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# Behavioural factors influencing the development and expression of chemotherapy induced side effects

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**Summary** Aversive side effects are commonly associated with potentially curative chemotherapy treatments. Despite the advances in the development and testing of antiemetic medication, nausea and vomiting remain prevalent and troublesome side effects of chemotherapy. Four studies (from 1978–1990) of 2,499 consecutive cancer patients being treated with a variety of chemotherapy agents showed that 62–72% were experiencing posttreatment nausea/vomiting despite the use of available antiemetic medication.

In addition to occurring during, or up until days following, treatment with cytotoxic drugs, nausea and vomiting may begin to occur in anticipation of chemotherapy treatments. This phenomenon is called anticipatory nausea and vomiting (ANV) and it occurs in at least one in four patients. Randomised clinical trials have shown that antiemetic drugs do not control ANV once it has developed.

No single clinical or patient variable has been found to be as significantly associated with the development of ANV as several in concert. We have examined the predictive value of eight clinical characteristics in a series of three clinical trials. The first of these trials was developmental; the other two have been longitudinal prospective trials. The eight clinical characteristics appear stronger in predicting those patients who will not subsequently develop ANV rather than those who will.

Anxiety has been proposed as a mechanism in the development and expression of anticipatory side effects. Here we show an association ($P < .05$) between patient self-report of anxiety on the State-Trait Anxiety Inventory (STAI) and the Symptom Checklist-90 (SCL-90) assessed at the first chemotherapy treatment, and subsequent development of anticipatory side effects within the first five treatments. Anxiety on the Profile of Mood States (POMS) was not found related ($P > .05$). It appears that anxiety when measured as a constellation of symptoms (such as is done on the SCL-90 and the STAI) is related to the development of ANV, while anxiety measured as a mood (POMS) is not.

Increasing attention is being paid to patients' quality of life during cancer treatment. Central to these concerns is a reduction in treatment related morbidity.

Aversive side effects are commonly associated with potentially curative chemotherapy treatments. In addition to being able to promote further potential cancer treatment complications such as metabolic imbalance, dehydration, anorexia and cachexia, and further psychological sequelae such as anxiety and depression, nausea and vomiting disrupt the daily functioning of cancer patients. Intractable and intolerable nausea and vomiting can also challenge patient compliance with the successful completion of a chemotherapy regimen (Penta *et al.*, 1983; Wilcox *et al.*, 1982; Laszlo & Lucas, 1980).

## Chemotherapy induced nausea/vomiting continue to be a major problem

Despite increasing attention being paid to the pharmacologic management of chemotherapy induced nausea and vomiting, it remains a prevalent and important side effect. Comparisons of the prevalence and severity of post-treatment nausea gathered in four independent surveys of consecutive chemotherapy patients are summarised in Figure 1. Measures of nausea severity and the prevalence were gathered through patient self-report on a standardised instrument. All patients had histologically confirmed cancer and were receiving chemotherapy treatment alone at one of five hospitals affiliated with the University of Rochester Cancer Center. Some patients from the latest study were also gathered from community hospitals.

### *Prevalence and severity*

The insert to the top right of Figure 1 shows that from 62% to 72% of patients in the four samples surveyed during approximately a 12 year period reported experiencing nausea/vomiting at their fourth treatment despite normal clinical care including the use of antiemetic drugs. Reasonable comparability is seen across four time periods; 1,620 consecutive patients were studied starting in 1978; 380 patients in 1986; 113 patients in 1988; and 386 patients in 1990.

Figure 1 summarises data on nausea prevalence from the same four samples. Overall, approximately one third of the patients described their nausea as 'moderate', while approximately another third described it as 'severe', 'very severe', or 'intolerable'. These data are not idiosyncratic to our treatment center, but are consistent with other data (Gard *et al.*, 1988; DeAntonio, 1990).

Cohen *et al.*, reported in 1986 that 84% of 147 patients from a variety of treatment protocols studied reported post-treatment nausea. Jacobsen and his colleagues reported in 1988 that 71% of their series of patients on adjuvant breast cancer chemotherapy experienced postchemotherapy side effects. A 1989 article by Love *et al.*, reported 87% of patients experiencing postchemotherapy nausea.

These consistently high prevalence rates of patient reported nausea and its severity are inconsistent with a view that antiemetic control of chemotherapy side effects has eliminated the problem. This improvement, however, may not be as pronounced as it seems. Martin has outlined some prevailing myths about the efficacy of antiemetic treatments. Some of his observations may be supported by these data (Martin, 1991).

