

system that controls involuntary bodily functions, however specific neural pathways have not been identified for nausea. Vomiting is a reflex, which is controlled by a vomiting center in the brain stem.

The sensation of nausea and vomiting can be elicited by physiological, psychological, and environmental stimuli, such as an adverse drug reaction, post-operative changes during recovery, autonomic dysfunction, gastrointestinal dysfunction, mental stress, pain, smell, taste, motion, traumatic experiences, exposure to toxins, and many other stimuli. The major factors, which determine the incidence and severity of nausea and vomiting in patients receiving chemotherapy include the dose and type of chemotherapy given, treatment schedule, the use of combinations of chemotherapeutic agents, and individual patient characteristics.

Currently, there are several efficacious antiemetic regimens used for the treatment of nausea and vomiting produced by chemotherapeutic agents, such as benzamides and 5-HT₃ antagonists. Use of these antiemetic agents has decreased the incidence and severity of nausea and especially vomiting induced by chemotherapy; however, these agents have not totally eradicated the problem particularly as it relates to nausea. Given that the experience of *any* nausea and vomiting resulting from chemotherapy is undesirable from a modern medical perspective because it may lead to severe medical complications and decreased treatment compliance, as well as diminished quality of life for patients, more efficacious treatment options are needed. For developing more effective treatment options, a through understanding of the etiology of

nausea and vomiting may be helpful. Therefore, the purpose of this article is to review the specific pathophysiology of cancer-related nausea and vomiting, resulting from chemotherapeutic treatments and the etiological role of expectancy and psychological conditioning.

Nature of the problem

Nausea and vomiting caused by chemotherapy are further classified into three time differentiated types, known as anticipatory, acute, and delayed nausea and vomiting. Anticipatory nausea and vomiting occur before the start of a new cycle of chemotherapy, and appear much earlier than normally expected. Acute nausea and vomiting occur within 24 hours after the administration of chemotherapy, while delayed nausea and vomiting occur more than 24 hours after chemotherapy administration and may last several days. Current research indicates that nausea and vomiting are reported by 70–80% of all patients who receive chemotherapy (4). In one study, although vomiting was reported by only about 25% of the patients receiving adjuvant chemotherapy, nausea was reported by as many as 78% of the patients (5). Moreover, anticipatory nausea and vomiting are experienced by approximately 20% of patients during *any* single chemotherapy cycle, and by 25–30% of patients by the start of the fourth chemotherapy cycle (6–10).

Although treatments for nausea and vomiting have significantly improved, these chemotherapy-induced side effects continue to be troublesome, with nausea being far more debilitating for patients than vomiting.

In fact, cancer patients historically ranked nausea and vomiting as the first and second most severe side effects resulting from chemotherapy, respectively (11). However, after the introduction of 5-Hydroxytryptamine-3 (5-HT₃) receptor antagonist, a new antiemetic agent, along with alterations in standard chemotherapeutic regimens, patients reported nausea as the most severe symptom and vomiting fifth (12). Despite advances in treatment, chemotherapy-induced nausea and vomiting can be more distressing for a patient than concerns of life expectancy and have been reported to result in patients choosing to discontinue curative therapy, as well as cause serious associated illnesses (e.g., dehydration) in patients that require hospitalization.

Pathophysiology of nausea and vomiting

Although several effective antiemetics are available, there is no one antiemetic regimen that is effective all of the time. As such, it is plausible that different chemotherapeutic agents cause nausea and vomiting via different mechanisms by acting at different sites, and that some agents may induce nausea and vomiting by more than one mechanism by acting at multiple sites (13). The precise mechanism(s) by which chemotherapy induces nausea and vomiting are not clearly delineated. Chemotherapeutic agents may induce nausea and vomiting by one or a combination of the following mechanisms: (a) activation of the chemoreceptor trigger zone (CTZ) either directly or indirectly; (b) peripheral stimulation of the gastrointestinal (GI) tract; (c) vestibular mechanisms; (d) cortical

mechanisms; as well as (e) alterations of taste and smell. Presently, the most common mechanism is thought to be activation of the CTZ for the majority of chemotherapeutic agents.

