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Original Paper

Psychological Factors Predicting Nausea and Vomiting in Breast Cancer Patients on Chemotherapy

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A series of 100 breast cancer patients were included in a study to test the hypothesis that incidence of *anticipatory* nausea and vomiting during chemotherapy and towards the end of a patient's course of treatment is influenced by patient expectation, anxiety level and coping response. The role of psychological factors in *postinfusional* nausea and vomiting was also examined. Incidence of postinfusional and anticipatory nausea was high overall, with vomiting less frequently reported; 43% of patients reported nausea or vomiting before treatment at some stage over their chemotherapy cycles and 77% reported post-treatment symptoms. Anticipatory nausea was described by 47% of those experiencing it as being of moderate or severe intensity at some point throughout chemotherapy. Postinfusional side-effects were more intense; 21 and 10 patients, respectively, described severe or very severe levels as occurring at some point during their treatment. The majority of patients experiencing postinfusional symptoms indicated that these persisted for more than 24 h and were worse a day or two after chemotherapy administration. Incidence of anticipatory nausea or vomiting was found to relate directly to experience of nausea or vomiting during preceding cycles. Psychological variables were associated with symptoms of anticipatory nausea mid-treatment, but not with postinfusional symptoms. In particular, trait anxiety and a baseline expectation that nausea would be experienced during treatment were predictive in a multivariate model. Despite this, the overwhelming factor influencing ANV and PNV both mid- and towards the end of treatment was that of previous experience of the symptoms at earlier courses.

Key words: anticipatory, nausea, vomiting, anxiety, depression, psychological
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INTRODUCTION

THE LITERATURE indicates that some patients on chemotherapy (CT) develop psychologically based nausea and vomiting [1, 2]. This may occur before, during or after administration of CT but most psychological studies focus on the *anticipatory* effect (ANV). The most widely accepted explanation for ANV is that it is a conditioned (i.e. learnt) response. Neutral stimuli present at the time of CT administration and associated with the drug-induced effect, acquire the ability to trigger nausea and vomiting during, or immediately prior to, subsequent infusions. In psychological terms this is explained by a simple learning paradigm (i.e. classical conditioning). However, recent evidence suggests a more complicated explanation with cognitive and emotional stimuli being involved [3]. It was found that 48% of patients with ANV claimed that thoughts of CT could 'trigger' it off [4]. In Morrow's study [5] 70% of patients with ANV, when asked "Why do you think you have nausea and vomiting before a treatment?" gave nervousness, tension and dread as an explanation. Haut and colleagues [6] found that prior negative expectations consistently accounted for unique variance beyond pharmacological factors in predicting the frequency and severity of their symptoms and Kvale and associates [7] identified prechemotherapy nervousness as a predictor of anticipatory nausea. This suggests that a simple learning paradigm is insufficient to explain ANV.

Although occurring less commonly than the postinfusion symptoms, the importance of the anticipatory side-effect lies in its intractability once established and evidence which

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suggests that it may continue after CT has ceased, with some patients feeling nauseous when they return for follow-up outpatient visits. In this respect it impacts upon long-term quality of life.

Postinfusional nausea and vomiting (PNV)

Non-pharmacological factors may contribute to postinfusional nausea and vomiting (PNV). Symptoms which are out of proportion to the expected emetic challenge of the cytotoxics may indicate a psychological element. This is less well researched than the anticipatory effect. There can also be considerable variability in the levels of postinfusional nausea and vomiting occurring among patients on the same cytotoxic agents [8, 9]. This suggests that other factors account for some of this variability [6, 10]. Possible contributory non-pharmacological factors, in ANV and PNV include younger age, anxiety, coping style and prior negative expections about treatment side-effects.

A number of studies have drawn attention to the possible role of anxiety. It is intuitively appealing to explain unexpected high levels of nausea and vomiting in terms of 'nerves', yet no conclusion has been reached regarding any causal model because there are few prospective studies [11]. It has been suggested that anxiety *per se* does not cause these effects, rather it potentiates the conditionability of the patient [12]. One possibility is that those who are most anxious may condition more easily or that highly anxious patients may be more vigilant of their environment. They thereby become more sensitive to clinical stimuli surrounding CT which can then, by classical conditioning, develop into a conditioned stimulus [13].

