PATIENT EXPECTATIONS AS PREDICTOR OF CHEMOTHERAPY-INDUCED NAUSEA[1]

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ABSTRACT

We examined the relationship between patients' pretreatment expectations for nausea and vomiting and their subsequent development in a homogeneous group of 29 female cancer patients receiving platinum-containing chemotherapy as inpatients (Study 1) and in 81 subjects with any of a variety of cancer diagnoses treated largely as outpatients (Study 2). Each study found a significant relationship between patients' expectations for nausea development measured prior to their first treatment and their mean postchemotherapy nausea severity (both, $p < 0.05$). Patients' expectations accounted for unique variance in nausea severity in each study even after controlling for known pharmacological and physiological predictors of nausea (Study 1: $\Delta R^2 = .18$, $p < .04$; Study 2: $\Delta R^2 = .05$, $p < .03$). By contrast, we found no significant relationships between expectations for vomiting and subsequent vomiting.

Our results support the view that patients' expectations for nausea affect its subsequent development, indicating the presence of a significant psychological component in treatment-related nausea. Implications of this are discussed.

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INTRODUCTION

Although advances in antiemetic medications brought about by the introduction of the 5-HT_3 receptor antagonist class of antiemetics (ondansetron, granisetron, tropisetron) have greatly reduced chemotherapy-related vomiting, this has not been the case with treatment-related nausea (1). Together, the two symptoms remain among the most frequent side effects of cancer chemotherapy. Vomiting, defined as the forceful emptying of gastric contents through the sustained action of abdominal muscles and the opening of the gastric cardia (2), still occurs in approximately 25% of patients. Nausea, a subjective unpleasant feeling that may signal imminent vomiting that is accompanied by changes in autonomic nervous system activity (particularly parasympathetic activity), diminished gastric tone, and reduced peristalsis (3), is reported by as many as 78% of patients (1). Roughly one-third of patients report nausea of moderate or greater intensity. Both symptoms are inherently unpleasant and their prominent role in reducing quality of life has been widely documented (4–6).

Among patients, there is great variation in the frequency and severity of chemotherapy-induced nausea and vomiting (NV) that cannot be accounted for by pharmacological properties of the chemotherapeutic agents (7,8). Understanding patients' beliefs and expectations termed "response expectancies" concerning NV development may help us predict and explain some of this variation. Response expectancies have been predictive of symptom report in a number of studies from a variety of experimental perspectives including recovery from wisdom tooth surgery (9); postsurgical pain (10); resumption of work and sexual and social activities after coronary artery bypass surgery (11); return to work after a myocardial infarction (12); and experimentally induced pain (13–15).

If expectancies prove to be a reliable predictor of treatment-related NV, then knowing the patient's expectations concerning side effects would allow oncologists to target more aggressive antiemetic measures at patients who believe they are at high risk for developing NV. Also, to the extent that these expectancies are based upon inaccurate information or judgments, it provides an opportunity for an educational intervention that could be helpful in reducing overall symptom development.

Expectations as Predictors of Nausea and Vomiting

Researchers examining the relationship between response expectancies and the development of treatment side effects have reported mixed results. Zook and Yasco (16), in the earliest published study on this subject, found a significant relationship between an indirect measure of response expectancies with later nausea but not with later vomiting in 14 patients receiving chemotherapy for the first time. Contrary to this initial positive finding, Cassileth et al. (17), in the first reported study that directly assessed patients' pretreatment expectations for chemotherapy-related NV (on a 5-point Likert-scale), found no significant relationship between expectancies and either later nausea or later vomiting in their 56 study patients. Andrykowski and Gregg (18) replicated these null findings in a similar study of 65 patients.

Somewhat surprisingly, considering the aforementioned studies with negative findings, two other research groups, using methodologies similar to the Cassileth study, reported a positive association between nausea expectations and subsequent nausea report, even after controlling for the emetic potential of the chemotherapy drugs. The relationship was modest in the study of 45 patients by Jacobsen (19), but was relatively strong in the 36 patients studied by Haut et al. (20). Haut also reported a significant relationship between expectations for vomiting and subsequent vomiting.

In the largest study to date examining expectancies, Rhodes and colleagues (21), using their own expectancy measure, reported a significant relationship between expectations for nausea and nausea occurrence but not between expectations for vomiting and subsequent vomiting in 329 patients. Expectations were assessed during an interview, prior to chemotherapy, in which patients were asked what side effects they expected and to rate their anticipated

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severity on a 6-point scale. These researchers, however, did not control for the emetic potential of the chemotherapy drugs.

