The continuing problem of post chemotherapy nausea and vomiting: Contributions of classical conditioning

Dana H. Bovbjerg

Biobehavioral Medicine Program, Department of Oncological Sciences, Mount Sinai School of Medicine, Box 1130, 1425 Madison Avenue, New York, NY 10029-6574, USA

Abstract

Despite continuing improvements in antiemetic therapies, nausea and vomiting following chemotherapy treatments for cancer remain significant clinical problems for many patients. The role of classical conditioning in patients’ anticipatory nausea is well known, but little attention has been paid to possible conditioning effects on post treatment nausea.

The present study statistically examined the contribution of anticipatory (conditioned) nausea to patients’ subsequent post treatment nausea. Forty early stage breast cancer patients who developed anticipatory nausea were analyzed. Results revealed a significant correlation between the intensity of anticipatory nausea in the clinic prior to their treatment infusion and subsequent post treatment nausea during the 24 h after the infusion. These results provide support for the hypothesis that, once established, conditioned nausea may contribute to the severity of subsequent post treatment nausea in patients receiving repeated cycles of chemotherapy for cancer. The results suggest the importance of considering the contribution of conditioning process to nausea and other post treatment side effects.

© 2006 Elsevier B.V. All rights reserved.

Keywords: Breast cancer; Chemotherapy; Classical conditioning; Nausea

1. Introduction

Nausea and vomiting are nearly universal side effects of the cytotoxic agents commonly used in the chemotherapy treatment of cancer (Miller and Kearney, 2004; Grunberg et al., 2005). Although the emetogenic potential varies across chemotherapy agents, in the absence of prophylactic antiemetic therapy, the proportion of patients experiencing emesis (vomiting) after their first chemotherapy treatment would exceed 90% for several widely used agents (e.g. cisplatin). In the absence of effective "rescue" antiemetic therapy, the incidence of emesis generally becomes higher across the typically months-long course of repeated cycles of treatment (e.g. infusion followed by 3 weeks recovery) required for most curative chemotherapy regimens (Miller and Kearney, 2004). Uncontrolled vomiting can have serious medical consequences and require delays between treatments, reducing the efficacy of chemotherapy (Miller and Kearney, 2004). Nausea is viewed by patients as one of the most aversive side effects of chemotherapy, and vomiting is rated close behind (Lindley et al., 1999; Miller and Kearney, 2004; Foubert and Vaessen, 2005). Failure to control these side effects can thus increase the likelihood that patients will drop out of treatment altogether (Miller and Kearney, 2004).

Despite advances in the pharmacological management of emesis, a substantial proportion of patients continue to experience chemotherapy-induced nausea, and many continue to experience emetic episodes at some point during their cancer treatment regimen (Grunberg et al., 2005; Jordan et al., 2005). The addition of 5-HT antagonists (e.g. ondansetron) to clinicians’ antiemetic armamentarium has substantially reduced vomiting during the acute phase (within 24 h after treatment) and the more recent addition of neurokin-(NK1) antagonists (e.g. aprepitant), has reduced delayed emesis (2–5 d after treatment), but prevention of emesis is not complete and prevention of nausea has proven to be even...
more difficult (Grunberg et al., 2005; Herrstedt et al., 2005b). Even with the best available antiemetic therapy, a substantial number of patients experience an emetic episode at some point after their first chemotherapy treatment, while even more patients experience nausea. With repeated cycles of chemotherapy these numbers go up (Herrstedt et al., 2005a). For example, a recent clinical trial (Herrstedt et al., 2005b) examined the efficacy of an aprepitant regimen in a sample of 650 patients receiving moderately emetogenic chemotherapy (e.g. cyclophosphamide) for breast cancer. Patients on the aprepitant regimen did not show a significant reduction in nausea after their first chemotherapy treatment compared to patients on a control antiemetic regimen (ondansetron and dexamethasone without aprepitant), but they did have a significantly lower incidence of emesis. However, nearly a quarter of the patients in the aprepitant group still reported vomiting at least once over the 120-hour period following their first chemotherapy treatment. Moreover, the percentage of patients reporting emesis increased across subsequent cycles of chemotherapy, such that by the time patients received their fourth chemotherapy treatment over a third of the patients in the aprepitant group, and nearly two thirds of the control group, reported vomiting.