Anxiety is a complex response which may be influenced by the way in which a patient copes with cancer. Individuals who are confident in their ability to cope with cancer and its treatments may be less anxious and, therefore, less vulnerable to psychologically based nausea and vomiting. The evaluation of coping, alongside any assessment of anxiety, should clarify some of these complex psychological processes. Van Komen and Redd [14] found a personality profile including future despair, social alienation and inhibited style to be associated with anticipatory nausea, but the retrospective nature of the design limits conclusions about causality.

The present prospective study evaluated levels of nausea and vomiting, psychological morbidity, side-effect expectations and coping style in a group of breast cancer patients, in order to test the hypothesis that psychological factors have an effect upon incidence of anticipatory and postinfusional nausea and vomiting, during and towards the end of a patient's treatment. CT is an increasingly important treatment for breast cancer. Cytotoxics used with this diagnostic group are often mild to moderately emetogenic and patients are usually on CT for up to 6 months or longer. Data indicate that rates of anticipatory nausea are higher among breast cancer patients, suggesting they are a vulnerable group [15].

PATIENTS AND METHODS

Subjects

A consecutive series of 100 breast cancer patients attending for out patient intravenous (i.v.) infusion of cytotoxics were included. Entry criteria were age 18 years or over, literate in English, no evidence of gastro-intestinal obstruction or brain metastases, no evidence of cognitive impairment.

Procedure

Patients completed baseline assessments during the week prior to their first infusion and subsequent prospective assessments were made immediately prior to each following infusion until CT was completed, up to a maximum period of 7 months.

Outcome measures

Prevalidated measures were used to assess nausea and vomiting, anxiety and coping style and included the Morrow Assessment of Nausea and Emesis [16]—MANE; a patient report measure which separates post-treatment and anticipatory nausea and vomiting into three distinct topologic elements of frequency, severity (ranging from 'very mild' to 'intolerable') and duration, as well as asking patients to indicate when symptoms are at their worst. Where there were anticipatory symptoms, time of onset prior to CT infusion was recorded, along with any cue reactivity (i.e. triggering of symptoms by stimuli such as needles, sight of i.v. equipment). Anxiety and depression were assessed at baseline and for each pre-infusion period using the Hospital Anxiety and Depression Scale—HADS [17]. The patient's tendency to be generally anxious was assessed using the trait version of the Spielberger Anxiety Scale [18] and method of coping was assessed by the Mini-Mental Adjustment to Cancer (Mini-MAC) Scale [19]. A study specific questionnaire assessed patients' expectations at baseline of experiencing tiredness, nervousness, nausea, vomiting and loss of appetite during the forthcoming CT; the Side-Effect Expectancy Questionnaire (SEEQ) asks patients to indicate their response in terms of 'Expect not to have', 'Unsure', 'Expect to have'.

Trait anxiety and coping style were assessed at baseline whilst the latter was also assessed prior to CT courses 3 and 6 to determine stability. At all pre-infusion assessments following cycle one of CT, patients were asked about any nausea and vomiting using the MANE and Treatment Specific Responses (TSR) in terms of anxiety before, during and after previous infusion, whether they had developed food aversions and loss of appetite; the latter was assessed using visual analogue scales (VAS). The number of patients reporting an unpleasant taste in their mouth at each infusion was documented.

The emetic challenge of cytotoxics was classified using guidelines suggested by [20–22] dividing drugs into moderate (level 2) or mild (level 1) emetic challenge. Anti-emetics were categorised as previously described [19] in terms of a high, moderate or low value (i.e. patient prescribed a $5HT_3$ antagonist, an i.v. anti-emetic cocktail, but not a $5HT_3$, or an oral anti-emetic (metoclopramide) only).