### *Reasons problem has remained*

As patients have been better able to tolerate nausea/vomiting, oncologists have been able to use more potent doses of chemotherapy drugs on increasingly more aggressive regimens. While early randomised clinical trials of chemotherapy for breast cancer, for example, used single drugs, several recent treatment protocols have used up to a half dozen chemotherapy drugs in a rotating aggressive regimen.

Data from the first (1978) and the last (1990) of the four surveys previously described provides support for the hypothesis that more drug is being given on more aggressive regimens. Comparing the dosage of 11 chemotherapy drugs given to 386 patients in the study begun this year with

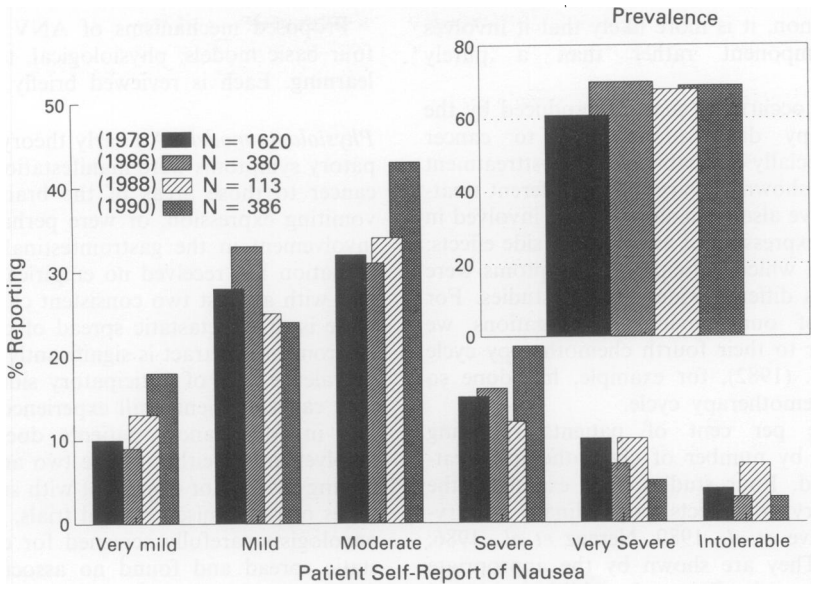


**Figure 1** The reported severity and prevalence of post-treatment nausea in consecutive patients receiving chemotherapy in four surveys over 12 years (N = 2499).

dosages previously recorded over 10 years ago in a sample of 1,620 consecutive patients showed that from 10 to 20% greater dosages were given per treatment of several common chemotherapy drugs such as 5-FU, and methotrexate. Furthermore, the average number of chemotherapy drugs given to each patient increased from a mean of 2.6 (SEM = 0.03) to a mean of 3.0 (SEM = 0.04); a statistically significant difference ($t = 5.6$, $P < .01$). Also, the rated emetic potential of the treatment regimen being given to patients significantly increased from an average emetic rating of 4.4 (SEM = 0.06) to an average rating of 5.4 (SEM = 0.1: $t = 5.07$, $P < .01$).

Another factor contributing to the apparent disparity between the common prevailing notion of better control of side effects and what patients report is that some recently developed chemotherapy drugs have a different time course of symptom generation than several previous agents. Emesis typically occurs within four hours after administration of the drug cisplatin, but 8 to 12 h after administration of its pharmacologic analog carboplatin. We have heard oncologists and nurses say there are no side effects with carboplatin; our experience has been that the side effects simply are not occurring in the clinic in front of the staff as often as previous treatment with cisplatin.

One or more of the potential explanations above may account for the reasonably constant reported rate of nausea and vomiting over the last decade. It seems reasonable to conjecture that nausea and vomiting will remain a concern in chemotherapy treatment. It is also reasonable to conjecture that better control of chemotherapy induced nausea and vomiting will result in increasingly more aggressive treatments which will, in turn, call for increasingly better control of the chemotherapy side effects.

Recent demonstrated clinical efficacy of two hematopoietic growth factors may promote even more aggressive cancer chemotherapy treatment in the future. Erythropoietin has shown effectiveness in altering chemotherapy induced anemia (Wallerstein & Dreisseroth, 1990) while colony stimulating factors seem able to influence chemotherapy induced neutropenia (Glaspy & Golde, 1990). Since these are two further common dose limiting factors in chemotherapy treatment, drugs given for their amelioration may promote even more aggressive future treatments.