The explanation for the continuing problem of nausea and vomiting in a substantial number of chemotherapy patients, particularly across repeated experiences of treatment, is not yet clear. Continued pharmacological research and development grounded in the biomedical model of these aversive side-effects of chemotherapy may provide new, more effective, antiemetic therapies (Hesketh, 2004a). Not yet considered, however, is the possibility that a broader biobehavioral model might yield insights relevant to increasing the range and effectiveness of interventions to reduce chemotherapy-induced nausea and vomiting. More specifically, classical (Pavlovian) conditioning processes may contribute not only to anticipatory nausea, but also to patients’ subsequent experiences of post treatment nausea and vomiting during the course of repeated cycles of chemotherapy.

It has been recognized for over two decades that cancer patients undergoing a typical chemotherapy regimen experience all the critical elements for classical conditioning that Pavlov established as necessary in his classic experiments on salivation in dogs (Nesse et al., 1980). In Pavlov’s well-known experiments, dogs were conditioned by contingent pairing of the ringing of a bell (the conditioned stimulus) with putting meat powder in the dog’s mouth, an unconditioned stimulus (unconditioned stimulus) for salivation (unconditioned response); after several such pairings (reinforced conditioning trials), ringing the bell began to elicit salivation (conditioned response) prior to the administration of meat powder, or even when meat powder was not presented (extinction trial) (Pavlov, 1928; Gormezano and Moore, 1969). Cancer patients are typically exposed to a distinctive clinic environment (conditioned stimulus) prior to receiving chemotherapy (unconditioned stimulus) that causes nausea and vomiting; reexposure to the clinic environment may then trigger “anticipatory” nausea or even vomiting in patients prior to subsequent treatments (Matteson et al., 2002; Aapro et al., 2005). Empirical support for the development of conditioned nausea and vomiting in chemotherapy patients comes from multiple lines of evidence consistent with various aspects of conditioning theory (see Table 1). The conditioning etiology of anticipatory nausea and vomiting prior to repeated chemotherapy treatments is now widely accepted by biomedical researchers (Stockhorst et al., 1998; Gralla et al., 1999) and supported by a voluminous clinical literature, which has been extensively reviewed elsewhere (Matteson et al., 2002; Aapro et al., 2005).

Currently lacking in the literature, however, is consideration of the possibility that classical conditioning processes may not only result in the development of anticipatory nausea in patients prior to later treatment infusions, but may also contribute to their subsequent experiences of nausea in the post treatment period. This possibility is entirely consistent with conditioning theory, since the relative timing of the conditioned response and unconditioned response are not critical aspects of the paradigm (Pavlov, 1928; Gormezano and Moore, 1969). Indeed, it was the use of extinction trials (conditioned stimulus not followed by unconditioned stimulus) in Pavlov’s classic experiments with salivation in dogs that allowed complete distinction between conditioned