Statistical method

Nausea and vomiting were considered as one unit for the purposes of analysis given the low number of patients reporting vomiting before or after treatment. Descriptive results for the incidence of anticipatory and postinfusional nausea and vomiting and level of psychological morbidity are shown for all courses of chemotherapy, presented as n (%), mean (S.D.) or median (IQR) as appropriate. Spearman rank correlation coefficients were used to investigate correlations between severity of nausea/vomiting before and after each course and reported HADS anxiety scores, and also between the VAS and other psychological scores used in the study. Chi-squared or Fisher's exacts, two-sample t-tests and

Table 1. *Demographic data at entry*

	$n = 100$
Age group	
< 40	8
40 – < 50	28
50 – < 60	31
60 – < 70	30
70 – < 80	3
Marital status	
Single	3
Married	75
Separated	1
Divorced	10
Widowed	11
In employment	
Yes	57
No	43
Stage of disease at entry	
Adjuvant	83
Advanced	17

Mann–Whitney U-tests were used to investigate univariate associations between occurrence of ANV/PNV and other exploratory variables, as appropriate to the type of variable being considered. Variables showing evidence of association within univariate analyses were included in multivariate stepwise logistic regression analyses to determine the predictive factors which together affect the incidence of ANV and PNV, based at courses 3 and 5 (i.e. during and towards the end of the treatment cycles).

RESULTS

Of 102 patients approached, two were excluded; one refused, one consented but died before commencing treatment. Sociodemographic and medical details are given in Table 1.

Mean (± S.D.) and median age at entry was 54 (± 10 years), ranging from 28 to 79 years. The majority of patients were married or living with a partner. Seventeen per cent were being treated for advanced disease at entry and of these, 4 patients had had previous CT in an adjuvant setting. Most were on CMF (cyclophosphamide, methotrexate and 5-fluorouracil (5-FU) $n = 35$) or 2Ms (mitozantrone and methotrexate, $n = 56$), with only 9 patients on other regimes (5 on 3Ms; 1 vincristine, cyclophosphamide and doxorubicin; 1 on doxorubicin; 1 on doxorubicin plus cyclophosphamide; and 1 on epirubicin, cyclophosphamide plus 5-FU). The majority of patients (91%) were on a level 2 toxicity regime. Only 19% had had previous radiotherapy.

Incidence of nausea and vomiting

43 patients reported anticipatory nausea occurring at some stage over their CT treatment and 76 reported postinfusional nausea. In comparison, only 6 patients reported anticipatory vomiting, all of whom also had anticipatory nausea. Of 39 patients reporting vomiting after treatment, only one did not also experience postinfusional nausea. Therefore, as experience of vomiting alone was rare in this group of patients, the main analysis considers nausea and vomiting as a combined reaction.

Overall, percentages of patients experiencing ANV or PNV ranged from 11 to 21% and 42 to 56%, respectively, across CT cycles, the proportion with a previous history of symptoms increasing steadily (Table 2). Most patients experiencing ANV at a course also had PNV after the previous course. Of those experiencing ANV, 20/43 (47%) described it as being of moderate or severe intensity at some point. No patients described their anticipatory symptoms as being very severe or intolerable.

Postinfusional side-effects were more severe. 29/77 (38%) reported PNV as being of moderate intensity, 21 (27%) reported severe levels and 10 (13%) described PNV as being very severe. There were 4 (5%) reports of postinfusional nausea or vomiting as being intolerable when at its worst. Only 10 of the 77 patients (13%) experienced postinfusional nausea lasting for 24 h or less; the majority indicated that symptoms persisted over a longer period and, in 15 cases, that nausea had been experienced constantly between at least two cycles. Responses on the MANE indicated that the worst postinfusional nausea and vomiting was generally experienced 24 h or more after CT administration.

Use of standard anti-emetics (i.e. metoclopramide/domperidone and dexamathasone) reduced steadily across cycles, from 92 (94%) at cycle 1 to 53 (68%) at cycle 6. Meanwhile the number of patients prescribed a $5HT_3$ anti-emetic (ondansetron or granisetron) increased steadily from 6 (6%) at cycle 1 to 26 (33%) by cycle 6.