## Anticipatory nausea/vomiting

In addition to occurring during, or for days after, treatment with cytotoxic drugs, nausea and vomiting may begin to occur in anticipation of a particular chemotherapy treatment (Morrow, 1982; Nicholas, 1982). This phenomenon has been called anticipatory nausea and vomiting (ANV) (Morrow, 1981; Morrow & Morrell, 1982). While occurring less frequently than posttreatment nausea and vomiting. ANV can be equally troublesome to patients. Patients often view it as a psychological problem (Andrykowski *et al.*, 1987; 1988). They are thus sometimes reluctant to discuss or even mention it to treating oncologists or other clinic staff (Morrow & Dobkin, 1988; Burish & Carey, 1987).

Following a discussion of the prevalence and how definitional issues can effect the prevalence estimates of ANV, data are presented to examine principal models proposed for the development of these anticipatory side effects. Results from ongoing studies are also presented to examine the potential role of patient anxiety in the etiology of anticipatory side effects.

### *Prevalence rates*

Close to 50 studies have reported prevalence rates for anticipatory nausea and vomiting in adult and pediatric chemotherapy patients (reviewed in Morrow & Dobkin, 1988; Burish & Carey, 1987). A range of estimates has been shown. For example, while Cella *et al.* (1984) reported that over 50% of their sample of 60 patients previously treated for Hodgkin's Disease developed anticipatory side effects, Nicholas (1982) reported a rate of 18% in 71 patients. Several factors have been proposed to account for this variability (Andrykowski, 1986; Morrow, 1984*a*).

(i) Some variability in the prevalence rates may be due to measurement methodology. A variety of self-report measures have been used to assess anticipatory side effects (Morrow, 1984*a*; Nicholas & Hollandsworth, 1986). While some studies have used patient completed logs during and following treatment, other studies have interviewed patients by asking retrospective questions, often of a considerable duration;

(ii) Some studies have reported rates for anticipatory nausea and vomiting symptoms independently of one another while other reports have combined them and viewed them as a single phenomenon. Unfortunately, it is sometimes not clear whether or not this was done when rates are reported;

(iii) Nausea and vomiting can occur during chemotherapy treatment with some drugs, as opposed to after treatment. This is especially possible during long infusions of the drug cisplatin. Some patients have reported becoming ill before the infusion has ended. While this may represent an

anticipatory phenomenon, it is more likely that it involves a physiological component rather than a purely anticipatory one;

(iv) Different rates of occurrence may be produced by the type of chemotherapy drug administered to cancer patients. This is especially probable since posttreatment side effects have been shown to vary across different treatment regimens and have also been shown to be involved in the development and expression of anticipatory side effects;

(v) The time frame in which anticipatory symptoms were studied has sometimes differed widely across studies. For example, in some of our previous investigations we assessed patients prior to their fourth chemotherapy cycle whereas Wilcox *et al.* (1982), for example, has done so prior to the tenth chemotherapy cycle.

Figure 2 presents the per cent of patients reporting anticipatory side effects by number of chemotherapy treatment cycles administered. Four studies have examined the occurrence of anticipatory side effects longitudinally (Andrykowski, *et al.*, 1985; Love *et al.*, 1989; Nerenz *et al.*, 1986; Morrow *et al.*, 1991). They are shown by the appropriate dotted and dashed lines on the Figure. In addition, selected studies that have reported the incidence at particular treatment cycles are shown in solid circles (i.e., Fetting *et al.*, 1983; Redd & Andrykowski, 1982; Love *et al.*, 1982; Alba *et al.*, 1989). While other studies have reported rates for assessments at particular treatment cycles, they are generally within the range of the values shown in Figure 2.

Two important aspects of anticipatory side effects are shown in Figure 2. The first is that the per cent of people reporting anticipatory side effects increases with the number of treatment cycles given. (This is also an important point when considering the potential learned etiology of the side effects, as explained later). The second is that approximately one out of three patients has ANV by the time the patient has been treated with four chemotherapy cycles. This rate shows anticipatory side effects to be clinically meaningful.

### *Models of ANV etiology*

A variety of mechanisms have been proposed for the development of anticipatory side effects (see reviews by Burish & Carey, 1987; Redd & Andrykowski, 1982; Morrow & Dobkin, 1988). Several models of how anticipatory side effects develop have been proposed. To date, no clear experimental data have conclusively proven one or another of these models. Conclusive proof would require the controlled, experimental induction of anticipatory side effects in cancer patients. While of theoretical interest, such an experimental demonstration is outside of proper and ethical clinical treatment of cancer patients. Thus, the evidence on which is the more appropriate model rests on judgements of the consistency of the models to observed clinical data.

