Understanding Anticipatory Nausea

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Purpose/Objectives: To address the concept of anticipatory nausea within the theoretical framework of classical conditioning.

Data Sources: Published articles, book chapters.

Data Synthesis: Although classical conditioning explains much in the development of anticipatory nausea, other factors also are at work. Preventing this phenomenon is necessary because it is difficult to treat and control once it develops.

Conclusions: Nurses are in a position to identify patients at highest risk for developing anticipatory nausea and implement interventional strategies to prevent/minimize it.

Implications for Nursing Practice: Many aspects of anticipatory nausea have not yet been researched well. Nurses must study how anticipatory nausea develops and interventions that can be used to reduce its prevalence.

As the population in the United States increases in age, so does the incidence of cancer. Nearly 80% of all cancers are diagnosed in individuals 55 years and older (American Cancer Society, 2000). As a result, an increasing number of individuals are receiving chemotherapy, radiation therapy, or both (Naylor & Rudd, 1996). With the advent of colony stimulating factors, chemotherapy agents are being administered in increasingly larger doses to effect a better response. Thus, the potential for side effects is greater than it was in the past (Wickham, 1996). The regimen prescribed by oncologists can only control or cure the cancer if patients complete the prescribed number of cycles. The side effects associated with these treatment modalities must be effectively controlled (Morrow, Lindke, & Black, 1991a).

Multiple studies have identified nausea and vomiting as common side effects of cancer treatments (Bovbjerg et al., 1992; Fetting et al., 1992; Foltz, Gaines, & Gullatte, 1996; Hursti et al., 1992; Jens, 1994). From patients’ perspectives, nausea and vomiting often are reported as the most distressing adverse effects associated with chemotherapy (Jenns).

Nausea

Often, nausea and vomiting are treated as a single entity when, in fact, they are two separate physiologic conditions. Nausea is a subjective sensation that may or may not precede vomiting. Jenns (1994) defined nausea as “an awareness of potential vomiting” (p. 488). Accompanying this awareness are physical changes, such as diminished gastric tone, reduced peristalsis, and reflux of intestinal content into the stomach. Vomiting is the actual emptying of the stomach (Fessele, 1996).

Types of Nausea

Although nausea is associated with chemotherapy, patients with cancer also experience nausea for other reasons. Nurses must assess their patients to determine the reason(s) for their nausea, as treatment varies with the cause. Metabolic alterations such as hypercalcemia, found in 10% of patients with cancer, and uremia may trigger the chemoreceptor trigger zone (CTZ) in the brain. Narcotics can cause a gastric stasis that leads to

Key Points . . .

➤ Ineffective treatment of chemotherapy-induced nausea leads to the development of anticipatory nausea.

➤ As a result of uncontrolled anticipatory nausea, patients may delay or discontinue treatment, or clinicians will delay or reduce the prescribed dose of chemotherapy. Any one of these can affect patient survival.

➤ Although prevention is the best strategy, behavioral interventions such as hypnosis, guided imagery, and progressive muscle relaxation, have been shown to mediate the effects of anticipatory nausea.

➤ The majority of studies reporting successful interventions have been described mainly in the psychology literature. Nurses need to be aware of and implement these strategies to make a positive impact on patients’ quality of life.

Objectives for CE Enrollees

On completion of this CE, the participant will be able to

1. Discuss key characteristics of anticipatory nausea.
2. List factors associated with the development of anticipatory nausea.
3. Discuss nursing interventions relevant to the treatment of anticipatory nausea.

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decreased peristalsis. This then stimulates the CTZ, leading to nausea (Bilgrami & Fallon, 1993; Fessele, 1996).

Three distinct types of nausea are associated with the administration of chemotherapeutic agents. Acute nausea is the chemotherapy-induced nausea that occurs within the first 24 hours after treatment and may last up to 24 hours. Most antiemetic studies focus on this type of nausea and its associated vomiting (Pisters & Kris, 1998).