Psychological scores

Mean (± S.D.) scores for HADS depression and anxiety across cycles are given in Table 3 along with number of

Table 2. *Incidence of nausea/vomiting*

	Numbers (%) of patients having any nausea or vomiting before and after each course						
	CT course number (number of patients still continuing)						
	1 $n = 100$ (%)	2 $n = 97$ (%)	3 $n = 94$ (%)	4 $n = 91$ (%)	5 $n = 84$ (%)	6 $n = 79$ (%)	Overall $n = 100$ (%)
Anticipatory							
No N or V	77 (79)	83 (88)	73 (79)	76 (84)	70 (83)	64 (82)	57 (57)
N/V (with previous CT)	–	7 (7)	11 (12)	12 (13)	12 (14)	13 (17)	43 (43)
N/V (first experience)	21 (21)	4 (4)	8 (9)	2 (2)	2 (2)	1 (1)	
Postinfusional							
No N or V	48 (49)	54 (57)	47 (51)	42 (47)	37 (44)	38 (49)	23 (23)
N/V (with previous CT)	–	33 (35)	36 (39)	42 (47)	45 (54)	37 (47)	77 (77)
N/V (first experience)	50 (51)	7 (7)	9 (10)	6 (7)	2 (2)	3 (4)	
Not known	2	3	2	1	0	1	

% based on known data. CT, chemotherapy; N, nausea; V, vomiting.

Table 3. Psychological scores—hospital anxiety and depression scores

	CT course number (number of patients still continuing)						
	0* $n=100$ (%)	1 $n=100$ (%)	2 $n=97$ (%)	3 $n=94$ (%)	4 $n=91$ (%)	5 $n=84$ (%)	6 $n=79$ (%)
Depression							
Mean ± S.D.	2.9 ± 2.7	4.0 ± 3.6	3.9 ± 3.3	4.1 ± 3.6	4.4 ± 3.7	4.3 ± 3.4	4.3 ± 3.6
Absent (0–7)	94 (94)	83 (85)	79 (83)	74 (80)	73 (81)	70 (83)	64 (81)
Borderline (8–10)	3 (3)	8 (8)	12 (13)	12 (13)	10 (11)	8 (10)	10 (13)
Present (11 or above)	3 (3)	7 (7)	4 (4)	6 (7)	7 (8)	6 (7)	5 (6)
Anxiety							
Mean ± S.D.	6.9 ± 4.6	5.9 ± 4.1	5.5 ± 4.0	5.6 ± 4.0	5.8 ± 4.2	5.8 ± 4.5	5.9 ± 4.3
Absent (0–7)	57 (57)	69 (70)	71 (75)	70 (76)	65 (72)	58 (69)	52 (66)
Borderline (8–10)	23 (23)	15 (15)	12 (13)	13 (14)	14 (16)	15 (18)	14 (18)
Present (11 or above)	20 (20)	14 (14)	12 (13)	9 (10)	11 (12)	11 (13)	13 (16)
Not known	0	2	2	2	1	0	0

% based on known data. *Baseline. CT, chemotherapy.

patients exhibiting levels of 'caseness' as Absent/Borderline/Present. Cases of depression (defined as a score of 11 or above) were generally low throughout, ranging from between 3 and 8%. Cases of anxiety tended to be higher, ranging from 10 to 20% with the highest number being at baseline and the lowest at cycle 3 (i.e. mid-treatment).

HADS anxiety before each course showed no evidence of statistically significant correlations with descriptions of worst nausea/vomiting severity over courses 1–3. Some association was evident at courses 4 and 5, but only at borderline levels of statistical significance, whereas HADS anxiety level before cycle six was strongly correlated with worst nausea/vomiting before that cycle ($r_s = 0.4$, $P < 0.001$). Post-treatment nausea/vomiting showed very little evidence of correlation with the HADS anxiety scores, the only significant associations of the two variables being seen after course 2 ($r_s = 0.4$, $P = 0.02$).

