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# Recent Advances in the Management of Chemotherapy-induced Nausea and Vomiting: A Post-MASCC 2009 Discussion

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## Abstract

Chemotherapy-induced nausea and vomiting (CINV) is a common but debilitating side effect of anticancer therapy. Acute, delayed, and anticipatory CINV can require different approaches, and there have been advances in the prevention of acute CINV in recent years. 5-$HT_3$ and NK-1 receptor antagonists are effective in the prevention of nausea and emesis. Corticosteroids, dopamine receptor antagonists, and cannabinoids have also been introduced in this setting. Clinical guidelines for the management of CINV have been promulgated by the National Comprehensive Cancer Network, the American Society of Clinical Oncology, and the Multinational Association of Supportive Care in Cancer. The etiology of CINV and risk classifications; various treatment approaches, including their mechanisms of action, efficacy findings, and safety issues; and the treatment guidelines are discussed.

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## Target Audience

This activity has been designed to meet the educational needs of hematologists and oncologists involved in the management of patients with chemotherapy-induced nausea and vomiting (CINV).

## Statement of Need/Program Overview

Advances in the treatment of cancer patients with CINV have improved response rates and quality of life outcomes dramatically. In order to maintain and further these advancements, it is essential that cutting-edge medical developments be communicated as effectively and efficiently as possible in order to optimize patient care.

## Educational Objectives

After completing this activity, the participant should be better able to:

1. Describe the importance of new study findings and clinical trial data in the treatment of CINV in cancer patients.
2. Assess the results of these new study findings including updates on guidelines for highly and moderate emetogenic chemotherapy and radiotherapy.
3. Discuss how to integrate the latest knowledge and methods for treating cancer patients with CINV into clinical practice in an effort to improve current quality of life.
4. Identify future research directions for all therapies in CINV in cancer patients.

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# Overview

Chemotherapy-induced nausea and vomiting (CINV) is one of the most common, yet most debilitating, side effects of cancer therapy. Clinical consequences of CINV can include severe dehydration, metabolic imbalances, nutrient depletion, anorexia, wound dehiscence, and esophageal tears.[1] CINV is also one of the most distressing side effects for patients receiving chemotherapy: patients rank nausea and vomiting first and third, respectively, among their chemotherapy fears.[2,3] Moreover, CINV can result in the discontinuation of potentially beneficial or curative cancer treatments.[4]

The timing of symptom onset is an important consideration in CINV management. Acute CINV occurs in the first 24 hours following chemotherapy. Delayed CINV persists after the first 24 hours or develops only after the first 24 hours. The third type of CINV, anticipatory vomiting, occurs in the time before chemotherapy is administered, typically between cycles.

Significant progress has been made in recent years in the prevention of CINV, particularly in the acute phase. The development of effective therapies, including the serotonin ($5\text{-}HT_3$) receptor antagonists and the neurokinin-1 (NK-1) receptor antagonists, has dramatically diminished the incidence and severity of CINV. Various clinical guidelines have been developed for the management of CINV, based on strong empirical evidence and, in some cases, on expert opinion. By following these guidelines, clinicians can minimize the risk of CINV.

Despite these advances, a significant proportion of patients do not attain complete control of CINV with available therapies. A 2007 study of 151 patients showed that 67% of patients undergoing a new chemotherapy regimen developed CINV: 31% of patients only in the delayed phase, 8% only in the acute phase, and 28% in both phases.[5] Ongoing research is continuing to investigate new approaches in order to gain greater control over this significant side effect.

