CONTINUING EDUCATION

EDUCATIONAL OBJECTIVES

After participating in this activity, clinicians should be better able to

- Describe the physiologic mechanisms of chemotherapy-induced nausea and vomiting (CINV)
- List three actions that can help to manage CINV
- Describe three CAM modalities that are helpful in managing CINV

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Despite high-level studies showing that olanzapine (Zyprexa) has effectiveness against CINV, it is not FDA approved for this use.

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Approaches to chemotherapy-induced nausea and vomiting

Donald R. Fleming, MD

STATEMENT OF NEED/PROGRAM OVERVIEW

Even though a number of new antiemetic drugs have become available in the past two decades, chemotherapy-induced nausea and vomiting (CINV) remains among the top three complaints of patients undergoing chemotherapy. Excellent progress has been made in the prevention of acute-onset CINV, but delayed CINV remains a problem. Nurses should understand the various medications available and be aware of the underlying pharmacology of these drugs in order to manage CINV most successfully.

CE INFORMATION

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Free continuing nursing education credit of 0.75 in pharmacology is available. After reading the article, go to mycme.com to register, take the posttest, and receive a certificate. A score of 80% is required to pass.

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Target audience: This activity has been designed to meet the educational needs of registered nurses and nurse practitioners involved in the management of patients with cancer.

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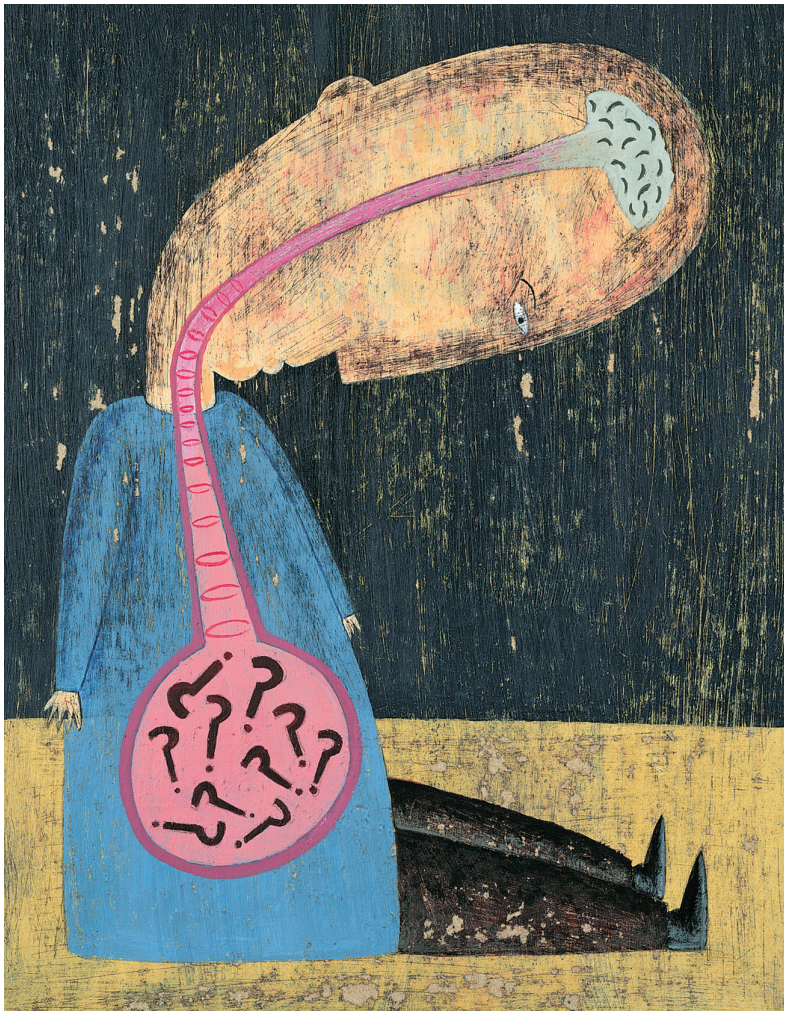
Approaches to chemotherapy-induced nausea and vomiting

Our ability to prevent acute CINV has improved greatly as a result of drugs that inhibit 5HT-3 and substance P, but delayed CINV remains a problem.



GETTY IMAGES

DONALD R. FLEMING, MD

In addition to fatigue and alopecia, nausea and vomiting are among the most common side effects experienced by patients undergoing chemotherapy. These patients are concerned not only about the practical issues related to nausea and vomiting—such as weight loss and the so-called cancer wasting syndrome—but also that poor nutrition can worsen fatigue, the most widespread complaint in those undergoing chemotherapy. Patients often claim that one of the worst things about nausea is that it takes away from the pleasure of eating, an activity that is frequently involved in socializing with family and friends.[1,2] The effective management of chemotherapy-induced nausea and vomiting (CINV) is essential to helping patients to get through cancer treatment. Current guidelines are available from the National Comprehensive Cancer Network (NCCN) at www.nccn.org/professionals/physician_gls/PDF/antiemesis.pdf.