Scores on the individual Mini-MAC scales were stable over the three timepoints at which this was measured and means were similar to those from the test development sample [19]. Mean (± S.D.) score for trait anxiety, as measured by the Spielberger STAI scale at baseline, was 34.1 (± 9.0) indicating this was not an unusually anxious sample in terms of trait tendencies. On the Side-effect Expectancy Questionnaire (SEEQ), 58% of patients expected to have tiredness and 42% expected to be nauseated by treatment when assessed at baseline, but on the other measures of nervousness, vomiting and loss of appetite the majority were unsure of whether or not they would experience these symptoms.

Levels of Treatment Specific Response (TSR) in relation to anxiety, as measured on the VAS scales, tended to decrease after course 1 and remained relatively stable over courses 2–6 (Table 4). Correlations between the VAS anxiety

Table 4. Treatment specific responses (TSR)

	Summary TSR VAS scores over CT courses					
	C1 ($n=98$)	C2 ($n=95$)	C3 ($n=92$)	C4 ($n=90$)	C5 ($n=84$)	C6 ($n=79$)
Level of anxiety	–	–	–	–	–	–
Before last CT infusion						
Mean ± S.D.	54.9 ± 33.5	34.6 ± 28.7	34.1 ± 29.9	32.5 ± 29.4	34.9 ± 31.8	30.7 ± 28.5
Median	51.0	34.0	24.5	23.5	26.5	22.0
(IQR)	(25.0–92.3)	(8.0–54.0)	(10.0–51.0)	(6.8–52.0)	(5.3–61.5)	(7.0–47.0)
During last CT infusion						
Mean ± S.D.	45.9 ± 32.1	3.10 ± 27.4	29.1 ± 27.2	29.2 ± 26.8	33.2 ± 29.5	31.7 ± 28.1
Median	42.5	20.9	18.5	19.0	23.0	20.0
(IQR)	(17.3–75.5)	(9.0–46.0)	(8.0–45.0)	(7.0–45.8)	(7.0–60.8)	(8.0–53.0)
After last CT infusion						
Mean ± S.D.	38.4 ± 32.6	28.7 ± 27.7	25.6 ± 24.3	25.7 ± 24.8	28.9 ± 26.5	28.1 ± 26.8
Median	32.5	19.0	17.5	14.5	18.5	17.0
(IQR)	(7.0–64.8)	(7.0–45.0)	(6.3–42.5)	(4.0–44.3)	(7.0–50.0)	(5.0–48.0)
How affected by CT:						
Food aversion						
Mean ± S.D.	25.9 ± 30.6	24.3 ± 27.0	28.2 ± 28.7	32.5 ± 31.0	31.6 ± 31.4	33.1 ± 32.0
Median	10.5	11.0	17.5	23.0	20.0	21.0
(IQR)	(3.0–43.3)	(3.0–54.0)	(3.0–50.8)	(4.0–66.3)	(4.3–62.8)	(4.0–65.0)
Lost appetite						
Mean ± S.D.	24.2 ± 29.3	20.8 ± 25.2	25.9 ± 27.9	24.8 ± 26.6	24.8 ± 27.7	27.4 ± 29.0
Median	10.0	7.0	15.5	13.0	13.0	17.0
(IQR)	(3.8–39.5)	(2.0–38.0)	(3.0–43.0)	(4.0–46.3)	(3.3–35.0)	(3.0–47.0)

n = number with treatment specific response available at each course, high score = worse outcome. CT, chemotherapy; VAS, visual analogue scales.

scores before, during and after each infusion were strong ($r_s \geq 0.6$) and highly statistically significant ($P < 0.001$) across all courses. VAS food aversion and loss of appetite scores were similarly strongly related throughout. Correlations between these two variables and the VAS anxiety scores were statistically significant, but at a far lower magnitude ($r_s \approx 0.3$) across all courses.

