Biobehavioral Factors in Chemotherapy-Induced Nausea and Vomiting

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Key Words
Nausea, emesis, chemotherapy, biobehavioral, expectancy

Abstract
Although emesis can be considered a reflex to clear toxins from the body and involves mostly lower brain structures, nausea's purpose appears to be a warning signal to the individual not to engage in behaviors that he or she was doing at the time. As such, it involves the functioning of cognition and memory from higher developed neural structures. Given this, it should not be surprising that biobehavioral factors are important in predicting and controlling nausea. This article reviews the individual characteristics that are clinically useful in predicting which patients will have an increased probability of experiencing nausea or emesis during chemotherapy treatment, and also briefly review psychologic and biobehavioral treatments that can be useful in managing chemotherapy-related nausea. (JNCCN 2004;2:501–508)

Antiemetic medications have provided unqualified benefits to cancer patients. The development of several novel classes of agents over the past three decades has given oncologists the ability to increase both the doses of chemotherapy agents and the types of agents used. However, in many cases, a patient's inability to tolerate nausea and emesis can result in dose reductions and treatment delays, causing a prolonged course of less than optimal chemotherapy. This series of events may challenge successful cure. Such side effects surely contribute to the consistent findings that dose reduction and treatment schedule prolongation are very frequent occurrences in clinical oncology practices.¹

Along with the pharmacologic development of new antiemetic agents has come the realization that these medicines have limitations, especially for the control of nausea. The view that nausea is largely “pre-emesis” is both dated and unsupported by research. Although neurotransmitters such as dopamine and serotonin have been implicated in the development of emesis, there has been no equivalent finding associating any specific neurotransmitter with the onset of nausea.

Neural mechanisms and structures involved in emesis have been fairly well characterized. Interestingly, they involve mostly lower brain structures without general involvement of the cerebral cortex and other areas of higher development. Emesis can be considered a reflex. This is consistent with a view that “lower or old brain” anatomic structures are evolutionary in nature and designed primarily for protection of the species. Certainly, emesis is a first-line physiologic defense to get rid of toxins ingested into the body and has been found in virtually all species except the rat. Even fish experience emesis.

Considerably less is known about the etiology of nausea. Few anatomic structures involved in its occurrence have been identified; none have been conclusively implicated. Nausea is a multidimensional experience that can involve a variety of potential causes, ranging from aberrant motion on the sea, to reproducing the species, or to ingestion of too many celebratory beverages. Nausea's purpose appears to be to alert the individual not to do again what he or she was doing at the time. Therefore, it involves the functioning of cognition and memory from higher developed neural structures.

Given this, it should not be surprising that biobehavioral aspects are important in predicting a patient's response to cancer treatment, in general, and that several
biobehavioral approaches have been found to be clinically useful in the management of these side effects.

This article reviews the individual characteristics that are clinically useful in predicting which patients will have an increased probability of experiencing nausea or emesis during chemotherapy treatment and also briefly reviews psychological and biobehavioral treatments that can be useful in managing chemotherapy-related nausea.

Patient Characteristics Associated With Increased Nausea and Emesis

Table 1 outlines demographic and clinical characteristics shown to predict heightened nausea or vomiting (NV) with chemotherapy. Clearly, the chemotherapy agents given to the patient are the primary determinant of subsequent NV. Virtually 100% of patients given any dose of cisplatin or the combination of adriamycin + cyclophosphamide without an effective antiemetic will vomit. (Unfortunately, many also do so with maximum antiemetic treatment.) Beyond the emetic challenge of the treating agent, however, are established roles for gender, age, and alcohol consumption, along with minor roles for a susceptibility to motion sickness and a history of NV with prior pregnancy.

Women have more NV with the same drugs and dosages than men. This is in line with findings that women are generally more sensitive to any medication than men. Younger patients (generally, younger than 50 years old) experience more NV than older patients. This is usually attributed to a combination of decreasing receptor sensitivity with aging and greater familiarity with NV because of more experience with illness. The third major potential determinant of the probability and severity of NV is prior alcohol consumption. Alcoholics do not generally have much of a problem with chemotherapy treatment. Although both a susceptibility to motion sickness and a history of NV with prior pregnancy may add to possible NV, their contributions are not major. Emerging research suggests that a patient’s expectation that nausea or emesis is likely to occur is a further risk factor that appears to contribute substantially to the development and expression of chemotherapy-related nausea and emesis—especially nausea.