UNDERSTANDING CINV

The nausea and vomiting associated with chemotherapy takes three clinical forms: acute, delayed, and anticipatory.[3,4]

- **Acute** nausea and vomiting occurs within 24 hours after the chemotherapy treatment, with a peak period anywhere from 1 to 6 hours after treatment. Before the 5HT-3 receptor antagonists became available, acute chemotherapy-

induced nausea and vomiting was a major event in the chemotherapy infusion suite, and patients were routinely handed emesis basins to manage the experience.

- **Delayed** nausea and vomiting usually occurs at least 24 hours after the chemotherapy has been administered. This form of CINV occurs more often in patients receiving cisplatin (Platinol, generics), carboplatin (Paraplatin, generics), or higher doses of alkylating agents such as cyclophosphamide (Cytoxan, generics).
- **Anticipatory** nausea and vomiting is a conditioned psychological response to past chemotherapy treatment. For some patients, for example, simply seeing their chemotherapy nurse outside the health care setting, or driving past the cancer treatment center, can trigger the onset of the nausea and vomiting.[3,4]

EFFECTIVE THERAPIES FOR CINV

Major improvements in the pharmacologic management of nausea and vomiting have occurred over the past two decades. The extensive use of 5HT-3 receptor antagonists has had a huge impact on reducing acute CINV. Despite our ability to prevent most chemotherapy patients from experiencing acute nausea and vomiting, delayed CINV remains a major challenge. This form of nausea and vomiting has been the primary focus of pharmaceutical industry research of late.[2,3]

Stimulation of neurotransmitter receptors in both the central nervous system (CNS) and the gastrointestinal (GI) tract is the cause of both delayed and immediate-onset chemotherapy-induced nausea and vomiting. The medulla in the brain contains an area known as the chemoreceptor trigger zone, or CTZ. The rich blood supply provided to this area brings the chemotherapy agent to the scene and induces the episode of CINV. The CTZ contains dopamine, serotonin, and substance P receptors. Outside the CNS, the GI tract also has serotonin and substance P receptors.[1-3]

Dopamine The antiemetics used in the past have worked primarily to block dopamine receptors. These agents include the phenothiazines, including promethazine, chlorpromazine (Thorazine, generics), and prochlorperazine (Compazine, Compro, Procomp, generics); the benzamide metoclopramide (Metozolv ODT, Reglan, generics); and butyrophenones such as haldoperidol (Haldol, generics) and droperidol (Inapsine, generics).

Serotonin In the early 1990s, 5HT-3 antagonists, which act as serotonin receptors, became commercially available. There are four FDA-approved agents available in the United States: dolasetron (Anzemet), granisetron (Kytril, Sancuso), ondansetron (Zofran), and palonosetron (Aloxi). Two of these—palonosetron and the granisetron transdermal patch (Sancuso)—are indicated for prevention of delayed CINV.[3-5]

TABLE 1. Managing CINV

Emesis potential	Acute-onset CINV	Delayed-onset CINV	Refractory CINV
High to moderately high[a]	5HT-3 antagonist plus corticosteroid plus aprepitant	Aprepitant plus corticosteroid	Add olanzapine or CAM technique, or ultimately change treatment
Moderately low to low[b]	5HT-3 antagonist or corticosteroid	Not typically indicated	Elevate intervention as indicated for high to moderately high risk

[a] Platinum, higher doses of alkylating agents, and/or combination regimens
[b] Single agents not including platinums, especially at lower, more fractionated dosing regimens

The granisetron patch should be applied at least 24 hours prior to initiating chemotherapy to ensure adequate bioavailability of the medication.

Clinical trials of subcutaneous and inhaled forms of 5HT-3 antagonists have been conducted to see if these new formulations might contribute to prolonging the effects of the medication. While studies of the transdermal delivery of granisetron have led to the approval of Sancuso, the inhaled/intranasal preparations completed phase I trials in early 2010 and results are pending publication.[5]

Substance P The third CNS receptor in the CTZ is triggered by substance P, also referred to as neurokinin. This receptor, which also exists in the GI tract, is believed to play a major role in delayed nausea and vomiting. While other agents are in the advanced clinical stage of testing, aprepitant (Emend) is the only substance P antagonist currently FDA-approved to prevent delayed nausea and vomiting. Recent in vitro and in vivo studies have suggested that the 5HT-3 antagonist palonosetron also inhibits neurokinin by way of cross talk between the 5HT-3 and substance P receptors.[4,5]

Planning for prevention When treatment decisions are being made, the emetogenicity of the desired chemotherapy regimen should be evaluated, and plans should be made for how to prevent CINV using the smallest number of medications needed to achieve a good result. Keep in mind that the more chemotherapy agents involved in a patient's regimen, the greater the risk for chemotherapy-induced nausea and vomiting **(Table 1)**. Alkylating agents, especially platinum-based, and drugs used in higher dosages also increase risk. A patient receiving a low emetogenic regimen can be treated using a 5HT-3 antagonist alone. As regimens become more emetogenic, glucocorticoids such as dexamethasone (Decadron, generics) can be added to the 5HT-3 antagonist to increase their effectiveness against acute-onset CINV.