VAS anxiety scores were significantly correlated with baseline HADS anxiety levels ($r_s \approx 0.3$, $0.01 < P < 0.001$ throughout) to course 4, but this did not persist to courses 5 and 6. HADS depression levels were correlated ($r_s = 0.03$, $0.01 < P < 0.001$) with VAS anxiety scores at course 1, but this did not continue at courses 2 onwards. STAI scores and Mini-MAC measures of anxious pre-occupation, fighting spirit and (to a lesser extent) helplessness/hopelessness showed persistent correlations (fighting spirit negative correlation, others positive) with VAS anxiety across all courses at varying levels of statistical significance, but no such evidence was apparent with the cognitive avoidance and fatalism scores.

Reported loss of appetite and food aversions varied only slightly across treatments; by cycle 6 the median percentage food aversion was 21% and 17% for appetite loss. The percentage of patients reporting an unpleasant taste in the mouth at the CT infusion was approximately 42% overall and ranged from 39 to 47% across individual treatment cycles. 25 patients reported a prechemotherapy history of travel sickness.

Typical comments to the question about what appears to trigger nausea and vomiting were 'Thoughts of coming to hospital', 'smell in hospital', 'nerves, worry, feeling uptight'.

Logistic regression analysis

Stepwise logistic regression models were used to determine predictive factors for ANV and PNV, with analyses centred around courses 3 and 5 i.e. mid-way through and towards the end of that patient's treatment. By course 5 experience of postinfusional NV was at its maximum and all but one of the patients who reported ANV already had a previous history over the course of this treatment. Given the high correlation existing between the psychological scores being evaluated, only variables showing any evidence (taking $P \leq 0.05$) of a univariate association with ANV and PNV at either course were entered into the stepwise procedure, thus lessening potential problems with co-linearity. Age, marital status, employment, previous history of travel sickness and scores on the HADS anxiety and Mini-MAC scales showed no evidence of statistical association before or after either course 3 or 5. Variables entered into the models were therefore as follows—categorical: previous history ANV/PNV during present treatment (as appropriate to the particular model); PNV/ANV immediately previous (again as appropriate); anti-emetic use; SEEQ baseline expectations of tiredness; nausea and nervousness; and presence of an unpleasant taste in the mouth at the first CT infusion (of the appropriate course); continuous: STAI, HADS depression and two TSR scores (anxiety during CT and loss of appetite). Although the TSR scores were not normally distributed, repeated modelling using logged scores (a transformation which normalised the scores successfully) gave the same results and for ease of interpretation final models incorporating the untransformed scores are presented. TSR anxiety during the appropriate course and TSR loss of appetite were chosen for the modelling procedure as their effects appeared to be more persistent across courses than those of TSR anxiety before or after the course and TSR food aversions.

Results of the stepwise modelling are shown in Tables 5 and 6. In all models, a history of ANV or PNV was persistently the strongest predictor of the outcome. Higher trait anxiety scores showed some evidence of an effect on ANV at course 3 (Table 5; odds ratio (OR) = 1.09, 95% confidence interval (CI) = 1.02–1.16) along with SEEQ baseline expectations of nausea (OR = 4.59, 95% CU = 1.16–18.13) but these were no longer evident as predictive factors by course 5 (Table 6). Postinfusional NV after course 3 (Table 5) indicated combined predictive effects of use of $5HT_3$s at course 3 and anticipatory experience of NV before C3, but these were

Table 5. Stepwise logistic regression models predicting nausea and vomiting at CT course 3