## References

1. National Comprehensive Cancer Network. Clinical Practice Guidelines in Oncology: antiemesis. V.4.2009. December 15, 2009.
2. Sun CC, Bodurka DC, Weaver CB, et al. Rankings and symptom assessments of side effects from chemotherapy: insights from experienced patients with ovarian cancer. *Support Care Cancer.* 2005;13:219-227.
3. de Boer-Dennert M, de Wit R, Schmitz PI, et al. Patient perceptions of the side-effects of chemotherapy: the influence of 5HT3 antagonists. *Br J Cancer.* 1997;76:1055-1061.
4. Richardson JL, Marks G, Levine A. The influence of symptoms of disease and side effects of treatment on compliance with cancer therapy. *J Clin Oncol.* 1988;5:1746-1752.
5. Cohen L, de Moor CA, Eisenberg P, Ming EE, Hu H. Chemotherapy-induced nausea and vomiting: incidence and impact on patient quality of life at community oncology settings. *Support Care Cancer.* 2007;15:497-503.

# Guidelines for the Management of Chemotherapy-induced Nausea and Vomiting

Gary R. Morrow, PhD, MS

## Guidelines for the Prevention of CINV

The management of chemotherapy-induced nausea and vomiting is a clinical area in which guidelines are particularly helpful. Because clinical trials in CINV are evaluating a defined circumstance—the benefit of various antiemetic approaches in patients undergoing chemotherapy—there is less heterogeneity in these trials than in therapeutic clinical trials, which inherently carry more variability due to differences in the diseases being treated. Therefore, the clinical evidence for CINV treatment guidelines is largely strong, and clinicians should adhere closely to these guidelines.

Multiple organizations have published CINV management guidelines, including the Multinational Association for Supportive Care in Cancer (MASCC), the American Society of Clinical Oncology (ASCO), and the National Comprehensive Cancer Network (NCCN).

One important concept of CINV management across all guidelines is that prophylaxis, rather than treatment, should be the focus (Table 1). It is much more difficult to control symptoms once they develop. Thus, although it may seem economically attractive to start with the most affordable antiemetic treatment and progress to more expensive combination regimens if needed, this approach is flawed. Treating uncontrolled nausea and vomiting requires substantially more time, effort, and expense than does active prevention. CINV guidelines are therefore based on the notion that clinicians should start with the most effective agents possible.

The degree of control of CINV is an important issue in determining the optimal antiemetic prophylaxis. Although symptom severity certainly affects patients' quality of life, the biggest change in quality of life is noted when patients progress from having no CINV to reporting any degree of CINV. Thus, complete control, defined as an absence of vomiting and no requirement for rescue medications for nausea, should be the goal of CINV prophylaxis.

**Table 1.** Pharmacologic Agents to Prevent CINV

- Corticosteroids
- Dopamine antagonists
- Serotonin (5-HT3) antagonists
- NK-1 receptor antagonists
- Cannabinoids

## Antiemesis Guidelines

Given its focus on supportive care in cancer, the MASCC was well poised to propose the first guidelines for the prevention of CINV. This multinational group brought together investigators and diverse clinicians from around the world to present and evaluate data on the management of CINV. Based on the literature and on expert opinion in the case of insufficient data, these experts then published the first MASCC Antiemetic Guidelines in 1998.[1] One year later, ASCO convened a group of experts (many of whom had participated in drafting the MASCC guidelines) to develop recommendations for the use of antiemetics.[2] Other organizations have since developed antiemetic guidelines, including NCCN[3] and the Oncology Nursing Society (ONS; www.ons.org).

Although there is some overlap between the guidelines, they are not identical. Several factors account for these differences. First, each iteration of a guideline represents a snapshot in time, as it draws upon the body of literature available when those guidelines are developed. As additional data become available, there may be modifications to the recommended regimens, dosages, or administration. Second, the clinical experiences of the experts involved in drafting the guidelines also help shape the recommendations.

These guidelines provide solid recommendations for practicing clinicians. However, they should not be regarded as rules, given the evolving nature of the field and the different perspectives of clinicians developing the guidelines.