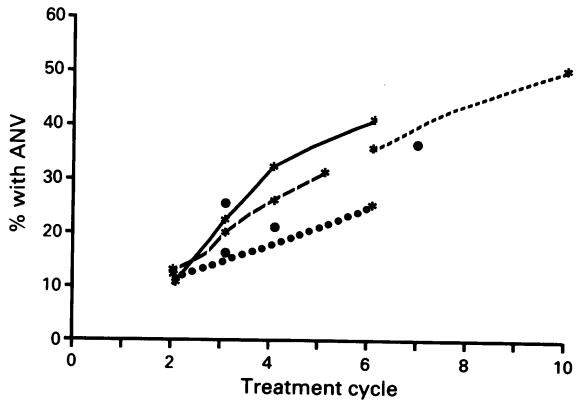


**Figure 2** The prevalence of anticipatory nausea and vomiting (ANV) in relation to the number of chemotherapy treatments. Andrykowski *et al.*, 1985, n = 78 (------); Nerenz *et al.*, 1986, n = 192 (———); Love *et al.*, 1989, n = 126 (· · · · · ·) and Morrow *et al.*, 1991, n = 351 (– – – – – –).

Proposed mechanisms of ANV development generally fit four basic models: physiological, taste aversion, anxiety and learning. Each is reviewed briefly below.

*Physiologic model* An early theory hypothesised that anticipatory symptoms were manifestations of metastatic spread of cancer to those areas of the brain controlling nausea and vomiting expression, or were perhaps effects of local cancer involvement in the gastrointestinal tract. This potential explanation has received no empirical support and is inconsistent with at least two consistent clinical findings. The first of these is that metastatic spread of cancer to the brain or the gastrointestinal tract is significantly less pronounced than the prevalence rate of anticipatory side effects. Roughly one in four cancer patients will experience anticipatory side effects; one in four cancer patients does not experience cancer involvement in either of the two areas mentioned. A second finding that is not consistent with such a model is that in our series of randomised clinical trials, we and our collaborating oncologists carefully screened for clinical evidence of metastatic spread and found no association between metastatic disease and the development of anticipatory side effects (Morrow, 1981; 1984*b*; 1984*c*; 1985; 1986).

*Taste aversion model* This phenomenon has been proposed for the development of anticipatory side effects since the type of conditioning appears uniquely dependent on tastes and smells associated with nausea-inducing food and it produces a reasonably rapid response. In the taste aversion model (sometimes also called bait shyness in the animal literature) animals use taste and smell of particular foods as cues for avoiding foods or substances that have made them ill in the past. This happens even when the nausea or emesis occurs many hours after the food consumption. Part of its uniqueness is that the learning frequently occurs with a single exposure. A tie in with the taste and smells research are studies by Nerenz *et al.* (1986) and Fetting *et al.* (1983), reporting that patients who noticed a taste of drugs during chemotherapy injection were more likely to develop anticipatory nausea and vomiting than patients who did not notice a taste. On the other hand, neither Andrykowski (1987) or Morrow (1990; 1991) were able to replicate this.

*Anxiety model of the development of ANV* Several investigations have found an association between patient reported anxiety and the development of ANV (Andrykowski, 1990). A variety of potential mechanisms have been proposed for this association (Burish *et al.*, 1987; Morrow *et al.*, 1990). In order to investigate more clearly some of these potential mechanisms, patients in the second validation study described above have had anxiety at each of their chemotherapy cycles. Anxiety was measured both as a constellation of symptoms and as a psychological mood. The rationale behind using both methodologies is that several of the symptoms commonly reported for anxiety, such as alterations in appetite and sweating, may be common side effects of chemotherapy treatment irrespective of the patients experience of anxiety.

Patients were defined as anxious if they fell in the upper quarter of the distribution of anxiety on a particular measure. This was felt to be a more conservative examination of the role of anxiety than in previous investigations. A significant association was found between two measures of anxiety based on patient Symptom Checklist-90 (SCL-90: $\chi^2 = 4.6$; $P < .05$) and the State-Trait Anxiety Inventory (STAI: $\chi^2 = 3.9$; $P < .05$) and subsequent development of ANV. These are consistent with previous studies. However, anxiety as measured by the Profile of Mood States (POMS) subscale on anxiety showed a nonsignificant relationship between POMS values obtained at baseline and the subsequent development of anticipatory side effects anytime during the first five chemotherapy cycles ($\chi^2 = .005$; $P > .05$).

The role of anxiety in the development and expression of anticipatory side effects is not as likely as an enduring personality characteristic. This is supported by the finding that

trait or personality measure of anxiety from the STAI was not related to the subsequent development of ANV ($\chi^2 = .003$; $P < .05$).