		Anticipatory ($n = 86$)				Post-treatment ($n = 87$)			
Variable*		*n*	Odds ratio	95% CI	*P*-value	*n*	Odds ratio	95% CI	*P*-value
PNV at C2	No	49	1.0	–		70	1.0	–	
(ANV at C3)	Yes	37	1.25	(0.27–5.67)	0.78	17	4.69	(1.06–20.80)	0.04
Any CT ANV	No	65	1.0	–		36	1.0	–	
(PNV)	Yes	21	12.39	(3.15–48.69)	< 0.001	51	6.91	(2.23–21.40)	< 0.001
Anti-emetics used	Standard	74	1.0	–		71	1.0	–	
at C2 (C3)	5HT3s	12	0.47	(0.05–4.10)	0.50	16	6.17	(1.15–33.22)	0.03
Unpleasant taste in	No	48	1.0	–		53	1.0	–	
mouth C2 (C3)	Yes	38	1.70	(0.43–6.75)	0.45	34	1.08	(0.36–3.21)	0.90
SEEQ expect	No/unsure	34	1.0	–		35	1.0	–	
tiredness	Yes	52	1.34	(0.28–6.50)	0.72	52	2.90	(0.93–9.02)	0.07
SEEQ expect	No/unsure	57	1.0	–		58	1.0	–	
nervousness	Yes	29	2.59	(0.60–11.23)	0.21	29	1.87	(0.61–5.74)	0.28
SEEQ expect	No/unsure	51	1.0	–		52	1.0	–	
nausea	Yes	35	4.59	(1.16–18.13)	0.03	35	1.81	(0.59–5.53)	0.30
STAI		86	1.09	(1.02–1.16)	0.01	87	0.98	(0.92–1.04)	0.48
HADS—depression		86	0.97	(0.70–1.34)	0.85	87	0.99	(0.79–1.25)	0.96
TSR Anxiety during C2 (C3) CT		86	1.02	(1.00–1.04)	0.11	87	1.00	(0.97–1.02)	0.68
TSR loss of appetite C2 (C3)		86	1.00	(0.97–1.03)	0.88	87	1.00	(0.98–1.03)	0.72

*Post-treatment variable shown in parentheses. STAI, SEEQ, HADS–baseline assessment. Treatment specific response (TSR) taken at each course. Estimates shown are adjusted for the effects of significant variables in the model.

Table 6. Stepwise logistic regression models predicting nausea and vomiting at CT course 5

Variable*		Anticipatory ($n = 80$)				Post-treatment ($n = 84$)			
		n	Odds ratio	95% CI	*P*-value	*n*	Odds ratio	95% CI	*P*-value
PNV at C4	No	38	1.0	–		70	1.0	–	
(ANV at C5)	Yes	42	8.97	(1.01–79.94)	0.05	14	4.33	(0.49–37.93)	0.19
Any CT ANV	No	53	1.0	–		25	1.0	–	
(PNV)	Yes	27	13.33	(2.55–69.78)	0.002	59	43.09	(8.26–244.8)	< 0.001
Anti-emetics used	Standard	64	1.0	–		63	1.0	–	
at C4 (C5)	$5HT_3$s	16	0.34	(0.05–2.15)	0.25	21	1.53	(0.40–5.88)	0.54
Unpleasant taste in	No	43	1.0	–		47	1.0	–	
mouth C4 (C5)	Yes	37	0.50	(0.11–2.25)	0.37	37	3.90	(1.12–13.56)	0.03
SEEQ expect	No/unsure	33	1.0	–		36	1.0	–	
tiredness	Yes	47	0.64	(0.14–2.98)	0.57	48	1.82	(0.54–6.09)	0.33
SEEQ expect	No/unsure	53	1.0	–		56	1.0	–	
nervousness	Yes	27	3.17	(0.73–13.67)	0.12	28	1.18	(0.34–4.07)	0.80
SEEQ expect	No/unsure	47	1.0	–		51	1.0	–	
nausea	Yes	33	0.62	(0.14–2.70)	0.52	31	0.95	(0.29–3.08)	0.93
STAI:		80	0.99	(0.92–1.07)	0.76	84	1.02	(0.95–1.09)	0.59
HADS–depression		80	0.95	(0.68–1.33)	0.78	84	0.96	(0.75–1.22)	0.72
TSR Anxiety during C4 (C5) CT		80	0.98	(0.96–1.01)	0.22	84	1.02	(1.00–1.04)	0.11
TSR loss of appetite C4 (C5)		80	0.98	(0.95–1.01)	0.16	84	1.02	(1.00–1.04)	0.11

*Post-treatment variable shown in parentheses. STAI, SEEQ, HADS–baseline assessment. Treatment specific response (TSR) taken at each course. Estimates shown are adjusted for the effects of significant variables in the model. CT, chemotherapy.

again dwarfed by the dominance of a history of PNV at earlier courses and were no longer evident by course 5. Previous history of ANV at earlier courses, along with PNV after course 4 were the only two predictors of ANV before course 5 with no other variables entering the model. Postinfusion NV after course 5 was once again dominated by the effect of a history of PNV at earlier courses.