Central neurocircuitry, neurotransmitters, and neuropeptides involved in the control of nausea/vomiting

Central neurocircuitry

The area postrema is located on the dorsal surface of the medulla oblongata at the caudal end of the fourth ventricle and is thought to contain a chemoreceptor trigger zone (CTZ) for vomiting. This area is not protected by the blood-brain barrier, and thus, can be reached by emetogenic chemicals via the cerebrospinal fluid or the blood (14). The essential region that coordinates vomiting is located in the brain stem between the levels of the obex and the retrofacial nucleus (just caudal to the facial nucleus). Within this region, the nucleus of the solitary tract (NTS) receives convergent input from different sources that can trigger vomiting, including the vagus nerve, area postrema, and vestibular and limbic systems. In turn, the NTS emits projections to the ventrolateral medulla and dorsal motor nucleus of the vagus. Projections to the ventrolateral medulla may be important for mediating the respiratory motor components of vomiting and those to the dorsal motor nucleus of the vagus for its gastrointestinal components (15). The interaction between this central neurocircuitry and the chemotherapeutic agent appears to be mediated by the release of neurotransmitters.

Neurotransmitters and Neuropeptides

Chemotherapeutic agents prompt the release of various neurotransmitters and neuropeptides, which in turn activate the vomiting center separately or in combination. Although the exact neurotransmitters that are released in the CTZ and vomiting center are not clearly defined, there is strong evidence that dopamine plays a role in mediating vomiting via the dopamine (D_2) receptors. Thus, dopamine D_2 -receptor agonists, such as apomorphine, levodopa and bromocriptine, commonly cause nausea and vomiting, and dopamine D_2 -receptor antagonists, such as metoclopramide, domperidone and haloperidol are effective antiemetics. However, these pharmaceuticals show a high degree of variability in dopamine receptor binding affinity (16). In addition to dopamine, recent studies have identified numerous neurotransmitters and neuropeptides, such as serotonin, histamine, norepinephrine, apomorphine, neurotensin, angiotensin II, vasoactive intestinal polypeptide, gastrin, vasopressin, thyrotropin-releasing hormone, leucine-enkephalin and substance P, which are located in the area postrema of the mammalian brain (17). These newly identified neurotransmitters and neuropeptides may play key roles in the development of chemotherapy-induced nausea and emesis.

The available literature concerning chemotherapy related nausea and vomiting indicates that histamine, and more recently, serotonin and substance P are the main foci of many research studies. Histamine receptors were identified in abundance in the CTZ. Importantly, it was noted that H_1 antagonists, not the H_2 antagonists,

alleviate nausea and vomiting induced by vestibular disorders and motion sickness, but not nausea and vomiting induced by chemotherapy (18). The discovery of serotonin (5-hydroxytryptamine [5-HT]) and its receptors, specifically the $5-HT_3$ receptors, in the CTZ, area postrema, and the gastrointestinal tract has led to the development of $5-HT_3$ receptor antagonists, such as ondansetron and granisetron. These pharmaceutical agents are effective in preventing nausea and vomiting induced by several chemotherapeutic agents, including cisplatin, cyclophosphamide and doxorubicin (19, 20). The role of the 5-HT type 3 ($5-HT_3$) receptor in chemotherapy-induced emesis was recognized by examining the mechanisms of action responsible for the ability of high-dose metoclopramide in decreasing cisplatin-induced emesis. Metoclopramide is a weak antagonist of peripheral $5-HT_3$ receptors. High-dose metoclopramide, unlike other D_2 -receptor antagonists, blocks $5-HT_3$ receptors and is shown to have an exceptionally good capacity to decrease the emesis induced by cisplatin administration (21). The GI tract is the major supply of serotonin in the body, and it has been suggested that perhaps chemotherapy administration causes a release of serotonin from the enterochromaffin cells of the GI tract, which then stimulates emesis via the vagus, greater splanchnic nerve, and the area postrema in the brain. After cisplatin administration, there is an increase in urinary excretion of 5-hydroxyindoleacetic acid, which is the main metabolite of serotonin, and this increase parallels the number of episodes of emesis (19, 22).