Delayed nausea starts 24 hours or more after chemotherapy administration. This type tends to be less intense than acute nausea, but often lasts longer. Occasionally, delayed nausea persists up to three weeks after completion of chemotherapy. Because few studies have addressed delayed nausea, this phenomenon is not well understood (Pisters & Kris, 1998).

The third type of nausea associated with chemotherapy, and the focus of this article, is anticipatory nausea. In 1981, Morrow first identified and named this phenomenon (Morrow & Rosenthal, 1994). Initially, anticipatory nausea was defined as nausea that occurred within the 24-hour period before chemotherapy administration. This definition has been narrowed to include only the nausea that occurs within the 24-hour period before the scheduled chemotherapy administration on day one of the cycle (Andrykowski, 1988; Kvale, Psychol, & Hugdahl, 1994).

Although some patients reported nausea before their very first chemotherapy infusion, this nausea was the result of anxiety or nervousness at the prospect of receiving chemotherapy. They expected to get sick, and this caused their nausea (Blasco, 1994; Montgomery & Bovbjerg, 1997).

How Anticipatory Nausea Develops

Classical Conditioning

The development of anticipatory nausea usually is described in terms of classical conditioning. This also may be called Pavlovian conditioning after the Russian scientist who was able to cause dogs to salivate at the sound of a bell. The basic assumption is that anticipatory nausea is a learned response (Montgomery & Bovbjerg, 1997).

In classical conditioning, a neutral stimulus (e.g., the nurse), a smell, or the clinic environment (called the conditioned stimulus) is present during the chemotherapy treatment. Over time, this conditioned stimulus is associated with the unconditioned response (i.e., the drugs that cause the post-treatment nausea and vomiting). As the treatment progresses, the conditioned stimulus will come to elicit nausea as a conditioned response. Figure 1 graphically depicts classical conditioning as it relates to anticipatory nausea. In other words, re-exposure to the sights, smells, and sounds of the clinic or the clinic staff can produce nausea even if the patient is not actively receiving chemotherapy (Burish, Carey, Krozely, & Greco, 1987; Montgomery et al., 1998; Tomoyasu, Bovbjerg, & Jacobsen, 1996).

VonKomen and Redd (1985) discovered that thoughts related to the chemotherapy triggered nausea in 75% of patients with anticipatory nausea. For 22%, smells associated with the treatment or clinic triggered the nausea, and for 3%, sights associated with the treatment were the trigger.

Montgomery and Bovbjerg (1997) presented four arguments to support the idea that anticipatory nausea was a learned response. First, studies with animals and humans have shown the ability to take a neutral cue and change it into a conditioned response for nausea after it has been paired with an emetogenic drug. For example, Bovbjerg et al. (1992) conducted a study with 47 women undergoing outpatient chemotherapy for breast cancer. The women in the experimental group received a lemon-lime flavored drink prior to their chemotherapy infusion, whereas the women in the control group did not. After repeated pairings of the beverage with the chemotherapy infusion, researchers assessed the amount of nausea present when the women were given a glass of the lemon-lime drink. The women in the experimental group reported more nausea than the women in the control group.

Second, many patients can recall a particular cue (e.g., the smell of the clinic, the sight of the chemotherapy nurse) that triggered nausea prior to their treatment. These cues were remembered years after the end of the treatment (Montgomery & Bovbjerg, 1997). The third argument is that the prevalence of anticipatory nausea is higher among patients who received more emetogenic regimens of chemotherapy. This means the unconditioned stimulus (the chemotherapeutic agent) was stronger (Montgomery & Bovbjerg). Wickham (1996) described a well-recognized hierarchy of chemotherapeutic agents grouped by their emetogenic property. Most clinicians easily recognize the highly emetogenic agents.

The final argument that supported anticipatory nausea as a learned response is that the incidence is higher among patients who received more infusions of an emetogenic agent. In other words, the number of conditioning trials or pairings was greater (Montgomery & Bovbjerg, 1997). Studies showed a linear progression of the frequency of anticipatory nausea with the number of chemotherapy infusions. Approximately 25% of patients reported anticipatory nausea by the fourth treatment cycle, whereas 81% reported anticipatory nausea by the sixth cycle (Andrykowski & Redd, 1987; Montgomery & Bovbjerg; Morrow, 1984; Morrow & Rosenthal, 1996).