Evidence That Patient Expectation Can Influence the Development of Nausea

Among patients, great variation is seen in the frequency and severity of chemotherapy-induced nausea and vomiting (NV) that cannot be accounted for by pharmacologic properties of the chemotherapeutic agents and the factors previously described, although the extent to which genetic polymorphism in drug handling contributes to these variations has not been fully explored. Understanding patients’ beliefs and expectations, also termed “response expectancies,” about whether or not they will experience NV from chemotherapy helps us to 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; postsurgical pain; resumption of work, and sexual and social activities after coronary artery bypass graft surgery; return to work after a myocardial infarction; and experimentally induced pain.

According to one psychological theory, information (sensory data) will be interpreted through a relevant inherent belief system, meaning that an individual expecting a symptom (such as nausea) will be more likely to interpret sensations as nausea than an individual not expecting the symptom.

Patients receive information about the possibility of nausea from a variety of sources: health care providers, family and friends, and media. Even though a given piece of information may not have been scientifically derived or validated for that particular patient, it may nonetheless be a strong factor in the formation of his or her response expectancy regarding nausea.

<table>
<thead>
<tr>
<th>Table 1 Patient Characteristics Associated with the Development of Nausea and Vomiting</th>
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<tbody>
<tr>
<td>• Age less than 50</td>
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<tr>
<td>• Female gender</td>
</tr>
<tr>
<td>• Susceptibility to motion sickness</td>
</tr>
<tr>
<td>• Expectations of posttreatment nausea</td>
</tr>
<tr>
<td>• History of morning sickness during pregnancy</td>
</tr>
<tr>
<td>• Anxiety (associated with the development of anticipatory nausea)</td>
</tr>
<tr>
<td>• History of heavy alcohol use (decreases likelihood of nausea and vomiting)</td>
</tr>
</tbody>
</table>
Although sometimes contradictory, past studies generally support an association between expectations and nausea. Two groups of researchers have reported that expectations are associated with chemotherapy-related nausea and vomiting,\textsuperscript{12,13} and two other groups partially confirmed these findings by reporting a statistically significant relationship between expectations for nausea and nausea development but not between expectations for vomiting and subsequent vomiting.\textsuperscript{14,15} The association between expectations and chemotherapy-induced nausea does not appear to be dependent on characteristics or consequences of chemotherapy treatment.\textsuperscript{15} Expectations for nausea were assessed before the first treatment in a homogeneous group of 29 subjects with ovarian cancer receiving platinum-containing chemotherapy as hospital inpatients (study 1), and in 81 subjects with a variety of cancer diagnoses treated largely as outpatients (study 2). Figure 1 shows that, in both studies, patients who expected to get nausea had significantly more severe nausea than patients who did not. The relationships remained significant after controlling for emetic potential of the chemotherapeutic agents.

Additional research involving the 63 female cancer patients from study 2 indicated that response expectations may also influence the development of anticipatory nausea (AN).\textsuperscript{16} These patients’ expectations of nausea were assessed before the first treatment on a five-point semantic rating scale anchored at one end by “1” = “I am certain I will not have nausea,” and at the other end by “5” = “I am certain I will have nausea.” Expectations of developing nausea predicted the development of AN (yes/no) before the third cycle of treatment ($P = .001$). None of the women who chose “1” or “2” on the expectations about nausea question developed AN compared with 13% of those who chose “3,” 22% of those who answered “4,” and 55% of those who chose “5.” The latter two categories indicated women who were quite certain they would have nausea. Expecting to experience nausea as a result of chemotherapy was the strongest predictor of AN before the third chemotherapy cycle (Figure 2).

5-HT3 receptor antagonists

Despite a great deal of progress in preventing and controlling chemotherapy-induced nausea, it continues to be commonly reported. Although control of vomiting by the 5-HT3 class of serotonin antagonists has resulted in a minority of cancer patients experiencing vomiting during chemotherapy, nausea continues to be reported by a majority of patients at some time during a course of chemotherapy.