Table 1

<table>
<thead>
<tr>
<th>Line of evidence</th>
<th>Representative publications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients receiving more emetogenic chemotherapy (stronger unconditioned stimulus) have greater risk of anticipatory nausea and vomiting (more conditioning trials)</td>
<td>(Morrow, 1982; Wilcox et al., 1982)</td>
</tr>
<tr>
<td>Patients with more severe post infusion nausea (stronger unconditioned response) have greater risk of anticipatory nausea and vomiting</td>
<td>(Montgomery and Bovbjerg, 1997)</td>
</tr>
<tr>
<td>Likelihood of anticipatory nausea and vomiting increases with the proportion of infusions followed by nausea (% reinforcement).</td>
<td>(Stockhorst et al., 1993)</td>
</tr>
<tr>
<td>Patients report particular cues (conditioned stimulus) trigger nausea even years after treatment. Conditioned nausea or vomiting develops to previously neutral cues (conditioned stimuli) experimentally paired with emetogenic stimuli in animals and humans.</td>
<td>(Tomoyasu et al., 1996)</td>
</tr>
<tr>
<td>Re-exposure to a distinctive cue (conditioned stimulus) experimentally paired with chemotherapy infusion elicits nausea outside the clinic setting on a day without impending chemotherapy.</td>
<td>(Divgi, 1989; Cameron et al., 2001; Pavlov, 1928; Klosterhalfen et al., 2005)</td>
</tr>
<tr>
<td>(Bovbjerg et al., 1992)</td>
<td></td>
</tr>
</tbody>
</table>
responses and unconditioned responses, as it was not unusual for the conditioned response to last longer than the typical interstimulus interval between the bell (conditioned stimulus) and presentation of meat (unconditioned stimulus) during reinforced conditioning trials (Pavlov, 1928). Similar findings have also been seen in an experimental animal model of conditioned vomiting (Wolff and Leander, 1994).

The purpose of the present study was to test one deductive consequence of hypothesized effects of classical conditioning on patients’ experiences of post treatment nausea. In this proof-of-principle study, it was predicted that, among patients who developed anticipatory (conditioned) nausea, individual variability in the severity of their subsequent post infusion nausea would be predicted by variability in anticipatory nausea. To test this hypothesis, the relationship between the intensity of patients’ conditioned nausea (operationally defined as their levels of anticipatory nausea at first manifestation following one or more previous treatment cycles) and their experiences of nausea over the 24 h following that treatment were statistically examined in a data set previously collected as part of an investigation of the development of conditioned effects during chemotherapy for breast cancer. The importance of conditioned nausea as a predictor of post treatment nausea was compared to that of patients’ unconditioned nausea responses (operationally defined as the severity of nausea experienced following their previous treatment), as well as other known predictors of acute post treatment nausea (e.g. age).

2. Materials and methods

2.1. Subjects

The study sample included 40 breast cancer patients, participating in a broader investigation of chemotherapy related side effects, as previously described (Montgomery and Bovbjerg, 1997), who developed anticipatory nausea at some point during their first 8 cycles of outpatient chemotherapy treatment. Participants met the following criteria: 1) diagnosed with Stage I or II breast cancer, status post radical, modified radical, or segmental breast surgery; 2) Karnofsky performance status over 70 at the start of treatment; 3) no prior chemotherapy treatment; 4) no radiation treatment during the course of chemotherapy; 5) 18 years of age or older; 6) not pregnant; 7) no history of neurological or psychiatric disorders; 8) no concurrent serious illness; 9) English speaking; 10) no hearing impairment interfering with study completion; 11) no oral chemotherapy; 12) no nausea in the clinic prior to the first infusion; 13) complete data on anticipatory and post treatment nausea over eight cycles.

A review of patients’ medical records indicated that they were treated with then standard combinations of chemotherapy agents: (1) CMF (cyclophosphamide [C] [600 mg/M2], methotrexate [M] [40 mg/M2], and 5-fluorouracil [F] [600 mg/M2]) I.V. q 21/28 d (n=32); (2) Adriamycin (75 mg/M2) I.V. q 21 d followed by CMF as above (n=6); (3) CAF (C [500 mg/M2], Adriamycin [50 mg/M2], and F [600 mg/M2]) I.V. q 28 d (n=2). Patients received a standard regimen of I.V. antiemetic medications at each infusion, including dexamethasone (10–40 mg) and lorazepam (0.5–2.0 mg). This regimen was supplemented on an individual basis by each patient’s attending oncologist with one or more of the following: prochlorperazine (10 mg), metoclopramide hydrochloride (40–100 mg), ondansetron (0.15 mg/kg), or diphenhydramine hydrochloride (25–50 mg). Participating patients ranged in age from 29 to 69 years with a mean age of 48 years (SD=10.4). The sample was predominately white (75.0%), married (72.5%), and well educated, with 55.0% having a college degree.