Personal Characteristics

If anticipatory nausea were strictly a classical conditioned response, all patients receiving chemotherapy would develop anticipatory nausea (Kvale et al., 1994). Because not all patients do, many researchers assume that differences exist in the personal or treatment characteristics between those who develop anticipatory nausea and those who do not. Researchers felt that if they could identify these factors, clinicians then...
could predict which patients were at highest risk for developing anticipatory nausea and intervene appropriately (Dibble, Chapman, Mack, & Shih, 2000; Morrow et al., 1996; Morrow & Rosenthal, 1996; Tyc, Mulhern, Barclay, & Bieberich, 1997; Tyc, Mulhern, & Bieberich, 1997; Wickham, 1996). Figure 2 presents a summary of these characteristics and the strengths of their association to anticipatory nausea.

Some of the personal characteristics studied included age, gender, and alcohol use. Although females overall seemed to be at increased risk for developing anticipatory nausea, prepubescent and postmenopausal women showed the same risk as the males in the study. For that reason, the role of female hormones was examined (Wickham, 1996).

One study found that patients younger than 50 years of age had a higher rate of anticipatory nausea than older patients. It was thought the younger patients might have received higher doses of more emetogenic drugs (Morrow & Rosenthal, 1996). This, however, has not been supported by other studies (Morrow, Lindke, & Black, 1991b; Tyc, Mulhern, Barclay, et al., 1997; Weddington, Miller, & Sweet, 1982).

Alcohol use/abuse implies chronic, regular use. Wickham (1996) defined chronic, regular use as consuming one to five drinks per day. In a retrospective review of 157 patients treated with cisplatin, Sullivan and Leyden (1983) found that patients who drank this amount of alcohol reported less nausea and vomiting than those who drank less alcohol.

Another characteristic associated with anticipatory nausea is a previous history of motion sickness or a propensity for nausea and vomiting related to other conditions, such as hyperemesis of pregnancy (Tyc, Mulhern, & Bieberich, 1997; Wickham, 1996). These patients reported more frequent, more severe, and longer lasting episodes of nausea after treatment. Of the patients with a history of motion sickness, up to 78% developed anticipatory nausea by the seventh cycle (Leventhal, Easterling, Nerenz, & Love, 1988).

Anxiety, fear of treatment, or anticipated pain may serve several roles in the development of nausea. These conditions stimulate the sympathetic nervous system, which causes changes in the neurotransmitters and triggers the release of hormones from the pituitary and adrenal glands. The hormones mediate the stress response and may cause nausea (Fessele, 1996; VonKomen & Redd, 1985). In addition, highly anxious patients may be more aware of their environment and pay more attention to clinical stimuli. These neutral stimuli then are associated with the emetogenic agent. This enhances the pairing of the neutral conditioned stimulus with the nausea unconditioned response, which increases the development of anticipatory nausea (Burish & Carey, 1986).

Andrykowski and Redd (1987) measured state and trait anxiety of 80 patients receiving chemotherapy and correlated that value with the development of anticipatory nausea. They reported that patients with a higher state and trait anxiety score had a greater amount of anticipatory nausea. Symptoms of increased anxiety and depression have been reported for as many as 55% of the patients receiving chemotherapy (Ouwerkerk & Keizer, 1990).

Several studies explored the effect of patients' pretreatment expectations on the development of anticipatory nausea (Montgomery et al., 1998; Tyc, Mulhern, Barclay, et al., 1997). Patients with a greater expectation of being nauseated after treatment were more likely to develop anticipatory nausea. This may be because individuals are able to predict how their body will respond to the chemotherapy. It also could be that expectations of nausea may exacerbate the intensity of subsequent experiences of nausea during the chemotherapy.