The 5-HT3 receptor antagonists are clinically more effective in controlling emesis, particularly that caused by regimens containing high-dose cisplatin, than previously available agents.\textsuperscript{17,18} Disappointingly, however, these drugs do not appear to be more effective than previous antiemetics in reducing nausea, as indicated...
in the data presented in Table 2. In addition, the 5-HT3 receptor antagonists may become less effective over repeated chemotherapy administrations, and they remain relatively expensive. The most common adverse effects of 5-HT3 receptor antagonists are headache and diarrhea or constipation, which develop in 8% to 20% of patients. These symptoms are generally mild and usually do not lead to patients’ refusal to continue on the medication.

Table 2 shows the prevalence of chemotherapy-related NV in 300 consecutive patients treated in community practices before 5-HT3 receptor antagonists were available (9/87 to 1/91) compared with NV in a second sample of 300 patients treated after the commercial introduction (9/93 to 2/95). Eighty-six percent of the latter patients received 5-HT3 antiemetics and significantly fewer (43.3%) reported one or more episodes of post-treatment vomiting compared with the earlier group of patients (55.0%). Identical numbers in both groups (79.3%) reported at least one episode of post-treatment nausea. In addition, a significant increase in the average duration of both post-treatment nausea (from 28.1 hours to 37.2 hours) and post-treatment vomiting (from 10.9 hours to 16.5 hours) occurred.

A recent study showed the problem of poorly controlled nausea to persist and to be added to by delayed nausea. Three hundred sixty chemotherapy-naive patients (73% women) were enrolled in a study testing the ability of an information intervention to reduce nausea. In the study, 322 subjects completed the Morrow Assessment of Nausea and Emesis (MANE) and a 5-day self-report diary at chemotherapy cycle one (300 at cycle two). All patients received a 5-HT3 receptor antagonist (ondansetron) with dexamethasone on the day of treatment. Results are shown in Table 3.

Seventy-six percent developed nausea during the 5-day period beginning with the cycle-one infusion; 73% reported delayed nausea (DN) during days 2 to 5. Proportions were similar at cycle two, and 55% described their DN as of moderate or greater intensity compared with 28% for acute nausea. Carboplatin was less likely to cause DN than either of the other agents (56% of 106 patients compared with 75% of 47 receiving cisplatin and 83% of 169 taking doxorubicin). Mean peak DN severity was 4.34 (range, 1–7) for doxorubicin, significantly higher than for carboplatin (3.66) but not significantly different from cisplatin (4.26). In the study, 18% did not experience nausea until day three or later.

Despite prophylaxis with ondansetron, the majority of patients receiving one of these common chemotherapy agents experienced nausea. The frequency of DN was nearly twice that of acute nausea. Results show the need for continued development of antiemetics effective against DN. Given the continuing less than optimal control of chemotherapy-induced nausea, several biobehavioral interventions may be

### Table 2 Patient Report of NV Before and After the Introduction of 5-HT3 Antiemetics to Clinical Oncology Settings

<table>
<thead>
<tr>
<th></th>
<th>Pre 9/87-1/91</th>
<th>Post 9/93-2/95</th>
<th>N of cases</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Anticipatory Nausea</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Frequency*</td>
<td>31.0%</td>
<td>32.0%</td>
<td>600</td>
<td>.73</td>
</tr>
<tr>
<td>Duration†</td>
<td>24.6 (33.3)</td>
<td>20.9 (27.8)</td>
<td>169</td>
<td>.44</td>
</tr>
<tr>
<td>Severity‡</td>
<td>2.1 (0.8)</td>
<td>2.0 (0.9)</td>
<td>188</td>
<td>.86</td>
</tr>
<tr>
<td><strong>Anticipatory Emesis</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Frequency*</td>
<td>7.7%</td>
<td>6.3%</td>
<td>600</td>
<td>.52</td>
</tr>
<tr>
<td>Duration†</td>
<td>20.2 (28.1)</td>
<td>23.6 (26.4)</td>
<td>35</td>
<td>.71</td>
</tr>
<tr>
<td>Severity‡</td>
<td>2.5 (1.1)</td>
<td>2.5 (0.9)</td>
<td>42</td>
<td>.92</td>
</tr>
<tr>
<td><strong>Post Rx Nausea</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Frequency*</td>
<td>79.3%</td>
<td>79.3%</td>
<td>600</td>
<td>1.00</td>
</tr>
<tr>
<td>Duration†</td>
<td>28.1 (28.3)</td>
<td>37.2 (29.6)</td>
<td>474</td>
<td>.001***</td>
</tr>
<tr>
<td>Severity‡</td>
<td>2.7 (0.9)</td>
<td>2.7 (1.0)</td>
<td>475</td>
<td>.80</td>
</tr>
<tr>
<td><strong>Post Rx Emesis</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Frequency*</td>
<td>55.0%</td>
<td>43.3%</td>
<td>600</td>
<td>.004**</td>
</tr>
<tr>
<td>Duration†</td>
<td>10.9 (18.1)</td>
<td>16.5 (22.2)</td>
<td>293</td>
<td>.02*</td>
</tr>
<tr>
<td>Severity‡</td>
<td>3.0 (0.9)</td>
<td>3.0 (1.0)</td>
<td>295</td>
<td>.85</td>
</tr>
</tbody>
</table>