A relationship between expectations for nausea and subsequent anticipatory nausea has also been reported. Montgomery et al. (22) found a significant relationship between pretreatment expectations for nausea and the development of anticipatory nausea measured prior to the sixth treatment in 59 breast cancer patients receiving chemotherapy. This finding remained significant even after controlling for both the severity and frequency of occurrence of posttreatment nausea.

Response expectancies in regard to chemotherapy-induced nausea and vomiting are likely based upon three sources of information. The first is information on the emetic potential of the chemotherapeutic agents and on the efficacy of the antiemetic medications learned from oncologists, treatment nurses, consent forms, and other treatment center-provided information. The second source is the patient's knowledge of his or her own propensity to experience nausea based upon past experience (e.g. nausea during pregnancy or susceptibility to motion sickness). The third information source is the world at large and, unfortunately, includes information that is not necessarily accurate from an amalgam of sources, including acquaintances, television, magazines, and other patients. It is not clear what role each of these sources of information plays in forming the response expectancy and it probably varies from patient to patient.

In summary, research to date examining the relationship between measured response expectancies (measured prior to first treatment) for chemotherapy-related nausea and vomiting and its subsequent development is inconsistent, perhaps due to substantial methodological differences among the studies. Three of five studies reported finding a significant relationship between expectations for nausea and later nausea report, while only one of four studies reported a similar relationship between expected vomiting and the occurrence of that symptom.

We report on two companion studies, with similar methodologies but different patient populations, in which we examined the relationship between response expectancies and treatment-related side effects. These two studies are methodologically stronger than previous research in this area because we controlled for the emetic potential of the chemotherapeutic agents, type of antiemetic medication, and for three known physiological predictors of treatment-related NV (age, nausea during pregnancy, and nausea from motion) (23). In addition, the second and larger of these two studies is unique in that it extends this research into the era of 5-HT_3 receptor antagonist antiemetics.

PATIENTS AND METHODS

We extend previous investigations of a relationship between response expectancies and symptom development in cancer patients through two studies which examined the relationship between chemotherapy patients' pretreatment expectations for NV and subsequent symptoms. The first investigation was of a homogeneous sample of patients with ovarian cancer treated as inpatients, while the second was a study in a more heterogeneous patient group treated largely in an ambulatory setting. We hypothesized in both that greater pretreatment expectations of developing NV would be associated with more frequent and severe symptom development.

Procedures

Data were collected as part of two larger studies examining the association between patients' autonomic nervous system (ANS) responses and chemotherapy-induced NV. Patient assessment times were the only aspect, other than the already mentioned differences in setting, patient population, and available antiemetics, in which the studies differed. For reasons relating to the ANS monitoring, patient responses, including NV symptoms, were assessed following treatments 1 and 2 in the first study and following treatments 1 and 3 in the second study. The Institutional Review Boards of each participating institution approved the studies. Chemotherapy naïve patients were asked to participate in the research study prior to receiving their first chemotherapy treatment for histologically confirmed cancer.

After providing informed consent but before beginning treatment, patients' expectations of developing vomiting and nausea were assessed on separate 5-point Likert scales. These scales, which were developed by Cassileth and colleagues and used by three subsequent research groups (mentioned earlier), are anchored at one end by 1 (*I am certain I will NOT have this*) and at the other end by 5 (*I am certain I WILL have this*). Patients who indicated a response of either 4 or 5 on this form were scored as expecting the symptom. We also asked patients if they ever had motion sickness and whether or not they had experienced nausea during pregnancy.

Nausea and vomiting were measured by a patient report diary developed for this purpose (24,25). Each day was divided into four segments (morning, afternoon, evening, night) and patients reported the severity of nausea and number of vomiting episodes for each period on the day of treatment and on the 2 following days (12 total reporting times). Severity of nausea was assessed on a 7-point semantic rating scale anchored at one end by 1 (*Not at all Nauseated*) and at the other end by 7 (*Extremely Nauseated*). The description *Moderately Nauseated* was centered on the scale below the 4. A score >1 indicated nausea.