The potential association of anxiety with the development of anticipatory side effects over time was examined using two complementary approaches. First, the patient's measures of state anxiety were compared with whether or not anticipatory nausea and vomiting developed during any of the five treatments. The development of anticipatory nausea and vomiting was found associated with state (but not trait) anxiety measures on the STAI for chemotherapy treatment 2 ($\chi^2 = 7.2$; $P < .01$); chemotherapy treatment 3 ($\chi^2 = 6.2$; $P < .01$) and chemotherapy treatment 4 ($\chi^2 = 5.3$; $P < .05$). Thus, the measures of anxiety through symptoms were found to be associated with the development of anticipatory side effects not only for baseline measures, but also for measures taken during the treatment cycles.

Anxiety might also increase the salience of the potentially conditionable stimuli (Morrow *et al.*, 1991). This would lead to the prediction that increases in anxiety resulting from a particular chemotherapy treatment would increase the probability of the development of anticipatory side effects in the subsequent treatment. If an increase in patient anxiety rather than a steady state of anxiety is the potential mechanism, then differences in anxiety between subsequent chemotherapy treatments should be associated with the subsequent development of anticipatory side effects. For example, an increase in anxiety experienced after the second chemotherapy treatment compared with the first chemotherapy treatment would be predicted to increase the probability of the development of ANV associated with the third chemotherapy treatment. Some support for this hypothesis was found. Patients who were in the upper quarter of anxiety increase for their second chemotherapy treatment compared with their initial chemotherapy treatment were found more likely to experience ANV prior to their third chemotherapy treatment ($\chi^2 = 6.1$; $P < .01$) than patients who had a lower degree of anxiety increase. However, this finding did not hold for the development of ANV prior to the fourth or fifth chemotherapy treatments.

*Learning model* Figure 3 outlines how anticipatory side effects may develop through a conditioning process. As shown in the top part of the Figure an unconditioned response (posttreatment nausea and vomiting) which follows an unconditioned stimulus (chemotherapy drugs administered) in the context of potentially conditionable stimuli (such as thoughts, images of the clinic, nurse or treatment related sensations) will after a number of repeated trials (chemotherapy treatments) enable the conditioned stimulus, such as the chemotherapy nurse or thought of the clinic to elicit or produce the conditioned reponse of anticipatory nausea and vomiting.

None of the consistent characteristics of how anticipatory side effects develop contradict this model (Morrow *et al.*, 1991). A classically conditioned response follows several well defined principles. The first of these is that the probability of the development of a learned response increases with the number of conditioning trials given. In the context of anticipatory side effects, previous data show that the prevalence of anticipatory side effects is related to the number of chemotherapy administrations. A second characteristic is that the intensity of the unconditioned response (posttreatment nausea and vomiting) effects the development of the conditioned response. As explained in greater detail further on, the severity of postreatment nausea and vomiting has been consistently implicated in the development of anticipatory side effects.

A further characteristic of a learned response is that there must be a correspondence between the unconditioned and the conditioned responses. Anticipatory nausea and vomiting closely resemble posttreatment nausea and vomiting. There has not been a study reporting the presence of anticipatory nausea or vomiting in the absence of posttreatment nausea or vomiting. Finally, a commonly occurring characteristic of a

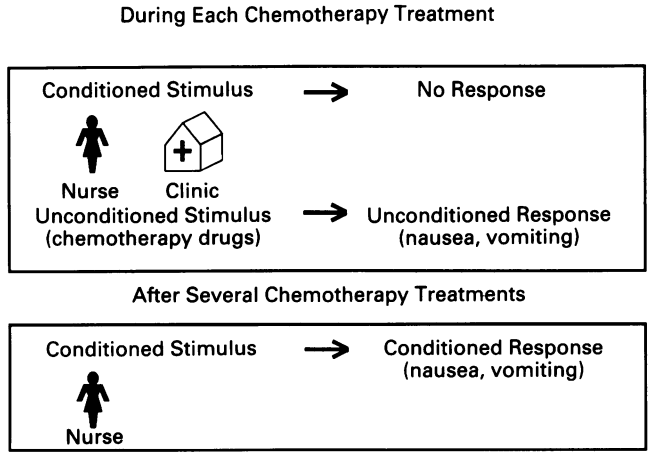


**Figure 3** A model based on learning theory of how anticipatory side effects develop.

conditioned response is stimulus generalisation where a response is elicited by stimuli that are similar to the original conditioned stimulus. It is not uncommon for patients to report nausea initially when they see the clinic nurse who administers their chemotherapy drugs and then, after a few more chemotherapy treatments to report that the sight of any clinical nurse can induce the unwanted conditioned side effects.

Studies examining anticipatory side effects/etiology yield two principal conclusions: (1) the response is most probably classically conditioned in some fashion; and (2) susceptibility is determined by more than a single variable. Most likely, variables associated with a learning phenomenon as well as individual differences such as reactivity to anxiety are involved.