2.2. Methods

The study procedures have previously been described in detail (DiLorenzo et al., 1995; Montgomery and Bovbjerg, 1997). Briefly, consecutive patients with early stage breast cancer, scheduled for standard outpatient infusions of chemotherapy, were recruited prior to their first treatment. Participants completed study measures before and after each of their first 8 infusions of chemotherapy. The intensity of pretreatment nausea and state anxiety were assessed in the clinic waiting area before each outpatient treatment infusion, using visual analog scales to provide (0–100) quantitative ratings. The intensity of acute post treatment nausea over the 24 h following each treatment infusion was assessed (on a scale of 0–100) as part of a telephone interview conducted for research purposes after each infusion. In addition, patients completed a standard demographic data form, a life history of nausea questionnaire addressing nine common emetogenic situations (e.g. motion, anxiety, pregnancy) and scored as the total number of positive items, as well as a classic measure of trait anxiety, the Taylor Manifest Anxiety Scale (TMAS), to allow exploration of possible effects of these variables on the intensity of post treatment nausea levels.

To address the specific study hypothesis, the infusion at which patients first reported anticipatory (conditioned) nausea was determined (target infusion, Mean=4.6, SD=1.6). The

<table>
<thead>
<tr>
<th>Variable</th>
<th>Statistics</th>
<th>Probability</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>r(40)=−0.33</td>
<td>0.04</td>
</tr>
<tr>
<td>Global Adjustment to Illness</td>
<td>r(37)=−0.17</td>
<td>0.32</td>
</tr>
<tr>
<td>Karnofsky Status</td>
<td>r(36)=−0.38</td>
<td>0.02</td>
</tr>
<tr>
<td>Life history of nausea</td>
<td>r(40)=0.37</td>
<td>0.02</td>
</tr>
<tr>
<td>Taylor Manifest Anxiety score</td>
<td>r(40)=0.33</td>
<td>0.04</td>
</tr>
<tr>
<td>Pretreatment State Anxiety</td>
<td>r(40)=0.40</td>
<td>0.01</td>
</tr>
<tr>
<td>Unconditioned nausea response (PN)</td>
<td>r(40)=0.48</td>
<td>0.01</td>
</tr>
<tr>
<td>Conditioned nausea response (AN)</td>
<td>r(40)=0.37</td>
<td>0.02</td>
</tr>
<tr>
<td>Number of prior infusions</td>
<td>r(40)=0.05</td>
<td>0.78</td>
</tr>
<tr>
<td>Chemotherapy regimen</td>
<td>F(2,38)=0.90</td>
<td>0.42</td>
</tr>
</tbody>
</table>

Number of replicates differ due to missing data for particular variables. Mean AN=20.0, mean PN=31.2.
dependent variable of interest was the post treatment nausea rating (Mean = 31.2, SD = 32.8) following this target infusion. Patients’ conditioned nausea responses were operationally defined as the level of nausea reported in the clinic prior to this target infusion (Mean = 20, SD = 20.4). Patients’ unconditioned nausea responses were operationally defined as the level of post treatment nausea elicited by the infusion preceding this target infusion (Mean = 31.3, SD = 34.1).

### Table 3

<table>
<thead>
<tr>
<th>Step/variable entered</th>
<th>$R^2$ change</th>
<th>Probability</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Unconditioned nausea response</td>
<td>0.26</td>
<td>0.01</td>
</tr>
<tr>
<td>2. Conditioned nausea response</td>
<td>0.10</td>
<td>0.03</td>
</tr>
<tr>
<td>3. Age</td>
<td>0.07</td>
<td>0.07</td>
</tr>
<tr>
<td>4. Karnofsky Status</td>
<td>0.06</td>
<td>0.07</td>
</tr>
<tr>
<td>5. Pretreatment State Anxiety</td>
<td>0.03</td>
<td>0.17</td>
</tr>
<tr>
<td>6. Life history of nausea</td>
<td>0.01</td>
<td>0.42</td>
</tr>
<tr>
<td>7. Taylor Manifest Anxiety score</td>
<td>0.001</td>
<td>0.65</td>
</tr>
</tbody>
</table>

Model: $p = 0.002$.