Recent evidence supports the notion that

substance P plays a key role in emesis, and that the use of neurokinin 1 (NK-1) receptor antagonists in the management of emesis may be effective. Substance P is a neuropeptide found in the GI tract and the CTZ of the area postrema. Substance P exerts its emetic effects by binding to a specific neuroreceptor, neurokinin 1 (NK-1). The NK-1 antagonists, compounds that selectively block NK-1, demonstrate a wide spectrum of antiemetic effects in the presence of numerous emetic stimuli in animal models. Moreover, these animal studies have demonstrated the antiemetic capabilities of NK-1 antagonists in the presence of several emetic stimuli that are not influenced by serotonin or dopamine receptor antagonists. Preclinical studies have also demonstrated that several NK-1 antagonists are effective in the prevention of both acute and delayed cisplatin-induced nausea and vomiting. A randomized double-blind study demonstrated the beneficial role of NK-1 antagonists in the prevention of delayed emesis (23). These agents may also provide additional benefits in the prevention of acute nausea and vomiting when combined with a 5-HT₃ antagonist and dexamethasone. The addition of the NK-1 antagonist, aprepitant, to standard antiemetics resulted in superior protection against cisplatin-induced nausea and vomiting in 72.7% of 260 patients compared to 52.3% in a standard therapy group of 260 patients (24). Moreover, the protective effect of the drug was persistent over multiple cycles (25).

In addition to histamine, serotonin, and substance P, reports are available that indicate the involvement of several other factors in chemotherapy related nausea/vomiting, such as opioids and arginine

vasopressin. Given that opiate receptors are found in abundance in the CTZ, opiates or enkephalins are thought to possess antiemetic properties. This is supported by the fact that narcotics have mixed emetic and antiemetic effects that are blocked by naloxone (26). Studies to date have shown that opiates can prevent chemotherapy-induced emesis in laboratory animals. However, neither butorphanol nor buprenorphine has proven to be an effective antiemetic in patients who received previous chemotherapy (27). Dexamethasone, which is often combined with the 5-HT₃ agents, is posited to act by reducing arginine vasopressin levels (26), and by the modulation of prostaglandin release (28).

In summary, current evidence suggests that no one neurotransmitter is likely to be responsible for all chemotherapy-induced nausea and vomiting. Presently, it appears that serotonin is particularly important in the pathophysiology of acute vomiting, whereas others may be more important in the pathophysiology of nausea and delayed emesis.

Gastrointestinal and other physiological systems involved in chemotherapy-related nausea and vomiting

Apart from the direct effect on CTZ, chemotherapeutic drugs may induce emesis by peripheral mechanisms that are thought to originate from the upper GI tract. Most likely, these drugs do not directly stimulate the peripheral receptors. Rather, they cause the release of several neurotransmitters, such as serotonin, dopamine, opiate, histamine, and substance P, probably as a result of local GI irritation or damage. The

peripheral effects may be abolished by vagotomy, indicating that impulses from the GI tract may reach the vomiting center via the vagus and sympathetic nerves (29).

Although chemotherapeutic agents induce nausea by acting mainly on the CTZ and the GI tract, there are studies indicating the involvement of the vestibular system and the cerebral cortex. Patients with a history of motion sickness experience a great severity, frequency, and duration of nausea and vomiting from chemotherapy than patients without a history of motion sickness. Thus, it appears that the vestibular system may be involved in chemotherapy-induced emesis. The mechanism by which the vestibular system may lead to chemotherapy-induced emesis is unclear. However, it is postulated that sensory information received by the vestibular system is different from information that was expected, and this sets up a cognitive mismatch that contributes to triggering an emetic response (30).

Additionally, some chemotherapeutic agents, such as cisplatin or gallium nitrate, are known to cause loss of taste sensation or to a metallic taste in the mouth, which may be responsible for the development of nausea and vomiting. Thirty six percent of a series of 45 patients with breast carcinoma who received cyclophosphamide, methotrexate, and 5-fluorouracil reported a bitter taste in their mouth. One-third of the patients thought that the bitter taste caused vomiting (31). The exact mechanism by which taste is altered by chemotherapy is unknown. However, it is thought that while the drugs are in the plasma or saliva, they have a direct effect on the oral mucosa or

taste buds. Changes in taste may contribute both to nausea and vomiting as well as to anorexia. Furthermore, animal studies have shown that nitrogen mustard partially causes emesis via direct stimulation of the cerebral cortex (18). The risk of developing nausea and vomiting is greater when a patient's roommate is experiencing nausea and vomiting. The amount of sleep before receiving chemotherapy is also known to influence whether a patient develops chemotherapy-induced emesis. Another study indicates that there are large differences in the severity and incidence of nausea and vomiting resulting from the same chemotherapeutic agents in different countries (32). These studies suggest the indirect effect of psychological factors on chemotherapy-induced nausea and vomiting.