Patients who complained of feeling warm or hot all over or began to sweat after their previous chemotherapy session also were more prone to develop anticipatory nausea (Morrow & Rosenthal, 1996).

**Treatment-Related Characteristics**

Time is certainly a factor in the development of nausea. Montgomery and Bovbjerg (1997) studied 82 women and measured the severity of their nausea the night before the scheduled infusion, the morning of their infusion, and immediately before the infusion. As they hypothesized, the reported severity of nausea increased from the assessment conducted the night before to the assessment conducted immediately before the chemotherapy administration. They also found that the severity of the nausea reported the night before the eighth cycle of chemotherapy was higher than the severity of nausea reported the night before the first cycle.

Studies by Morrow and Rosenthal (1996) of more than 4,000 patients reported that no patient developed anticipatory nausea without first experiencing post-treatment nausea at least once. They also found that the more severe the post-treatment nausea, the more frequent the development of anticipatory nausea. These patients described their post-treatment nausea or vomiting as moderate, severe, or intolerable. In a study of 59 women, Tomoyasu et al. (1996) found that the number of times a woman experienced nausea after the first five cycles was predictive of whether she would experience anticipatory nausea prior to the sixth infusion. This meant that patients with the greatest amount of post-treatment nausea (i.e., reinforcement) were more likely to develop anticipatory nausea.

Morrow and Rosenthal (1996) suggested that individuals with four or more of the personal or treatment characteristics are more likely to develop anticipatory nausea after their first chemotherapy. However, their study also showed that no single characteristic appears to be as clearly associated with the development of anticipatory nausea as two or more together.

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**Figure 2. Factors Associated With the Development of Anticipatory Nausea**

- **Strong association**
  - First cycle of chemotherapy
  - Severity of post-treatment nausea
  - Number of chemotherapy cycles
  - History of motion sickness or nausea with other condition
  - Pretreatment expectations
  - High anxiety

- **Possible association**
  - Age
    - < 45 years—high risk
    - 45–60—intermediate risk
  - Gender: Menopausal females
  - Alcohol use: 0–1 drinks per day associated with increased risk
  - Emetogenesis of chemotherapeutic agent
  - Amount of chemotherapy given

- **No association**
  - Type of cancer
Consequences of Untreated Nausea

Nausea, including anticipatory nausea, is still a problem that, if not managed appropriately, will negatively affect patients’ quality of life. Patients with nausea often are unable or unwilling to eat or drink, which can lead to nutritional deficiencies, dehydration, potentially life-threatening electrolyte imbalances, and changes in the immune system’s ability to function (Edwards, Herman, Wallace, Pavy, & Harrison-Pavy, 1991; Fessele, 1996). In addition, nausea disrupts patients’ daily functioning. Patients may feel that the treatment is not worth the side effects they experience and actually may discontinue therapy. Some studies have suggested the premature termination and noncompliance rate with the prescribed treatment ranges from 19%–59% (Banks, 1991). If the nausea is severe enough, clinicians may delay the scheduled treatment or reduce the dose of the chemotherapy agent (Edwards et al.; Leventhal et al., 1988). In either case, there could be an adverse effect on patient survival (Jenns, 1994).

Anticipatory nausea has psychological and medical significance. It is a major source of emotional upset and distress. It causes thoughts of cancer and the treatment to intrude into the patients’ nontreatment world. These thoughts begin to dominate patients’ daily lives and reduce their control (Leventhal et al., 1988).

Anticipatory nausea does not just strike while patients are waiting in the clinic before their infusions. Many patients experienced anticipatory nausea in their homes as they began to think about their treatment later that day. Other patients have reported that the nausea began as they drove toward the clinic for treatment. Some stated that anticipatory nausea occurred in other places, such as the gas station or grocery store, if they were exposed to the conditioning stimulus (Dobkin, Zeichner, & Dickson-Parnell, 1985).