### 2.3. Statistical analysis

To examine the relations between post treatment nausea following the target infusion and predictor variables, Pearson Correlation Coefficients were determined. Variables found to be significantly ($p \leq 0.05$) correlated with post treatment nausea were then entered into a stepwise regression analysis (DiLorenzo et al., 1995) to explore their relative contribution to variability in the intensity of patients’ post treatment nausea. In this analysis, the variable accounting for the most variance in post treatment nausea enters first, followed in turn by variables accounting for progressively less variance. The independent contributions of each predictor variable, controlling for previously entered variables, are indicated as $R^2$ change scores.

### 3. Results

As shown in Table 2, several factors were predictive of the intensity of patients’ post treatment nausea when examined individually in bivariate analyses. Consistent with the literature, several patient factors, including age, life history of nausea, and Karnofsky score, were significant predictors. Other significant predictors were psychological factors, including patients’ levels of trait anxiety and their state anxiety levels in the clinic prior to the treatment infusion. As expected, the intensity of patients’ acute nausea response to their most recent prior cycle of chemotherapy, their unconditioned response to treatment, was also a significant predictor. Finally, consistent with the study hypothesis, patients’ levels of anticipatory nausea were significant predictors of their subsequent acute post treatment nausea.

Patients’ levels of conditioned nausea were second only to their unconditioned nausea responses as predictors of the severity of patients’ post treatment nausea response following the target infusion, as shown in Table 3. The intensity of patients’ conditioned nausea responses accounted for an additional 10% of the variance in post treatment responses, a significant contribution above and beyond the 26% of the variance that could be attributed to patients’ unconditioned responses to treatment. None of the other variables made additional significant contributions to the variance in post treatment nausea following the target infusion, although age and Karnofsky status contributed 7% and 6%, respectively and came close to reaching significance.

### 4. Discussion

The results of this proof of principle study support the view that during the course of repeated outpatient chemotherapy treatment for cancer, conditioned nausea responses can contribute to the severity of patients’ subsequent experiences of post treatment nausea. The intensity of “anticipatory” nausea, at the first instance of this conditioned response in the clinic prior to a repeat treatment infusion was found to be a significant predictor of the severity of the post treatment nausea patients experienced during the 24 h after that infusion.

As expected, several other patient characteristics, including age, as well as state and trait anxiety, also predicted the severity of patients’ acute post treatment nausea after this treatment infusion in bivariate analyses. However, patients’ levels of conditioned nausea contributed more to the variability in their post treatment nausea responses than any other variable except their unconditioned nausea responses, operationally defined as nausea levels following the most recent previous infusion. Although the etiological role of classical conditioning in the development of anticipatory nausea responses in patients returning to the distinctive clinic environment where they had previously received emetogenic chemotherapy treatment has been well established (Aapro et al., 2005), the present study is the first to explore the possible continuing influences of conditioned responses on patients’ experiences of post treatment nausea.

Although novel in the context of chemotherapy-induced nausea, the results of the present study are entirely consistent with conditioning theory and with a large literature on conditioned effects in animal models. Indeed, in Pavlov’s classic studies, extinction trials (conditioned stimulus not followed by unconditioned stimulus) were used to demonstrate conditioned salivary responses to the bell, in part because these conditioned responses are otherwise difficult to distinguish from short latency unconditioned responses in this paradigm (Pavlov, 1928; Donahoe and Vegas, 2004). Particularly apposite to the results of the present study, is an experimental study on chemically induced vomiting in pigeons (Wolff and Leander, 1994). During the course of repeated treatments with the emetogenic agent in the study, these investigators found that some of the pigeons began to exhibit a short latency vomiting response when simply placed into the experimental chamber where they had previously received
drug. Further investigation confirmed the conditioning etiology of this short latency response and revealed that the duration of the conditioned vomiting, which was similar to that of the chemically induced emesis, was long enough to continue into the post drug period of the study protocol (Wolff and Leander, 1994).