Finally, most chemotherapeutic agents do not induce emesis in a monophasic way, as do the classic emetic agents and require a latency period emesis begins. Chemotherapeutic agents induce emesis with a delayed onset, and this emesis has a multiphasic time course (33). When managing chemotherapy-induced emesis, one should realize that there is most probably more than one mechanism involved, suggesting that there will not be one antiemetic regimen that will work for all patients all of the time. Although the release of various neuropeptides, along with input from the gastrointestinal system, vestibular system, and the cerebral cortex remain the focal points, the role of autonomic nervous system and hypothalamic-pituitary-adrenal (HPA) axis are also implicated by a substantial amount of research in the development of chemotherapy

related nausea/emesis. Changes in the autonomic nervous system finely regulate the secretory and motor functions of the gastrointestinal tract, which are known to be associated with chemotherapy-related nausea and vomiting.

The role of the autonomic nervous system in the development of nausea

Although the exact mechanism is unclear, the autonomic nervous system (ANS), which is a major link between the CTZ and GI tract, appears to be involved in the development of chemotherapy induced nausea and vomiting. There are numerous reports suggesting the involvement of the ANS in the development of treatment-related nausea and emesis among cancer patients. In a previous study by our research group, we found that a decrease in parasympathetic activity (vagal withdrawal) precedes the report of nausea symptoms (34). This is supported by another study showing an observed strong vagal withdrawal among subjects who reported nausea, as indexed by mean successive differences in heartbeat intervals during exposure to a rotating optokinetic drum (35). Using the same motion sickness simulation paradigm. Uijtdehaage found a decrease in cardiac vagal tone (indexed by Respiratory Sinus Arrhythmia: RSA measures) prior to reports of motion sickness (36). A peak in standard deviation of successive differences in R-R intervals (SDSD), a measure of parasympathetic activity as indicated by heart rate variability was observed just before the onset of nausea which decreases as the nausea ensues (34). We also found a higher percentage of abnormal clinical autonomic function tests in patients who

reported high levels of nausea compared to patients who experienced low levels of nausea (37). It appears that impaired autonomic nervous system function, particularly the parasympathetic system, is associated with the development of chemotherapy-induced nausea.

A likely contributor to a decrease in vagal tone is a change in sympathetic activity (38). The sympathetic efferents, which supply to the heart, are likely to be involved. This division of the ANS seems to be involved, especially in the genesis of other accompaniments of nausea, such as cutaneous vasoconstriction and sweating, resulting in the pale appearance and cold, moist "clammy" skin of nauseated patients (39). Further research is needed to adequately characterize the role of sympathetic activity in the development of nausea.

Hypothalamic-pituitary-adrenal (HPA) axis in the development of nausea

The HPA axis, in general, and cortisol, in particular, has been shown to be involved in the genesis or expression of nausea and perhaps vomiting. Low nocturnal urinary cortisol levels in cancer patients have been associated with a higher level of nausea when compared to patients with a higher level of urinary cortisol (40, 41). Cortisol production follows a circadian rhythm with blood levels being highest from 5 a.m.–9 a.m. and reaching a nadir in late evening. This has been linked to the observation that emesis after platinum is lower when the platinum is given at 6 p.m. than when it is given at 6 a.m. Nausea and vomiting are also clinical signs in patients with

cortisol deficiency (e.g., Addison's syndrome). The steroids, dexamethasone and methylprednisolone, as well as ACTH have all been shown to have antiemetic effects during chemotherapy. Moreover, dexamethasone has an antiemetic effect on post-operative nausea (42). Recently, evidence of a dose-related antiemetic effect from dexamethasone in cancer patients has been reported (43).

