in the waiting room; and (d) now, immediately prior to infusion.

Immediately following each of their chemotherapy infusions, patients rated the severity of the greatest degree of state anxiety experienced during their treatment infusion. Again, a VAS was used to obtain these ratings.

Other Dependent Measures

For each patient and for each chemotherapy infusion, the interviewer recorded the particular drugs received by the patient and the length of time required to complete that infusion. Length of infusion was recorded in minutes and was defined as the time elapsed between insertion and removal of the intravenous infusion apparatus by the attending nurse. Finally, the age and primary diagnosis of each patient were obtained from their medical records.

Results

Patients were classified as experiencing anticipatory nausea if they had ever reported nausea within the 24 hr preceding a chemotherapy infusion on Day 1 of a treatment cycle. This criterion was used to reduce the likelihood that reports of anticipatory nausea might have been attributable to the emetogenic effects of recent oral or intravenous medication (Andrykowski, in press). Pretreatment nausea reports were obtained from the PSC completed during the pretreatment interview. Using this criterion, 26 of 71 patients (37%) were classified as displaying anticipatory nausea. The remaining 45 patients composed the criterion group of patients without anticipatory nausea. The mean cycle number of initial occurrence of anticipatory nausea was 5.0 ($SD = 3.2$), whereas the corresponding mean infusion of initial onset was 6.9 ($SD = 3.5$). The number of patients who developed anticipatory nausea with each of the various drug regimens represented in the sample is shown in Table 2. Finally, of the 16 patients who received intramuscular antiemetic injections throughout their course of treatment, 6 patients subsequently developed anticipatory nausea (38%).

Following identification of the two criterion groups of patients who either displayed ($n =$

Table 3

Comparison of Patients With and Without Anticipatory Nausea (AN)

Variable	Without AN (<i>n</i> = 45)		With AN (<i>n</i> = 26)		Univariate <i>F</i> (1, 69)
	<i>M</i>	<i>SD</i>	<i>M</i>	<i>SD</i>	
Posttreatment nausea (1)	9.5	14.7	35.2	32.0	21.32**
State anxiety (1)	22.3	19.7	32.7	19.8	4.58*
State anxiety (2)	12.6	17.7	15.0	17.8	0.30
Length of infusion ^a	33.5	23.9	60.5	44.5	11.09**
Spielberger Trait Anxiety	34.2	7.6	34.2	10.3	0.00
EPI extraversion ^b	14.4	3.7	14.1	4.0	0.09
Age	61.1	10.8	56.0	12.5	3.35

Note. EPI = Eysenck Personality Inventory. Number in parentheses refers to infusion number.

^a Mean of Infusions 1 and 2. ^b Lower score indicates increasing introversion.

* $p < .05$, two-tailed. ** $p < .01$, two-tailed.

26) or did not display ($n = 45$) anticipatory nausea, a multiple regression analysis using the presence or absence of anticipatory nausea as the criterion variable was performed. Because of the large number of potential predictor variables, a principal-components analysis of the data available through a patient's initial two chemotherapy infusions was conducted. Results of this analysis suggested separate state anxiety factors for each of the first two infusions that comprised the five separate anxiety ratings (i.e., last evening, this morning, waiting room, now, and during chemotherapy) obtained. Therefore, these five ratings were combined to form separate indexes of mean state anxiety associated with each of the first two infusions. Other predictor variables included severity of posttreatment nausea following the initial chemotherapy infusion, mean length of the initial two infusions, age, trait anxiety (STAI), and extraversion (EPI).