Emetogenicity of the chemotherapy regimens was classified by historic frequency of acute emesis according to the method proposed by Hesketh and coinvestigators (26) with level 1 = <10% frequency, level 2 = 10%–30% frequency, level 3 = 30%–60%, level 4 = 60%–90%, and level 5 = >90% frequency of emesis (26). Their algorithm for determining the emetic potential of chemotherapy regimens containing multiple agents was followed.

Patients

Study 1: Thirty-six women with ovarian cancer who were being treated with either cisplatin or carboplatin as inpatients at the University of Rochester Cancer Center were studied. Data collection began in June 1989 and concluded in March 1993. Table 1 shows the demographic and clinical characteristics including chemotherapy drugs and type of antiemetics administered for the 29 patients (81%) who provided complete data for at least one treatment. These women ranged in age from 34 to 79 years with the average age being just over 60 years. Approximately one-third of these women had college experience and most (>90%) had graduated from high school.

Study 2: Eighty-six subjects with a variety of cancer diagnoses being treated with a variety of chemotherapy drugs at the University of Rochester Cancer Center, two locally affiliated hospitals, and a private oncology practice in Rochester, New York were studied. Data collection began approximately 1 year after the close of the previous study and concluded in April 1998. Table 1 shows the demographic and clinical characteristics for the 81 patients (94%) who provided complete data for at least one treatment. Four cancer diagnoses predominated among study subjects, with 59% of subjects having breast cancer and 17%, 11%, and 10% having gynecologic, lung, and hematologic malignancies,

respectively. The group was 88% female with 30% of the nonbreast cancer patients being male. More than 75% of the study subjects received their treatments as outpatients. The group as a whole was well-educated with over 65% of the patients who provided data having some college education and over 91% completing high school.

RESULTS

Study 1

Twenty-two patients provided complete data from both their first and second chemotherapy treatments; 7 patients provided data from their first treatment only. Nearly all patients (97%) reported nausea after at least one treatment, with nausea severity at its worst averaging 3.6 (range = 1–7) following the first treatment and increasing to 4.4 (range = 1–7) following the second. Most patients (79%) reported vomiting following their first treatment, and nearly all (95%) reported the symptom following their second treatment.

Expectations and Nausea: Of the 29 patients, 31% (9) expected to experience treatment-induced nausea, and 20 reported they were either unsure about what would occur or that they did not expect any nausea. One of the 20 patients (included in this later group for all analyses) failed to record a response to the expectation of nausea question but did report being certain that she would not experience vomiting. Expectations of nausea were significantly correlated with both age and education level in this sample, with younger age ($r = .45$, $p = 0.01$) and fewer years of education ($r = .58$, $p = 0.002$) being associated with greater expectations for nausea. Receiving cisplatin versus carboplatin was not significantly related to nausea expectancies ($r = .03$, $p = 0.88$).

The mean level of nausea severity across the 12 reporting times was calculated for each individual. Patients (Figure 1) expecting nausea reported significantly greater nausea severity than patients not expecting nausea at the first treatment (mean 2.6 versus 1.7), $t(27) = 2.44$, $p = 0.02$, but not at the second treatment (mean 2.1 versus 1.6), $t(20) = 1.76$, $p = 0.09$. Expectations for nausea development were not significantly related to the peak nausea severity at the first treatment (5.4 versus 3.9), $t(27) = 1.79$, $p = 0.09$, but were significantly related at the second (5.2 versus 3.4), $t(20) = 2.24$, $p = 0.04$. Nausea expectancies were also significantly related to the average level of nausea severity that each patient experienced (mean 2.5 versus 1.7), $t(27) = 2.50$, $p = 0.02$. (Note: All 29 patients were included in this analysis, with the mean severity averaged across both treatments used for the 22 patients reporting twice and nausea severity from only the first treatment used for the remaining 7 patients.)

Regression analyses were used to further explore the relationship between patient expectation and nausea severity by controlling for known pharmacological and physiological predictors of nausea occurrence. We entered the Hesketh rating of emetic potential of the chemotherapeutic agents and whether or not the patient received cisplatin, carboplatin, cytoxan, or a $5HT_3$ antiemetic at the first step in a hierarchical regression equation predicting average level of nausea severity. These factors combined accounted for a nonsignificant 11.4% of the variance in nausea severity ($p = 0.57$). Three known physiological predictors of treatment-related nausea (i.e. susceptibility to motion sickness, being younger than age 50, and having nausea during pregnancy), when added at Step 2 of this equation, accounted for a nonsignificant additional 5.5% of the variance. Nausea expectancy, when entered at Step 3 of this equation, accounted for significant unique