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With the more emetogenic regimens, delayed nausea and vomiting becomes an issue; and aprepitant, which acts on substance P-triggered receptors, can be added to the prevention regimen.[4,6]

Olanzapine A recent study by the Hoosier Oncology Group demonstrated that when the antipsychotic medication olanzapine (Zyprexa) was added to the standard intervention of glucocorticoids, benzodiazepines, and palonosetron, both the acute and delayed components of CINV were better controlled than when standard therapy was given.[7] Olanzapine has been found to interact with both 5HT-3 and dopamine receptors. This dual inhibition has also been seen with metoclopramide, but only when metoclopramide is used at dosages high enough to cause major CNS side effects. The dosage utilized in the previous trial was 10 mg orally daily for 2 to 4 days and starting the day of the chemotherapy.

Dietary supplements that contain ginger root may significantly reduce episodes of nausea and vomiting in chemotherapy patients.

Dronabinol Another medication often used to prevent and treat CINV is dronabinol (Marinol, generics). This cannabinoid medication was developed as a result of observing the effects of marijuana, especially in increasing appetite. Dronabinol not only reduces CINV, it also improves the patient's interest in eating. A major disadvantage, especially in elderly patients, is that the medication can cause dysphoria.[8]

Anticipatory nausea and vomiting This condition is considerably less common than it used to be, primarily because the 5HT-3 antagonists have had a major effect on reducing acute CINV. When anticipatory nausea and vomiting do occur, they are best managed with benzodiazepines such as lorazepam (Ativan, generics).[1,3]

CAM TECHNIQUES

In addition to highly scrutinized and ultimately FDA-approved pharmacologic agents for chemotherapy-induced nausea and vomiting, some less regulated and several less rigorously researched complementary and alternative medicine (CAM) interventions have demonstrated modest success. Not much is known about the use of CAM therapies for cancer, and finding scientific evidence that a particular CAM therapy is or is not effective is challenging. Pharmaceutical companies have little financial incentive to study these treatments; as a result, research must be done using limited government and privately funded resources.

Ginger Recently, a phase II/III study demonstrated that dietary supplements made from ginger root (Zingiber officinale) significantly reduced episodes of nausea and vomiting in chemotherapy patients.[9] This placebo-controlled, double-blind clinical trial included more than 600 patients with a history of chemotherapy-induced nausea. As part of the study, each patient received three or more additional cycles of the chemotherapy they had previously received at University of Rochester-affiliated community clinical oncology program member sites. Beginning before the chemotherapy and continuing afterward, patients received one of four different treatment doses of ginger; in addition, on the day of treatment, they received a 5HT-3 receptor antagonist. While all four dosage levels of ginger reduced CINV, dosages of 0.5 g and 1 g daily had the most effect.[9]

While an alternative intervention such as ginger would seem harmless, caution is still warranted as ginger can interact with certain medications, such as warfarin (Coumadin, generics). The potential for interactions should be investigated carefully for each patient.

Acupuncture and massage Other complementary and alternative medicine interventions have also demonstrated some limited success in reducing nausea and vomiting in patients receiving chemotherapy, in addition to improving fatigue and complaints related to neuropathy. In particular, acupuncture has been used to alleviate some of the side effects associated with chemotherapy administration.[10] Massage therapy has also been shown to improve symptoms such as nausea, vomiting, and fatigue.[11]

Interventions such as ginger, acupuncture, and massage can typically be used in patients receiving chemotherapy without fear that they will interfere with standard medical efforts to control CINV using available drugs. If a patient's nausea and vomiting prove to be refractory, additional outpatient visits for hydration and possibly hospitalization may be required. Very severe symptoms may require alterations to therapy in order to protect the patient's quality of life.

More information about CAM interventions is available through the National Institutes of Health's National Center for Alternative and Complementary Medicine (http://nccam.nih.gov) and particularly from the Cancer and CAM page (http://nccam.nih.gov/health/providers/digest/cancer.htm). Information is available for patients as well as for health care professionals. In addition, the *Journal for the Society of Integrative Oncology* published a clinical practice guideline on CAM in 2009.[12]

CONCLUSION

CINV has become much more preventable as a result of the availability of drugs that inhibit 5HT-3 and substance P. Some CAM techniques have also been studied and shown to have effectiveness for some patients. Despite these advances, however, delayed CINV remains a difficult problem and a focus of continued research. ■

Donald Fleming is an oncologist at the Cancer Care Center, Davis Memorial Hospital, Elkins, West Virginia, and a member of the *Oncology Nurse Advisor* editorial board.

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