n = 300 for each group; standard deviations are in ( ).
* t test for independent samples
† At least one occurrence within the four chemotherapy treatments assessed
‡ Average duration in hours per incident reported by patients
§ Average severity per incident reported by patients measured on a 6 point scale from 1 = mild to 6 = intolerable
* ≤ .05.
** ≤ .01.
*** ≤ .001.
useful to consider as adjuncts to pharmacologic antiemetics.

Behavioral Treatment of Nausea and Vomiting
Although it is apparent that factors such as the pharmacologic properties of chemotherapy agents and stable physiologic characteristics of individual patients (such as autonomic nervous system reactivity) play a large part in the frequency, timing, and severity of nausea and emesis related to chemotherapy, it is equally clear that psychologic and cognitive factors also influence whether, when, and how these symptoms are experienced and perceived. Thus, it should not come as a surprise that research has shown that certain psychologic or behavioral treatments are effective in preventing or mitigating NV caused by cytotoxic chemotherapy.

Progressive Muscle Relaxation Training
Progressive muscle relaxation training (PMRT), in which individuals are taught to practice alternate tensing and relaxing of specific muscle groups in a progressive manner before being placed in situations that induce tension or anxiety, is often combined with guided imagery, in which pleasant, relaxing, soothing scenes or images are visualized to enhance relaxation and increase the antianxiety effect of the procedure. PMRT has been successful in preventing or reducing adverse events that occur after administration of chemotherapy, including post-chemotherapy nausea and vomiting, anxiety, and autonomic arousal. It may also aid in preventing the development of conditioned side effects, including anxiety, and decrease the frequency and severity of conditioned effects that have already occurred.23-27 PMRT has not been effective against established anticipatory nausea and vomiting.28 It is best taught by a professional; merely giving patients written instructions or an audio tape and having them learn the procedure completely on their own was not successful in reducing symptoms in one study.29 Teaching PMRT in a group setting could result in decreased costs, currently an impediment to its clinical use.

Systematic Desensitization
Systematic desensitization (SD), also called counterconditioning, is often used to counteract anxiety-laden maladaptive responses, such as phobias. Individuals are taught to replace a maladaptive response (such as AN) to a stimulus (such as the thought of receiving chemotherapy) with one incompatible with the original response, such as PMRT, and then to associate the new response with the stimulus that initially incited the maladaptive response. A hierarchy of events related to the stimulus of interest is constructed with each individual patient, and the patient is taught to produce the alternative response to this hierarchy of events. In one study, 60 cancer patients who developed AN while undergoing outpatient chemotherapy were randomly assigned to receive SD, counseling, or on intervention. The frequency, severity, and duration of AN decreased significantly, and the frequency and severity of AV were