DISCUSSION

Incidence of postinfusional nausea and vomiting in this sample of women on moderately emetogenic chemotherapy was high; 77% experienced postinfusional nausea or vomiting (PNV) at some point throughout their course of treatment. The rates for PNV on a cycle by cycle basis were between 42 and 56%. Of those experiencing the postinfusional side-effect, 40% indicated that at some point throughout their treatment this was severe to very severe and 5% reported at least one episode where the side-effect was intolerable when at its worst. The experience of nausea was not transitory and in most cases lasted for more than 24 h; in 15 cases PNV had been experienced constantly between at least any two cycles. To counteract these effects patients were increasingly switched from a standard to a $5HT_3$ anti-emetic with one third of the sample on a $5HT_3$ by course 6 from only 6% initially having this type of anti-emetic.

The rate for the anticipatory effect was lower with 43% experiencing either nausea or vomiting on at least one occasion and of these only 6 patients reported anticipatory vomiting.

The primary hypothesis, tested prospectively, that anxiety would predict incidence of both ANV and PNV mid-treatment and towards the last course, received only limited confirmation. The logistic regression analysis indicated that ANV at mid-treatment (i.e. course 3) was determined primarily by the presence of NV before preceding infusions. This is consistent with the conditioning model. However, higher trait anxiety at baseline and the patients' expectation that nausea would be experienced whilst on treatment both contributed additionally to ANV by course 3 in the multivariate model. Postinfusional symptoms after course 3 were related to a history of NV after preceding infusions, ANV before course 3 and use of $5HT_3$s at C3. No psychological variables assessed at baseline predicted postinfusional nausea and vomiting at mid-treatment. By the end of treatment (i.e. course 5) only prior history of NV contributed very significantly to ANV or PNV. Psychological factors contributing to the anticipatory effect at mid-treatment were no longer contributing by course 5, perhaps suggesting that these variables may act in the early stage to potentiate the conditioned effect but are less important once the effect has become well entrenched. A number of variables previously reported as predictive showed no statistically significant effects; age, prior history of travel sickness and coping response.

Recent studies of the anticipatory effect have tended to move away from the traditional conditioning model to a more complex multifactorial explanation. The role of anxiety has been frequently invoked as a causal factor despite Andrykowski's review [11] which concluded that the evidence was equivocal. Certainly *state* anxiety has been highlighted. However, we assessed anxiety at each CT infusion and could find no evidence of a causal association with either ANV or PNV when assessed in a multivariate model. Trait anxiety was significantly predictive of ANV mid-treatment. Despite this, 'cases' of anxiety, as measured by the HADS, were at their lowest by mid-treatment and highest at baseline. Furthermore, patients who expected to be nauseated by treatment were also more likely to have developed ANV by mid-treatment. These data suggest that there may be a tendency in those who are more generally anxious individuals, expecting to experience nausea, to develop ANV. This relationship, however, depends upon the presence of ANV during preceding CT cycles which is the strongest predictive variable. There may be a synergistic effect of trait anxiety, nausea expectations and ANV in preceding cycles on ANV incidence. The HADS scores may also be less useful as a measure of anxiety in this context than the STAI measure which

was predictive. Psychological factors do contribute, but are not sufficient in themselves to cause the anticipatory effect. No psychological variables, according to our data, contribute to the post-treatment effect, when taken in a multivariate context.

It would appear that the prevention of postinfusional nausea and vomiting, through effective anti-emetics, will remain the primary approach to dealing with subsequent anticipatory effects. Whilst the use of $5HT_3$ anti-emetics has increased, reduction of nausea and delayed emesis still remains a challenge and ANV is likely to continue to be a problem requiring psychological treatment. In terms of future management of ANV by psychological methods it seems likely that the use of a de-conditioning method, such as systematic desensitisation, will remain the approach of choice, largely because it is based heavily on the conditioning model.

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