### Multivariate prediction of ANV development

Several studies have examined such a multivariate approach. We have examined eight clinical characteristics for their ability to predict anticipatory side effects (Morrow, 1984*b*; Morrow *et al.*, 1991). Based on learning theory and clinical observation, we found the sum of eight clinical characteristics to be associated with the development of anticipatory nausea in an early study of 176 cancer patients. Significantly more patients with four or more of the following eight characteristics had developed anticipatory nausea and vomiting by the time of their fourth chemotherapy treatment: (1) experiencing nausea and/or vomiting after their first chemotherapy treatment; (2) nausea after first chemotherapy treatment described as 'moderate, severe or intolerable'; (3) vomiting after first chemotherapy treatment described as 'moderate, severe or intolerable'; (4) younger than 50 years of age; (5) expressing a susceptibility to motion sickness; (6) feelings of generalised weakness following treatment; (7) sweating following treatment; (8) feeling warm or hot all over after treatment.

Results of this initial developmental study and two subsequent prospective studies designed to test the finding are summarised in Figure 4 in panels a, b and c. The number of characteristics is shown along the bottom of each panel while the percentage of patients having those numbers are shown on the y-axis. Panel a at the top of the figure presents results of the initial developmental study. Approximately 28% of patients without ANV in the initial developmental study had none of the eight characteristics while approximately 28% of patients with anticipatory nausea and vomiting had six of the characteristics. Visual as well as statistical inspection of results shown in panel a supported the view that the majority of patients without ANV experienced fewer than four of the eight characteristics while the majority of patients who subsequently developed ANV experienced four or more of the characteristics. The open bars representing patients without

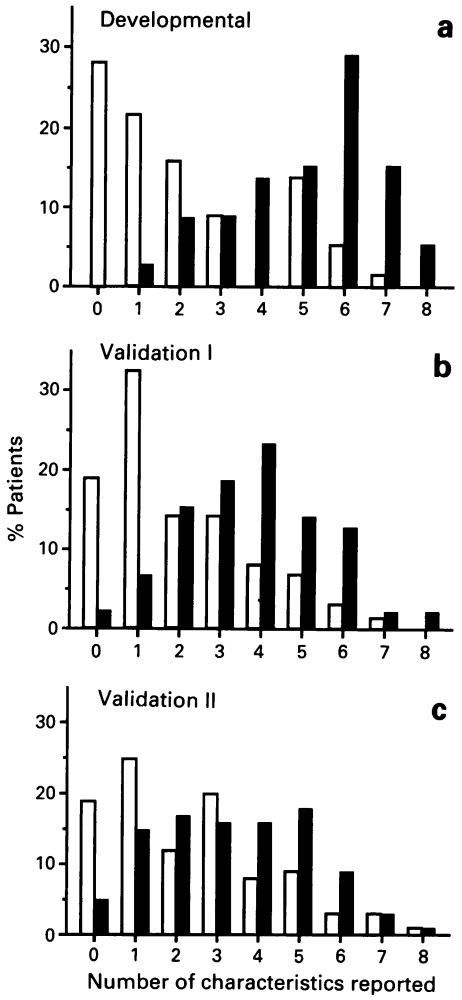


**Figure 4** The distribution of eight patient characteristics across three clinical trials for patients with (■) and without (□) anticipatory nausea and vomiting. **a**, development study (n = 297); **b**, validation study I (n = 366); **c**, validation study II (n = 299).

ANV are largely clustered to the left side of the chart (representing fewer than four characteristics) while the closed bars representing the number of patients with ANV are largely found towards the right end of the panel.

Based on these promising results, a validation study was conducted where 530 consecutive patients were predicted to develop or to not develop anticipatory side effects based on results of their first chemotherapy. The outcome was whether or not they had developed anticipatory side effects prior to the time of their fourth chemotherapy treatment. In the first study, the characteristics were assessed concurrently with whether or not the patient had developed ANV. This second study was a predictive study where the eight characteristics were assessed following the first chemotherapy treatment and patients with four or more were predicted to develop ANV by chemotherapy treatment four.

Three hundred and sixty six evaluable patients were examined. Results are shown visually as the panel labelled Validation I in Figure 5. Overall, the characteristics significantly predicted subsequent anticipatory nausea development ($P < .01$). Results were found to be independent of the type of cancer being treated. The accuracy of the prediction was, however, found to be less specific than prior research: 34% of the patients predicted to develop anticipatory nausea did so compared to 16% of the total sample. Overall, the schema was much more accurate in screening out those patients who subsequently did not develop anticipatory side effects than the accurate prediction of those who did.