Many of the adverse effects commonly associated with chemotherapy are also clinical characteristics of adrenal insufficiency. It is conceivable that chemotherapy drugs may directly or indirectly influence the activity of the hypothalamic-pituitary-adrenal (HPA) axis. A significantly reduced level of serum cortisol was observed immediately following the infusion of either cisplatin or carboplatin, suggesting that the effect is present by the end of the chemotherapy administration (44). Taken together these studies indicate that "low" levels of cortisol are associated with an increased incidence and magnitude of nausea and vomiting and hence endogenous cortisol may be antiemetic. The site and mechanism of action is not known, but reduction in cerebral edema, blood brain barrier permeability, prostanoid turnover and 5-HT₃ metabolism, along with increased endorphin release and modulation of neuronal membrane ion permeability have all been suggested (42).

Role of psychological conditioning in anticipatory nausea and vomiting (ANV)

Chemotherapy treatment typically involves having patients come to a clinic for administration of cytotoxic drugs every

2 to 4 weeks over a period of several months. After repeated experience of post-infusion nausea, some patients begin to experience nausea in the clinic even before the start of infusion. This anticipatory nausea and vomiting occur before treatment as a response to other triggers in the environment (e.g., certain objects, odors, or tastes). For example, a person who begins chemotherapy and smells an alcohol swab at the same time may later experience nausea and vomiting because of the smell of alcohol alone. Smells are more likely to trigger nausea, while thoughts of the treatment will trigger vomiting. The symptoms may occur outside the hospital, in the clinic, when talking about chemotherapy, or when patient perceives special tastes or odors.

Not all patients receiving chemotherapy experience nausea and/or vomiting before or during chemotherapy. The prevalence of anticipatory nausea and vomiting varies, depending on the study cited and whether nausea and vomiting are analyzed separately. Usually, the pattern of anticipatory nausea and vomiting is set by the third course of treatment. The incidence of ANV increases with repeated chemotherapy cycles. The trend appears to be linear and increasing. The prevalence of anticipatory nausea among patients receiving chemotherapy ranges between 14% and 63%, with a median of 33%. By the fourth cycle, approximately 20–50% of patients experience anticipatory side effects (8). While the control of posttreatment emesis has significantly improved, the incidence of anticipatory emesis has been shown to decrease and recently has been reported to be less than 10% (45).

Psychological mechanisms involved in anticipatory nausea/vomiting

Anticipatory nausea and vomiting always involve a psychological mechanism in that they are triggered by events that are not secondary to the direct administration of the chemotherapeutic agent itself. The specific characteristics of ANV suggest that its mechanisms might fit within a learning model (46, 45). Several studies have confirmed that the development of ANV involves elements of classical conditioning.

In the learning model, initially the unconditioned stimulus (chemotherapy drugs) produces an unconditioned response of nausea/vomiting. Over several trials (chemotherapy cycles), the conditioned stimuli (e.g., environmental cues such as seeing the nurse, hearing a sound, a specific smell, thoughts of the clinic) become associated with unconditioned stimulus (administration of chemotherapy drugs), and then begin to trigger the classical response of ANV. There is a plethora of evidence in support of this model. Current research indicates that ANV do not develop without a prior experience of post-treatment side effects, conditioning is more successful with a greater number of learning trials, and the increased severity of post-treatment side effects facilitates conditioning. These findings parallel classical conditioning theory, which states that conditioning is facilitated by increasing the intensity of the stimulus and a greater number of learning trials. Additionally, psychological factors such as trait anxiety and expectations of nausea appear to be involved in the development of ANV (47). There are several correlates and determinants of anticipatory

nausea/vomiting (see Table I). These factors contribute to the development of ANV by facilitating the conditioning process directly or indirectly by increasing the intensity of post-treatment nausea and vomiting (45, 46).

TABLE I: Correlates and determinants of anticipatory nausea/vomiting.