Additional research is needed to determine whether in chemotherapy patients a long duration conditioned nausea response to clinic cues is the mechanism for effects of conditioning on patients’ post infusion nausea levels, demonstrated in the present study. It is also possible that the infusion process itself may act as a supplementary conditioned stimulus, and/or even that during the post infusion period thoughts and images of chemotherapy may serve as conditioning stimuli and trigger further nausea in conditioned patients. Some support for the latter possibility comes from the results of a previous experimental study, demonstrating that once patients develop conditioned nausea, thoughts and images of chemotherapy can elicit nausea (Redd et al., 1993). This possibility is also entirely consistent with a large experimental literature on human subjects, documenting that thoughts and images can serve as conditioning stimuli in a wide range of conditioning paradigms (Dadds et al., 1997).

A third possible explanation for the observed relationship between the severity of patients’ anticipatory conditioned nausea and their subsequent post infusion nausea is an influence of the conditioned response on the unconditioned response to the chemotherapy. Although this possibility is more speculative, empirical support for such effects can be found in recent conditioning studies that have consistently indicated that conditioned responses can affect animals’ responses to various drugs following exposure to a conditioned stimulus, as well as responses to a wide variety of other USs (Domjan, 2005). Indeed, Domjan (2005) has argued that from a functional perspective the primary utility of conditioning for an organism lies in its ability to influence their responses to unconditioned stimuli in the environment, as these are more likely to be biologically important.

Although consistent with conditioning theory and conditioning studies with animal models, the results of this initial study documenting a significant predictive relationship between conditioned effects seen in the clinic prior to a treatment infusion and patients’ post treatment nausea levels should be interpreted with caution. Larger studies with more homogeneous patient samples with regard to demographics and treatment variables are needed to confirm the replicability and generalizability of these findings. It would also be of interest to explore the possible contributions of stable personality traits (e.g. neuroticism) to the outcome. While there is no reason to anticipate that similar effects of conditioning will not be seen, it will be important to explore the relationships between pretreatment levels of conditioned nausea and subsequent post treatment nausea and vomiting in the many patients who continue to experience these aversive side effects of chemotherapy despite receiving anti-5HT and NK1 antiemetic agents (Jordan et al., 2005). It is tempting to speculate that conditioned effects likely contribute to the continuing problem of post treatment nausea seen in recent antiemetic trials, particularly later in the course of repeated treatment cycles. However, explicit investigation of this possibility is needed, and based on the results presented here, is now clearly warranted.

Additional research to test other deductive consequences of the hypothesis that conditioned responses can contribute to subsequent post treatment nausea is also warranted. Combining prospective assessments with experimental manipulation of conditioning variables, for example, would not only provide strong evidence of causal relationships, it might also suggest the utility of behavioral interventions to ameliorate the multiple negative consequences of classical conditioning during chemotherapy. For example, based on the conditioning principle of latent inhibition, experimental preexposure to the clinic environment before patients’ first treatment would be expected to reduce conditioned nausea and vomiting responses to clinic cues (Fantino, 1992), as has been demonstrated in an experimental model of rotation induced nausea (Klosterhalfen et al., 2005), and would also be expected to reduce conditioned effects on post treatment nausea (Stockhorst et al., 2006-this issue). The results of the present study also suggest the potential importance of additional research to follow up on initial evidence (Stockhorst et al., 1998) suggesting that the conditioning procedure of overshadowing can be harnessed to reduce post treatment nausea by reducing conditioned nausea, consistent with extensive research with animal conditioning models (Symonds and Hall, 2002; Hall and Symonds, 2006-this issue).