This can be seen visually in the panel where, compared to the chart above (reported the developmental study), it is seen that the distributions of patients who had ANV *vs* those who did not are more normally distributed across the number of characteristics rather than with patients who developed anticipatory side effects being skewed toward a higher number of the characteristics and patients who did not skewed to a lower number. These results are especially prominent in terms of the distribution of patients who did subsequently developed ANV. Unlike the developmental study where the majority were seen to cluster at four or more characteristics (and this is why the cut off was developed at four), the number of characteristics was more normally distributed with a mean value around four. In general, the majority of patients who did not develop anticipatory side effects were found to cluster at fewer than three of the characteristics. This is a reflection of the fact that the decision rule of four or fewer characteristics was still able to capture the majority of the patients who did not develop the side effects. Interim data from a second validation study currently underway are shown as the third panel in Figure 5. Thus far, 299 of 351 patients have been evaluable. Characteristics of patients in the study are shown in Table I. With few exceptions, the samples have been roughly comparable.

Once again, a statistically significant association has been found between the prediction of the development of anticipatory side effects prior to the fourth chemotherapy treatment based on clinical characteristics gathered following the first chemotherapy treatment ($P < .01$). Also, again, it appears that the eight questions were valuable in screening out patients who do not subsequently develop the anticipatory side effects rather than identifying the patients who subsequently do. Visually it can be seen from panel C in the figure the majority of patients without ANV are found to have reported fewer than three of the characteristics following their first chemotherapy treatment.

*Comparisons of three studies that have examined the usefulness of eight characteristics in predicting anticipatory nausea and vomiting development* The three studies may be compared on a common metric using two test statistics used to assess predicted power (i) sensitivity – which is the measure of a correct prediction of positive cases; (ii) specificity – which is a correct prediction of negative cases and positive predictive value which is the number of true positives compared with the number of predicted positives. A comparison of the three studies is shown in Table II.

For each of the eight characteristics as well as the total of sensitivity and specificity measures are shown for each of the characteristics. The first column lists sensitivity. Numerically, this is calculated by dividing the number of true positive identifications (patients with ANV who had the characteristic) by the total number of patients with ANV. Specificity is the accuracy of predicting the true negatives and is the number of true negative identifications (patients without the characteristic who did *not* subsequently develop ANV) divided by the total number of patients who did *not*

**Table I** Sample description for validation study II

| *Variable* | *No. of pts.* | *(%)* |
|---|---|---|
| Entered study/evaluable | 351/299 | (84) |
| *Sex:* | | |
| Male | 59 | (20) |
| Female | 238 | (80) |
| *Disease sites:* | | |
| Breast | 165 | (56) |
| Hematologic | 60 | (20) |
| Lung | 30 | (10) |
| Gastrointestinal tract | 13 | (4) |
| Genitourinary | 2 | (1) |
| GYN | 23 | (8) |
| Other | 4 | (1) |
| *Age:* | | |
| Mean | 54 | |
| Median | 53 | |
| Range | 20–83 | |

**Table II**

| Patient characteristic | Sensitivity | | | Specificity | | |
|---|---|---|---|---|---|---|
| | *Developmental* | *Validation I* | *Validation II* | *Development* | *Validation I* | *Validation II* |
| Age | .57 | .54 | .39 | .82 | .77 | .66 |
| Nausea severity | .87 | .55 | .44 | .60 | .77 | .78 |
| Vomiting severity | .63 | .45 | .29 | .68 | .84 | .82 |
| Motion sickness | .27 | .34 | .19 | .83 | .83 | .84 |
| Warm/hot | .52 | .27 | .23 | .74 | .79 | .74 |
| Generalised weakness | .72 | .54 | .63 | .56 | .54 | .53 |
| Nausea and vomiting | .93 | .79 | .83 | .55 | .52 | .53 |
| Sweating | .60 | .20 | .31 | .69 | .84 | .74 |
| Total (four or more of above) | .80 | .55 | .43 | .74 | .79 | .76 |

experience ANV. Overall, a general decline in the sensitivity of the total of eight questions is seen across the three studies. The sensitivity value for the developmental study where the characteristics were measured concurrently with the assessment of whether or not the patient had ANV shows a total value of .80. For the interim analyses of the current investigation, this is found to be 0.43. Also in the current investigation, a general reduction is seen for the majority of the characteristics with the exception of the patient having had nausea and vomiting which retains sensitivity values around .80.

Values for specificity or the prediction of true negative values have remained approximately constant across the three studies. They are seen to fall in roughly the 0.75 range consistently. These results mirror the visual interpretation of the previous figure. Across the three studies, the total of the eight questions to predict patients who will not develop anticipatory side effects has remained fairly constant; the ability to predict patients who have has been found less using a predictive methodology than when the schema was measured concurrently with the expression of ANV.