<table>
<thead>
<tr>
<th>Table 3 Frequency and Severity of Acute and Delayed Nausea and Delayed Vomiting by Chemotherapy Agent</th>
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<tbody>
<tr>
<td>Cycle 1</td>
</tr>
<tr>
<td>Acute (Day 1 at its worst)</td>
</tr>
<tr>
<td>No Nausea</td>
</tr>
<tr>
<td>Mild Nausea</td>
</tr>
<tr>
<td>Moderate Nausea</td>
</tr>
<tr>
<td>Severe nausea</td>
</tr>
<tr>
<td>Vomiting</td>
</tr>
<tr>
<td>Delayed (Days 2–5 at their worst)</td>
</tr>
<tr>
<td>No Nausea</td>
</tr>
<tr>
<td>Mild Nausea</td>
</tr>
<tr>
<td>Moderate</td>
</tr>
<tr>
<td>Severe</td>
</tr>
<tr>
<td>Vomiting</td>
</tr>
<tr>
<td>Cycle 2</td>
</tr>
<tr>
<td>Acute (Day 1 at its worst)</td>
</tr>
<tr>
<td>No Nausea</td>
</tr>
<tr>
<td>Mild Nausea</td>
</tr>
<tr>
<td>Moderate Nausea</td>
</tr>
<tr>
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<td>Vomiting</td>
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significantly lower in the group of patients assigned to receive SD compared with those assigned to the other two programs. \(^\text{5}\) Medical personnel other than clinical psychologists can be taught to administer SD. Although 2 hours of the therapist’s time are required, this time need not coincide with receipt of chemotherapy and can be scheduled separately. \(^\text{30,31}\)

**Hypnosis**

During hypnosis, also called suggestion or trance therapy, a pleasant or relaxed physiologic state incompatible with a maladaptive condition, such as feeling nauseated, is invoked. After the induction of total body relaxation and presentation of restful psychic images, suggestions for specific objectives such as increasing food intake can be introduced. Patients can undergo chemotherapy while in a hypnotic state, and other procedures similar to SD also can be used under hypnosis. \(^\text{32}\) In a few small studies, hypnosis has had some success in reducing the severity of post-chemotherapy nausea and vomiting, and has also been studied for ANV. \(^\text{33-35}\) Cognitive distraction is thought to be the mechanism by which hypnosis exerts its effects, which may help to explain why hypnosis has been most successful with children and adolescents, who are also most responsive to the effects of distraction.

**Cognitive Distraction**

Cognitive distraction (CD) is believed to decrease NV by focusing patients’ attention away from the aversive symptoms and their associated stimuli. CD using video game playing as the distraction has been successful in reducing AN in children receiving chemotherapy, \(^\text{36}\) and in one study of 60 adult patients randomly assigned to receive CD (video games), PMRT, or no intervention, both interventions reduced nausea relative to the control condition. The authors concluded that CD supplies at least part of the mechanism by which PMRT produces its effects on ANV. The efficacy of CD against ANV may decrease over successive cycles of chemotherapy. \(^\text{37}\) Cognitive distraction using video game-playing does not require training or involvement of a medical professional.

**Biofeedback**

With biofeedback training, patients can learn to control a specific physiologic response (such as blood pressure or skin temperature) by receiving moment-to-moment changes in that response. Electro-myographic and thermal biofeedback used in conjunction with PMRT showed promise in reducing nausea of chemotherapy in two pilot studies, but in a later study of 81 patients biofeedback without PMRT did not decrease the frequency of nausea. \(^\text{38}\)

**Exercise**

Physical exercise is a behavioral intervention receiving increased attention in cancer control research, which results in substantial physiologic and psychological changes. A randomized controlled trial of 42 stage II breast cancer patients receiving chemotherapy and assigned to an exercise condition (3 ×/week, WAIT protocol, 10 weeks), a stretching and conversation placebo, or a usual care control showed significant improvements in nausea among the exercising patients, but not among the placebo or control patients. \(^\text{39}\) However, a more recent quasi-experimental one-arm study with 78 breast cancer patients undergoing chemotherapy and assigned to a home-based exercise program (4 ×/week, aerobic activity, 15 to 30 min for 8 weeks) showed no significant changes in nausea. \(^\text{40}\)

Unhappily, behavioral treatments as adjuncts to traditional pharmacologic measures to control nausea and vomiting are not used as often as they would be useful. Patient acceptance may not be optimal, possibly because of popular misconceptions, especially about hypnosis, or cultural factors. Achieving the most satisfactory results often requires that patients spend time practicing the relaxation procedures, a key component of several techniques. To health professionals, they may be seen as somewhat labor intensive and therefore expensive. However, little training is needed to learn the techniques, which require little special equipment. Locating adequate space for behavioral interventions in busy cancer treatment clinics can also be a challenge at times.

Nonetheless, behavioral treatments are always a useful adjunct to consider as part of proper management of chemotherapy nausea.

**References**

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