The clinical significance of conditioned effects on patients’ experiences of post treatment nausea remains to be determined. There is reason to suspect that such influences, when viewed from at least two broader perspectives, may be more profound than currently appreciated, but additional research is needed. The first perspective is that of the context in which the conditioning has been examined. A major limitation of the current literature on conditioned nausea and vomiting in patients undergoing chemotherapy is its nearly exclusive focus on anticipatory effects in the clinic environment prior to the repeat treatments. In addition to the results of the present study, several previous studies have suggested that the conditioning is robust and may generalize to contexts similar in only some respects to the original. For example, previous reports have demonstrated conditioned effects when patients are exposed to the clinic environment a year or more after finishing treatment (Cella et al., 1986; Cameron et al., 2001). Conditioned responses have also been documented in patients following the sight of their oncologist in another setting (Divgi, 1989). Moreover, as noted above, it has been experimentally demonstrated that even thoughts and mental images of chemotherapy can elicit nausea in conditioned patients (Redd et al., 1993), raising the possibility that these conditioned effects could occur in virtually any setting.
A second reason why conditioned effects on nausea and vomiting may prove to be more clinically significant than currently recognized is that the research literature has yet to explore the possibility that conditioning will be stronger for stimuli that are more evolutionarily salient than clinic cues. The tacit assumption in the literature that the distinctive clinic environment (including the people and procedures experienced there) is the preeminent source of cues serving as conditioned stimuli during chemotherapy. While not surprising given the origins of this area of research in the clinical phenomenon of anticipatory nausea and vomiting, this assumption may also have contributed to an underestimation of the possible clinical significance of conditioning in these patients. Considerable experimental research with animal models indicates that strong conditioned responses are far more likely to develop to a salient conditioned stimulus that is naturally related to the unconditioned stimulus, including stimuli early in a causal chain leading up to an unconditioned stimulus, than to arbitrary, previously neutral, conditioning stimuli (Domjan et al., 2004). Perhaps the best-studied example of such effects can be found in the literature on sexual responding in animal models (Domjan et al., 2004).

Conditioned effects of early arousal stimuli on subsequent orgasm have been clearly demonstrated (Krause, 2003; Domjan et al., 2004), which raises the question of possible analogous conditioning effects of nausea on vomiting. Based on the theoretical and empirical considerations highlighted above, it is tempting to speculate that nausea may serve as a conditioned stimulus for vomiting during chemotherapy, as well as in other settings. While nausea is generally thought to be part of chain of escalating enterceptive stimuli that lead up to vomiting (Hesketh, 2004b), indeed, nausea is sometimes defined as the urge to vomit (Thomas Lathrop Stedman, 2000), it is neither necessary nor sufficient to unconditionally elicit vomiting. Chemotherapy patients on optimal antiemetic therapy are much more likely to report nausea than vomiting, and vomiting can occur without prior nausea (Martin et al., 2003). Based on conditioning theory, it can be hypothesized that the likelihood that nausea will lead to vomiting will be function of one’s reinforcement history (proportion of nausea experiences followed by vomiting). In addition to one’s lifetime experience prior to chemotherapy, the likelihood of a conditioned vomiting response to nausea during chemotherapy may be strongly shaped by conditioned contextual cues associated with the chemotherapy setting, consistent with a large experimental literature documenting the importance of context to conditioning (Bouton and Moody, 2004).

In summary, the results of the present study provide proof of principle that in addition to the well-recognized role of classical conditioning in the development of anticipatory nausea and vomiting during chemotherapy for cancer, classical conditioning may also influence patients’ experiences of nausea and vomiting following treatment infusions. Additional research is needed to confirm and explore the theoretical and clinical implications of the novel findings reported here.

Acknowledgements

The financial assistance of a research grant from the American Cancer Society (RSG-01-180-01-PBP) is gratefully acknowledged.

References