TABLE 1
Demographic and Treatment Details

	Study 1 ($N = 29$) 6/89–3/93	Study 2 ($N = 81$) 2/94–4/98
Age:		
Mean (*SD*)	60.5 (11.4)	54.1 (11.8)
Range	34–79	33–83
Sex:		
Male	0	10
Female	29	71
Ethnicity:		
White	28	68
Black	1	11
Other	0	2
Education:		
>4 years college	4	36
<4 years college	4	12
High School graduate	15	19
Non-High School graduate	3	6
Missing data	3	8
Diagnosis:		
Hematologic neoplasms	—	10%
Lung	—	11%
Gynecologic	100%	17%
Breast	—	59%
Other	—	2%
Medications:		
Adriamycin	—	39%
Carboplatin	76%	11%
Cisplatin	24%	22%
Cytoxan	86%	60%
Fluorouracil	—	25%
Methotrexate	—	15%
Novantrone	—	11%
Taxol	—	23%
Vincristine	—	9%
Other	—	6%
Number of drugs[a] (mean)	1.9	2.2
Hesketh Emesis Score[b]	5	4.3
$5\text{-}HT_3$ receptor antagonists	3%	86%

Notes: [a] total number of different chemotherapeutic agents administered; [b] emetogenic ratings of the chemotherapeutic agents according to Hesketh's algorithm (see text).

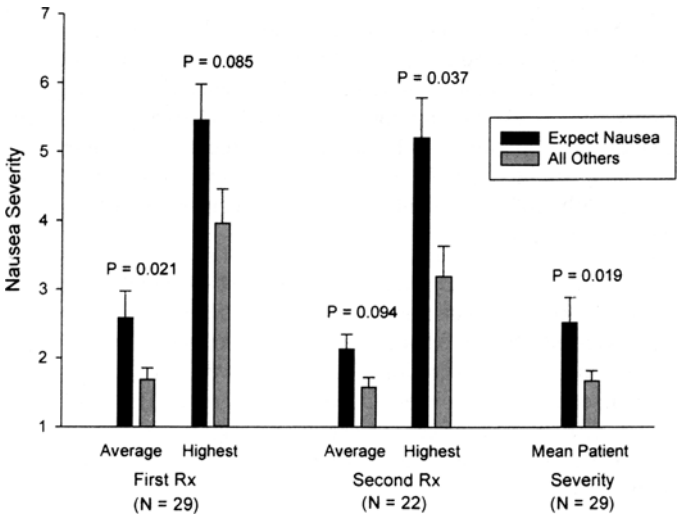

FIGURE 1: Reported levels of nausea severity in Study 1.

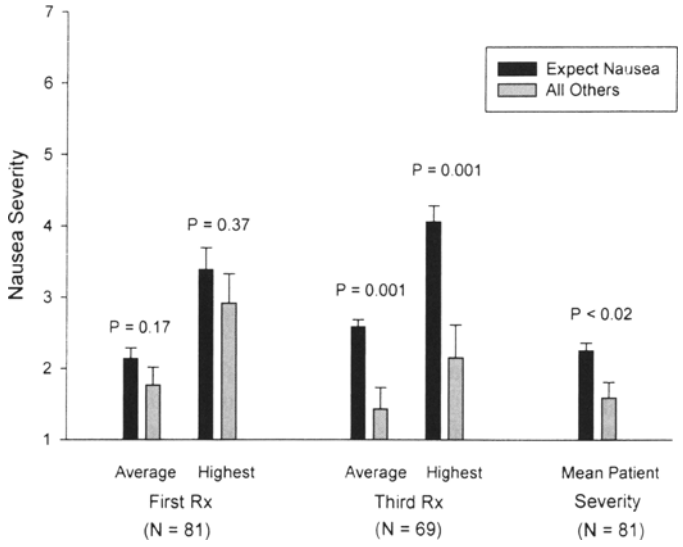

FIGURE 2: Reported levels of nausea severity in Study 2.

variance in nausea severity ($\Delta R^2 = .18$, $p < 0.04$). In a similar stepwise regression analysis using the same predictors, expectation of nausea entered first and was the only significant predictor of average nausea severity ($R^2 = .18$, $p < 0.03$).