Treatment of Anticipatory Nausea

Because patients develop anticipatory nausea in response to poorly controlled nausea following chemotherapy administration, it seems reasonable that controlling the acute and delayed nausea would decrease the prevalence of anticipatory nausea. The process of treating or preventing chemotherapy-related nausea is still often one of a trial-and-error approach (Anastasia, 2000). Table 1 contains a summary of several interventions used to treat or prevent nausea and their reported effectiveness.

A clinician’s personal preferences may drive the choice of the antiemetic regimen selected for patients. Many times, a single agent is used to treat almost all patients regardless of how emetogenic the regimen (Johnson, Moroney, & Gay, 1997).

Pharmacologic

Because of the availability of new antiemetics, such as the 5-HT3 antagonists, clinicians are better able to control chemotherapy-related nausea and vomiting. Unfortunately, these medications often control the severity of the nausea and vomiting but not its frequency (Morrow & Rosenthal, 1996). Without adequate antiemetic therapy, 70%–80% of all patients receiving chemotherapy reported experiencing nausea and vomiting (Jenns, 1994). Even with aggressive antiemetic therapy, several studies estimate that 10%–60% of all patients still experience nausea following chemotherapy (Bovbjerg et al., 1992; King, 1997; Morrow & Rosenthal, 1996; Tyc, Mulhern, Barclay, et al., 1997).

The effectiveness of a given antiemetic may decrease over time. In a study of 31 patients after bone marrow transplant, the antiemetic effects of ondansetron decreased from 100% on the first and second days to only 67% effectiveness by day six (Mehta, Reed, Kuhlman, Weinstein, & Parsons, 1997). In another study of 59 patients with cancer, 80% took antiemetics to relieve their nausea, but only 65% reported relief. On average, they rated the effectiveness of their antiemetics as 3.4 on a 1–5 scale. This ineffective treatment of chemotherapy-related nausea predisposes them to the development of anticipatory nausea (Foltz et al., 1996). Although chemotherapy-induced nausea can be treated and perhaps controlled with antiemetics, pharmacologic interventions are not effective once anticipatory nausea develops.

Table 1. Review of Research Studies and Effectiveness of Interventions

<table>
<thead>
<tr>
<th>Researcher(s)</th>
<th>Population</th>
<th>Treatment</th>
<th>Effectiveness</th>
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<tbody>
<tr>
<td>Mehta et al., 1997</td>
<td>31 patients after a bone marrow transplant</td>
<td>Ondansetron versus perphenazine and diphenhydramine</td>
<td>Ondansetron was more helpful, but 33% still reported severe nausea.</td>
</tr>
<tr>
<td>Foltz et al., 1996</td>
<td>59 patients with cancer</td>
<td>Prescribed antiemetics, such as lorazepam and metoclopramide Dietary changes, such as eating less; changing the foods eaten</td>
<td>Only 52% reported relief from nausea. Reported as being mildly effective.</td>
</tr>
<tr>
<td>Morrow, 1984</td>
<td>10 patients with cancer</td>
<td>Systematic desensitization (taped versus live)</td>
<td>Taped relaxation not as effective as live.</td>
</tr>
<tr>
<td>Burish et al., 1987</td>
<td>24 patients with cancer</td>
<td>Progressive muscle relaxation and guided imagery</td>
<td>Experimental group reported significantly less nausea and vomiting than control group.</td>
</tr>
<tr>
<td>Dibble et al., 2000</td>
<td>17 women with breast cancer</td>
<td>Acupressure</td>
<td>Women receiving acupressure reported less frequent and less severe bouts of nausea.</td>
</tr>
</tbody>
</table>
Prevention

Once anticipatory nausea develops, it may persist for years. In interviews with patients who were 6–140 months past all chemotherapy, 63% still reported nausea associated with sights, sounds, tastes, thoughts, and smells that they identified with treatment. This phenomenon did lessen over time; those who were 140 months past treatment reported fewer and weaker episodes of anticipatory nausea than those who were only six months past their treatment (Cella, Pratt, & Holland, 1986).