The seven predictor variables were entered hierarchically into the regression analysis with respect to their presumed theoretical relevance to a respondent learning model of anticipatory nausea (Cohen & Cohen, 1975). Four sets of variables were entered in the following order: (a) posttreatment nausea for the initial infusion; (b) mean length of Infusions 1 and 2; (c) state anxiety for each of the initial two infusions; and (d) age, trait anxiety, and extraversion. Means and standard deviations for these variables for the two criterion groups are presented in Table 3. Results of the

multiple regression analysis are presented in Table 4. Together, the seven variables accounted for 47.4% of the variance in criterion group membership ($R = .689$), $F(7, 63) = 8.11$, $p < .001$. Posttreatment nausea alone accounted for an initial 23.6% of group membership variance, $F(1, 69) = 21.32$, $p < .001$, whereas length of treatment infusion and state anxiety yielded significant increments in explained variance of 7.9%, $F(1, 68) = 7.84$, $p < .01$, and 13.6%, $F(2, 66) = 8.25$, $p < .01$, respectively.

Discussion

The results are consistent with prior research in this area with respect to factors associated with the development of anticipatory nausea. Posttreatment nausea and state anxiety were elevated in patients who displayed anticipatory nausea. However, unlike previous research, the use of a prospective methodology provides unequivocal evidence that elevated anxiety and nausea levels precede the initial occurrence of anticipatory nausea.

Trait anxiety, extraversion, and age contributed little to the discrimination of patients with and without anticipatory nausea. Trait anxiety and extraversion are constructs that presumably reflect the probability that an individual will exhibit a particular behavior or set of behaviors—in this case anxiety, emotionality, or arousability. They do not indicate the actual presence or magnitude of

Table 4

Hierarchical Multiple Regression Analysis of the Development of Anticipatory Nausea

Variable	ΔR^2	F	df	Beta ^a	Simple r^b
Posttreatment nausea					
Infusion 1	.236	21.32*	1, 69	.50*	.49
Length of infusion	.079	7.84*	1, 68	.39*	.37
State anxiety	.136	8.25*	2, 66		
Infusion 1				.41*	.25
Infusion 2				-.42*	.07
Patient characteristics	.021	0.84	3, 63		
Trait anxiety				-.12	.00
Age				-.07	-.22
Extraversion				-.05	-.04

^a Beta weight for simultaneous multiple regression model.

^b Pearson product-moment correlation with group criterion variable (1 = anticipatory nausea, 0 = no anticipatory nausea).

* $p < .01$, two-tailed.

these responses. Hence, it is not surprising that measures of these constructs provide little increase in discriminatory power beyond that accounted for by measurement of the theoretically relevant behaviors themselves (i.e., anxiety and posttreatment nausea).

It would appear that the frequently reported relation between age and anticipatory nausea is primarily attributable to the fact that younger patients tend to report more severe anticipatory nausea. The simple correlation between age and anticipatory nausea was $-.22$ ($p = .07$). However, when the effects of posttreatment nausea for the initial infusion were removed, the correlation between age and anticipatory nausea dropped considerably (partial $r = -.08$, $p = .49$).

Most significant, the results of the present research support the utility of conceptualizing the etiology of anticipatory nausea in terms of a respondent learning model. Patients who developed anticipatory nausea experienced greater posttreatment nausea and received lengthier infusions than did patients without anticipatory nausea. Theoretically, this constellation of characteristics was expected to facilitate the acquisition of a conditioned nausea response (i.e., anticipatory nausea). The primary factor contributing to the development of anticipatory nausea was the magnitude of posttreatment nausea patients experienced early in their course of treatment. Quite simply, no patient developed anticipatory nausea without previously reporting some degree of posttreatment nausea.

The importance of posttreatment nausea in the development of anticipatory nausea is difficult to reconcile with a strict anxiety-based explanation for the development of this response (Redd & Andrykowski, 1982). This model postulates that the experience of nausea prior to chemotherapy is simply a concomitant of what is essentially an anticipatory anxiety response. Chemotherapy infusions arouse severe anxiety in some patients, and the experience of nausea and vomiting is a potential physiological component of this anxiety response. Hence, posttreatment nausea need not be present at all. The status of the anxiety model is also weakened in light of research on the behavioral reactions of pediatric patients to painful bone marrow aspirations (Katz, Kellerman, & Siegel, 1980). Although nearly all of the children they studied exhibited severe anticipatory anxiety reactions, less than 2% of these children became nauseated or vomited prior to the procedure. Apparently, the much higher prevalence of anticipatory nausea in chemotherapy patients is related to the gastrointestinal consequences of this form of treatment.