Expectations and Vomiting: Only 24% (7) of the 29 patients reported that they expected to experience vomiting. One patient failed to answer the expectation of vomiting question and reported being unsure as to whether or not she would experience nausea. She was included in the group of patients that did not expect vomiting for all analyses. Age, education, and receiving cisplatin versus carboplatin were not significantly related to expectations for vomiting (all, $p > 0.05$).

All 7 of the patients (100%) expecting to vomit following their first treatment subsequently reported the symptom, whereas 16 of the 22 (73%) patients not expecting emesis reported the symptom. This difference was not statistically significant (Fisher's Exact Test $p = 0.29$). No analyses examining vomiting at the second treatment are reported because only 3 of the 7 patients who reported that they expected to experience vomiting provided evaluable data.

Study 2

Sixty-nine patients provided complete data from both their first and third chemotherapy treatments; 12 patients provided data only from their first treatment. Most patients (75.3%) reported nausea at at least one treatment, with nausea severity at its worst averaging 3.06 (range = 1–7) following the first treatment and dropping slightly to 2.76 (range = 1–7) following the third treatment. Only 20% of patients reported an occurrence of treatment-related vomiting.

Expectations and Nausea: Of the 81 patients, 32% (26) expected to experience treatment-induced nausea, and 55 reported they were either unsure about what would occur or that they did not expect nausea. Expectations of nausea were not significantly correlated with age, gender, education level, or the Hesketh emetic potential ratings of the chemotherapeutic regimens (all, $p > 0.05$).

Patients (Figure 2) expecting nausea reported significantly greater nausea severity than patients not expecting nausea at the third treatment (mean 2.6 versus 1.4, $p = 0.001$) and for their average level of nausea severity (mean 2.2 versus 1.6, $p = 0.02$), but not at the first treatment (mean 2.1 versus 1.8, $p = 0.17$). Expectations for nausea development were significantly related to the peak nausea severity at the third treatment (4.0 versus 2.1, $p = 0.001$), but not at the first treatment (3.4 versus 2.9, $p = 0.37$). We also directly compared reported nausea in the 26 patients expecting nausea with the 15 patients not expecting nausea by repeating these five analyses, leaving out the 40 patients who reported being unsure about whether or not they would experience the symptom. No changes in the statistical significance of any of the equations resulted, although a larger difference between groups was seen in each when compared to the previous analyses.

Gender differences were examined by repeating the original five analyses with only the 71 female patients. No changes in statistical significance occurred.

A hierarchical regression analysis similar to the one in Study 1 (described above) was conducted. The pharmacological predictors entered at Step 1 in this equation were the Hesketh rating, the total number of chemotherapeutic agents each patient received, and whether or not the patient received a $5HT_3$ antiemetic. In addition, at this step we also entered individually the five chemotherapy agents used in this study that were rated level 3 or higher in emetic potential by Hesketh (i.e. cisplatin, carboplatin, cytoxan, adriamycin, and nitrogen mustard). These eight pharmacological predictors accounted for a nonsignificant 14.2% of the variance in average patient nausea severity ($p = .21$). The three physiological predictors, plus gender, when added at Step 2 of this equation, accounted for a significant additional 11.8% of the variance ($p = 0.04$). Nausea expectancy, when entered at the third step of this equation, accounted for significant unique variance in nausea severity ($\Delta R^2 = .05$, $p < 0.03$).

As in the previous study, we also conducted a stepwise regression analysis using all of the above predictors. Expectation of nausea was the strongest significant predictor of average nausea severity ($R^2 = .09$, $p < 0.01$), followed by receiving adriamycin and susceptibility to motion sickness.

Expectations and Vomiting: Only 20% (16) of the 81 patients reported that they expected to experience vomiting. Age, education, gender, and emetic potential of the chemotherapeutic agents were not significantly related to expectations for vomiting (all, $p > 0.05$). Expectations for vomiting were not significantly related to its subsequent development at either treatment (all, $p > 0.05$).

DISCUSSION

These data support previous findings from research groups reporting a relationship between patient expectations of nausea from chemotherapy and its subsequent development. Study 1 examined a relatively homogeneous group of 29 patients with ovarian cancer receiving platinum-containing chemotherapy as hospital inpatients, treated largely before the availability of $5\text{-}HT_3$ receptor antagonists antiemetics. Study 2 confirmed the results of Study 1 in 81 relatively heterogeneous patients with a variety of cancer diagnoses, treated largely as outpatients with a wide variety of chemotherapy agents when $5\text{-}HT_3$ receptor antagonists were in widespread use. Both studies showed a significant relationship between patients' expectations for nausea development measured prior to their first treatment and the average postchemotherapy nausea severity each patient experienced. Nausea expectations were also significantly related to peak nausea severity at the patients' second reporting time, although not at their first, in each study.