Nutritional Modification

Patients and family members often institute their own relief measures. Between 25% and 56% changed their dietary intake by eating less, avoiding food smells, eating only crackers, taking only clear liquids, or eating only cold foods. Patients reported that these measures were only mildly effective (Foltz et al., 1996).

Behavioral Techniques

As many as 50% of patients with nausea used rest or keeping busy as a means of relieving their nausea. Many studies have examined the effects of behavioral techniques on the treatment and prevention of anticipatory nausea. Both the frequency and severity have been reduced using these methods. The techniques that have been studied include relaxation, progressive muscle relaxation training, guided imagery, hypnosis, and acupressure (Burish et al., 1987; Dibble et al., 2000; Fessele, 1996; Morrow & Rosenthal, 1996; Pervan, 1990; Tomoyasu et al., 1996; Wickham, 1996).

Another behavioral intervention that has been studied is systematic desensitization. This is the same type of treatment used to help patients overcome fears and phobias. The goal of systematic desensitization is to teach patients to use muscle relaxation rather than nausea as the conditioned response to the chemotherapy. Nurses can be trained to use this technique, but it is time- and labor-intensive to learn and apply (Morrow & Rosenthal, 1996).

In a recent pilot study, Dibble et al. (2000) reported the effectiveness of acupressure. The eight women who were treated with acupressure reported less severe nausea than the nine women in the control group. Acupressure can be used either by the healthcare provider or the patient. It is not as time- or labor-intensive to learn as progressive muscle relaxation.

The effects of behavioral interventions can continue months after the intervention, unlike pharmaceutical interventions that only have an immediate effect. This lingering effect can improve patients’ long-term quality of life (Molassiotis, 1997).

References


Implications for Practice and Research

Nurses play a pivotal role in helping patients manage the side effects associated with chemotherapy treatment. Nurses administer antiemetics, teach patients how and why to take their medications at home, and assess the effectiveness of the medication. In addition, they can instruct patients in the use of behavioral techniques (Rhodes, McDaniel, Simms, & Johnson, 1995).

Morrow et al. (1991b) reported that nurses were as effective in using progressive muscle relaxation as behavioral psychologists. However, because this technique is time-intensive to learn and apply, clinic staffs may not have the time to use this type of intervention for all patients. Instead, patients at highest risk for developing anticipatory nausea should be targeted.

Nurses also are in the position to assess patients to determine whether they are at high risk for developing anticipatory nausea. Those patients at risk should receive aggressive antiemetic therapy and be monitored closely for the onset of acute or delayed nausea. Nurses can and must intercede early and quickly.

Nurses also can affect the amount of anxiety patients experience. Some patients become more anxious if they are placed in a room where they can see other patients receiving their treatment. These patients prefer to be in a private room for their treatments. Others find comfort and support being near patients and family members undergoing the same experience. Nurses must assess this source of anxiety and accommodate patients’ desires as much as possible. Patients’ anxiety also may increase if the medication preparation area is within their line of sight. This increases the amount of conditioned stimuli in the environment (Andrykowski, 1990).

Most studies regarding anticipatory nausea have been conducted by individuals within psychology and behavioral medicine departments. Very little research has been conducted or even reported in the nursing literature. Nurses must study what contributes to the development of anticipatory nausea. Nurses are in a key position to study this long-term phenomenon by virtue of their frequent contact with patients. Nurses also must study the effectiveness of interventions to reduce the prevalence and severity of anticipatory nausea. This ultimately may lead to an increased quality of life and even an increased survival rate for patients with cancer.

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For more information...

- Cancer Consultants: Management of Anticipatory Nausea
  [www.cancerconsultants.com/RxOverview/SupportiveCareOverview/Nausea&Vomiting.htm](www.cancerconsultants.com/RxOverview/SupportiveCareOverview/Nausea&Vomiting.htm)

- Memorial Sloan-Kettering Cancer Center: Anticipatory Nausea

- WebMD: Anticipatory Nausea
  [www.webmd.com/content/dmk/DMK_article_57763](www.webmd.com/content/dmk/DMK_article_57763)

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