Several questions remain unanswered by the present research. The exact process by which anxiety contributes to the development of anticipatory nausea needs to be identified. Spence's (1964) anxiety-conditionability hypothesis suggests that anxiety facilitates acquisition of a variety of conditioned responses. In the present context then, anxiety and posttreatment nausea would make indepen-

dent contributions to the likelihood that a particular patient would develop anticipatory nausea. Alternatively, infusion-related anxiety may exacerbate posttreatment nausea, with the latter being the primary factor facilitating conditioning. Of course, severe posttreatment nausea may then serve to heighten a patient's anxiety level associated with his or her next infusion, thus establishing a cycle of mutual exacerbation.

The precise manner in which infusion length contributes to the development of anticipatory nausea also remains to be explored. Research in which the timing of onset of posttreatment nausea is examined would be helpful in this regard. It was assumed that lengthier infusions facilitate conditioning because they reduce the temporal interval between exposure to infusion-related stimuli and posttreatment nausea. Infusion length may also be related to state anxiety. Although anxiety and infusion length were essentially unrelated for the initial infusion ($r = .12$), this relation was significant for the second infusion ($r = .34, p < .01$). Lengthier infusions may result in the experience of greater levels of anxiety during infusions, and this may facilitate conditioning. Alternatively, lengthier infusions may be a consequence, rather than a cause, of elevated anxiety. Staff may respond to an anxious patient by infusing drugs more slowly.

Because of the unique use of a prospective research design, the results of the present research merit replication. Results may vary as a function of characteristics (e.g., diagnoses and drugs) of the sample of patients employed. Because the sample included only chemotherapy regimens that were scheduled for outpatient administration, regimens with severe toxicities might have been underrepresented. For example, only 2 patients receiving cisplatin were entered into the present study. The relative contributions of pharmacological versus nonpharmacological factors in predicting the development of anticipatory nausea may vary as a function of the emetogenicity of the drug regimens represented in the research sample. Inclusion of a great number of highly toxic regimens may result in a significant decrement in the power of variables such as anxiety or infusion length to discriminate patients with anticipatory

nausea from those without. In this case, most of the variation between these two groups of patients may be accounted for strictly by variance in posttreatment nausea.

Finally, although the theoretical implications of the present study have been emphasized, the clinical implications of the current research should not be overlooked. Results suggest that the development of anticipatory nausea could be avoided or delayed by implementation of an effective antiemetic strategy. Although antiemetic injections did not reduce the probability of developing anticipatory nausea, their impact might have been partially obscured by the tendency for such injections to be prescribed primarily for patients receiving highly emetic regimens (e.g., those involving doxorubicin or cisplatin). Because of the importance of a patient's initial posttreatment nausea response, immediate prescription of a maximally effective and tolerable antiemetic regimen should be the goal. It might be preferable to initially overmedicate, rather than undermedicate, in this regard. Increased attention to patients' compliance with their antiemetic regimens should also be encouraged. Although antiemetics in both oral and suppository form were prescribed for all patients, whether patients used them properly or at all is not known. Clinical observation suggests less than optimal compliance may be common.

Oncology staff should also be alert to the presence of infusion-related anxiety in their patients. Anxiety may potentially be reduced through appropriate patient education or behavioral interventions such as hypnosis, desensitization, or relaxation training. Finally, many patients report that their anxiety level escalates during long waiting area and preinfusion delays. It may be fruitful to consider ways in which the chemotherapy infusion routine may be altered in order to improve the coping capabilities of these patients.

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