<i>Chemotherapy-associated factors</i>	<i>Patient characteristics</i>
<ul style="list-style-type: none"> • Type of chemotherapy (some are more likely to cause nausea and vomiting) • Sweating after the last chemotherapy • Feeling warm or hot after the last chemotherapy • Feeling dizzy or lightheaded after chemotherapy • Severity of nausea and vomiting after the last chemotherapy • Number of chemotherapy courses received long treatment infusions 	<ul style="list-style-type: none"> • Being female • Experiencing strange tastes during chemotherapy • Being younger than 50 years old • Having a high level of anxiety • A history of alcoholism • A history of motion sickness • Having distress, mood disorders, or a limited ability to cope • Having an active imagination

Numerous studies have revealed a relationship between severe post-chemotherapy side effects and the development of anticipatory nausea and vomiting (46). Although the occurrence and severity of post-chemotherapy nausea and vomiting are related to the emetogenicity (48) of the chemotherapeutic agents and to the length of chemotherapy (49, 50), they may be modified by individual patient characteristics, such as a history of motion

sickness and age. The schedule of chemotherapy also appears to be related to anticipatory symptoms. In addition, feeling warm or hot, as well as sweaty or generally weak after the previous chemotherapy infusion have all been associated with a greater likelihood of experiencing ANV.

Furthermore, motion sickness is a risk factor for the development of post-chemotherapy nausea and vomiting (30). We found a significant relationship between a history of motion sickness and anticipatory nausea and vomiting (46, 51). In some studies, age appears to be related to anticipatory symptoms. Anticipatory nausea and vomiting occur more often in patients younger than 45 years of age (48). It is possible that age is related to anticipatory symptoms in part, because younger patients receive stronger emetogenic chemotherapeutic agents, which may lead to increased post-chemotherapy nausea and vomiting, and therefore, increased anticipatory nausea and vomiting. Another proposed explanation is that younger patients have a higher level of anxiety while receiving chemotherapy, which may lead to increases in anticipatory symptoms. Anxiety just before a chemotherapy appointment has been associated with an increased tendency to develop ANV. Although anxiety may not be the only factor, it may speed up the development of anticipatory nausea and vomiting when other factors are present. Anxiety could also promote conditioning by enhancing fear of chemotherapy or increasing the salience of potential conditioned stimuli.

Other factors that have been reported to be related to anticipatory nausea and

vomiting include patient expectations. Several reports suggest that patients' pre-treatment expectations about developing nausea from chemotherapy can predict the occurrence of AN. Type and stage of cancer are also related (52). Cognitive factors seems to act independent of conditioning in the development of AN. Neuropathways from the limbic system and cerebral cortex support a role for cognitive involvement in nausea development and provide plausible explanations for how expectations could affect nausea. Patients' expectations play a larger role than conditioning in AN that occurs early in the course of cyclic chemotherapy (7), whereas the role of conditioning appears to become stronger as the number of infusions increases (53).

Antiemetics used in the treatment of acute nausea and vomiting induced by chemotherapy are ineffective in treating anticipatory nausea and vomiting. Many studies have indicated that behavioral techniques are effective in reducing anxiety, as well as reducing or eliminating anticipatory nausea and vomiting. Behavioral techniques that have been studied and found to be effective include progressive relaxation with guided imagery, systematic desensitization, hypnosis, and cognitive and intentional distraction (54-56). There is a study in which change in taste sensations produced by chemotherapy was masked by giving a lemon solution to a patient before the receipt of chemotherapy so that the patient experienced decreased anticipatory nausea and vomiting (57). Role of benzodiazepines, especially lorazepam, may be helpful in treating anticipatory nausea and vomiting, but this needs further investigation.

To summarize, it appears that nausea and vomiting continue to be worrisome side effects of chemotherapy in cancer patients. The majority of chemotherapeutic agents seem to induce nausea via activation of the CTZ through release of various neurotransmitters and neuropeptides like dopamine, serotonin, histamine, substance P, and others. Individual patient characteristics and psychological factors make a significant contribution to the development of nausea, particularly anticipatory nausea. Although introduction of the 5-HT₃ antagonist considerably reduced the incidence of chemotherapy induced vomiting, it remains

expensive for patients and is not effective all of the time. Clearly, there is a need for a better understanding of the modifiable physiological and psychological factors responsible for the development of these side effects. Such understanding will be helpful in designing pharmacological and non-pharmacological behavioral treatments for the management of these side effects. This is especially true for anticipatory nausea/vomiting, where the currently available antiemetics are ineffective, as well as, in conditions where antiemetics like 5-HT₃ antagonist become less effective, such as over repeated chemotherapy administrations.

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