The positive predictive value test statistic is the number of true positives divided by the total number of positive cases. For the developmental study 48 of the 71 patients who had four or more of the eight characteristics were found to have developed anticipatory nausea and vomiting (0.68). Sixty of the total patient sample of 148 (40%) of the total patients had developed anticipatory nausea and vomiting. Thus, the increase in 'yield' due to the predictive schema was 28%. A load value was found for the first validation study where the positive predictive value was found to be 0.34 compared to 16% of the total patients who developed ANV. Thus, the enrichment would have been 18%. This is approximately the same value found, thus far, in the second validation study where 50 of the 95 patients (0.53) who were predicted to have the anticipatory side effects have developed them. Thus far, 36% of the total sample has. The increase in yield is thus 17% (0.53 − 0.36).

Overall, the specificity of the schema has remained fairly constant. Patients who experienced fewer than three of the eight characteristics have been found consistently unlikely to develop anticipatory nausea and vomiting. This appears to be the case whether the measures are made concurrently (as was done in the developmental study) or predictively following the first chemotherapy treatment as related to the outcome of ANV or before the fourth chemotherapy treatment. On the other hand, sensitivity values have been shown to be much greater when measured concurrently than predictively. This may indicate that some type of interactive methodology is taking place, and that while the eight characteristics are associated with the subsequent development of ANV, they may also be influenced by the fact that the patient has developed ANV.

The positive predictive value has remained fairly consistent across the two predictive studies. On average, the 'yield' of positive cases in a sample may be increased by approximately 15–20% by predicting that patients who have four or more of the characteristics will subsequently develop ANV. This increased yield could potentially be important in clinical trials examining perhaps the retardation or prevention of the development of anticipatory side effects. Taken in conjunction with the value of the characteristics in screening out those patients who will subsequently not develop the side effects show that studies have begun to yield clinically and scientifically meaningful results in the etiology of anticipatory side effects. The degree to which such patient characteristics may prove useful in the control of posttreatment side effects is a rich topic for future research.

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# Discussion of Dr Morrow's paper

**Grunberg:** In this discussion session we shall address Dr Morrow's paper and also give people the opportunity to raise any other points they think should be considered.

**Morrow:** Dr Cull has raised the question of why anticipatory symptoms are more prevalent and persistent in the young. I cannot really answer this question. Certainly younger patients have more anaesthetic-induced emesis, I don't know if these factors are connected. Anticipatory symptoms do persist for some years. A follow up study of Hodgkin's patients, who had been treated up to 14 years previously, showed they still had anticipatory symptoms when they went for their annual check-up. So among the young it is a fairly robust phenomenon.

Distraction is a useful intervention with children; video games, hypnosis and the like are enormously effective with kids. They tend not to be with adults.

**Cull:** Can I come back to another point about your choice of anxiety measures? Is it not the case that there is quite a lot of overlap in the items of the POMS and STAI? What do you think the differences really are?

**Morrow:** The differences are quite clear. The STAI is much more oriented towards physical symptoms than POMS. Neither are perfect. We were trying to separate out cognitive involvement from simply a greater intensity of post-treatment symptoms. Trait anxiety did not separate groups at all. Rather it was the patient's reaction to the situation, their state anxiety, that showed the differences.

It is probably not the absolute magnitude of anxiety, but the change in anxiety between treatments that is important. An increase in anxiety should facilitate the conditioning which makes the subject more prone to vomiting. The problem in studying this is finding enough people whose anxiety has increased between treatments.

**Grunberg:** We have spent a lot of time talking about 5-$HT_3$ receptors, dopamine receptors and the pharmacology of nausea and vomiting. Is there a relationship between pharmacological parameters and anticipatory nausea and vomiting?

**Morrow:** The direct answer is no, although we are in the process of such studies. We are currently collecting blood samples from patients with ovarian cancer to measure catecholamines, especially dopamine and cortisol over the time period before and after treatment. I'm afraid I don't have the data yet. In some of our earlier work we found no change in vasopressin, which is though to be a 'marker' that changes with nausea and vomiting.

**Grunberg:** Since you have talked about the connection between motion sickness and anticipatory nausea and vomiting, do you see a role for scopolamine?

**Morrow:** Scopolamine has a bad record in terms of controlling anticipatory symptoms. However I don't think the studies have separated out and analysed the data from the sub-group of patients who are susceptible to motion sickness. I would suspect that scopolamine will hae some effect only in those people who are susceptible to motion sickness.

**Smyth:** I think a lot of us have been rather slow in