Surprisingly, correlational analyses revealed that nausea expectancies were not significantly related to the emetic potential of

the chemotherapeutic regimen in either study. In a similar vein, regression analyses in each study revealed that nausea expectancies accounted for significant unique variance in subsequent nausea severity, even after controlling for chemotherapy and antiemetic agents. In fact, expectancy proved to be a stronger predictor of nausea severity than any other single variable measured in this study, whether pharmacological or physiological.

Contrary to our findings on the predictive reliability of nausea expectancies, our data do not support the existence of a similar relationship between expectations for treatment-related vomiting and its later occurrence. This is consistent with the bulk of previous research on this topic. Differences in symptom etiology might help account for the fact that expectancies appear to be related to subsequent nausea but not to subsequent vomiting. Nausea, which is accompanied by flushing, perspiration, pallor, gastric stasis, and tachycardia, is mediated by the autonomic nervous system, while vomiting is coordinated through the somatic nervous system (27). It may be that humans are simply better able to predict their autonomic versus their somatic nervous system responses.

Our regression analyses, showing that expectations accounted for unique variance in nausea severity even after controlling for known pharmacological and physiological factors, suggest that a "self-fulfilling prophecy" effect may be reflected in our data. It is possible that the simple expectation of nausea makes the symptom more likely to occur, a sort of reverse placebo effect. Two studies suggest that this is not an unreasonable possibility.

Seasickness was reduced by an expectancy manipulation in an experiment using what the authors termed a "verbal placebo." The experimental manipulation accounted for 31% of the variance in later reported seasickness (28). The effect caused by a manipulation of patients' expectations for NV development can also be seen in a study examining the efficacy of acupressure for control of these symptoms (29). While the true acupressure arm participants in this experiment did better than those in the sham acupressure arm, indicating the presence of a modest treatment effect, patients in both groups reported substantially lower rates of NV than reported by patients in the control group, thereby indicating the presence of a strong expectancy/placebo effect.

Although our studies prospectively examined the relationship between expectations for nausea and its subsequent report, it is important to understand their limitations. The correlational nature of the data does not allow us to rule out possible "third" variables (e.g. patients' vitality or degree of infirmity) that could account for the relationships found. Moreover, even within a correlational approach, the patient's understanding of the emetogenicity of the chemotherapy drugs in relationship to the expected efficacy of the antiemetic medications they would be receiving, has yet to be examined.

Our studies provide additional evidence that expectancy cognitions play a role in chemotherapy-induced, side effect development. They join other psychological constructs, including conditioning (25,30) and anxiety (19,31) known to affect development of NV symptoms. Expectancies are closely related to these other two factors and may, in fact, be largely responsible for effects attributed to them. Negative expectancies are an instrumental factor in the development of anxiety (32,33). Likewise, expectancy is thought to play a role in the generation of conditioning effects (34–36). The magnitude of the effect of these psychological factors on NV development is amply demonstrated by the unfortunate fact that approximately 20% of chemotherapy patients experience NV prior to their treatment (1). These psychological factors are also thought to contribute to the development and severity of posttreatment symptoms (37).

How these response expectancies operate remains largely unknown. Kirsch (32) suggests that response expectancies account for the placebo effect and are self-confirming. While the biochemical and physiological mechanisms by which placebo effects influence treatment outcome are not well understood, it is clear that the effect is substantial and that expectations concerning treatment effectiveness are intimately associated with the process (38,39).

Knowledge of patients' expectancies and their source can potentially provide useful information to the treating oncologist. For example, it might be helpful to give a relatively more aggressive antiemetic therapy at the first treatment to a patient who has a high expectancy for treatment-induced nausea based upon her own general susceptibility to nausea. Control of NV at this treatment is particularly important as the early presence of NV is thought to deleteriously affect NV control at later treatments due to conditioning and further expectancy effects (40). In addition, the negative expectancies themselves can be targeted. A simple intervention, such as the clinician giving a little extra reassurance about the effectiveness of the antiemetic medications, may influence outcome. More sophisticated interventions to positively affect patients' expectations should be developed and evaluated.

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