## References

1. Antiemetic Subcommittee of the Multinational Association of Supportive Care in Cancer (MASCC). Prevention of chemotherapy- and radiotherapy-induced emesis: results of Perugia Consensus Conference. *Ann Oncol.* 1998;811-819.
2. Gralla RJ, Osoba D, Kris MG et al. Recommendations for the use of antiemetics: Evidence-based, clinical practice guidelines. American Society of Clinical Oncology. *J Clin Oncol* 1999;17:2971-2994.
3. National Comprehensive Cancer Network. *Clinical Practice Guidelines in Oncology: antiemesis*. V.4.2009. December 15, 2009.

# Overview of Antiemetic Agents

Susan G. Urba, MD

The past 20 years have yielded dramatic advances in the management of chemotherapy-induced nausea and vomiting. We now understand that chemotherapy can stimulate nausea and vomiting through peripheral mechanisms in the intestines and centrally in the brain. By targeting both of these pathways, we can attain greater protection against CINV.

## Mechanisms of Action of Antiemetic Agents

### *Serotonin Receptor Antagonists*

In 1986, Miner and Sanger first reported the role of the serotonin (5-$HT_3$) receptor in the development of chemotherapy-induced vomiting.[1] Subsequent investigations revealed that chemotherapy induces vomiting peripherally by stimulating the enterochromaffin cells, causing release of serotonin. Serotonin then binds to 5-$HT_3$ receptors, leading to stimulation of the vagus nerve. This stimulus travels to the brain, where it is perceived centrally, leading to stimulation of the dorsal vagal complex. The area postrema, a component of the dorsal vagal complex, serves as a chemoreceptor trigger zone for vomiting.[2] The 5-$HT_3$ receptor antagonists interfere with the binding of serotonin to its receptor, thus preventing the stimulation of the area postrema.

### *NK-1 Receptor Antagonists*

Imaging studies showed that the binding of substance P to neurokinin-1 (NK-1) receptors in the central nervous system is also involved in the development of CINV.[3] These studies revealed the NK-1 receptor as an attractive target for antiemetic therapy.

### *Dexamethasone*

The mechanism of action of dexamethasone is not well understood. However, it provides an efficacy benefit when added to an antiemetic regimen containing a 5-$HT_3$ receptor antagonist.[4] Omission of dexamethasone from the regimen often leads to failure to attain adequate CINV control.

## Efficacy of Antiemetic Therapy

The mainstay of prevention of CINV from highly emetogenic chemotherapy is a serotonin receptor antagonist, an NK-1 receptor antagonist, and dexamethasone. The 5-$HT_3$–receptor antagonists are primarily effective in preventing acute CINV, with no efficacy differences noted among the four first-generation agents, dolasetron, granisetron, ondansetron, and tropisetron.[5] The second-generation 5-$HT_3$–receptor antagonist palonosetron is characterized by a different molecular structure from the first-generation agents in this class, with a fused tricyclic ring system conjugated to a quinuclidine moiety. This agent has a longer half-life and greater receptor binding affinity.[6] A single dose of intravenous palonosetron was found to be superior to dolasetron in preventing delayed emesis in a randomized trial.[7]

The addition of an NK-1 antagonist to 5-$HT_3$ receptor antagonists and dexamethasone has been shown to improve efficacy in both acute and delayed CINV.[8] This agent, aprepitant, is available in oral form and a recently released intravenous infusion. Dexamethasone has been tested in numerous randomized trials, in which the patients were treated with a serotonin antagonist with or without dexamethasone. In virtually every instance, the addition of dexamethasone gave a superior outcome.[9]

## Safety Issues with Antiemetic Agents

As a group, antiemetic agents are well tolerated; patients rarely complain about side effects. This development represents an improvement over the earlier antiemetics such as metoclopramide, which was associated with various side effects, including a rare risk of dystonic reactions.[10] The most common side effects with the 5-$HT_3$ receptor antagonists are headache, constipation, and, rarely, other effects including dizziness.[11] NK-1 receptor antagonists are also associated with some side effects, though these are generally mild to moderate and not clinically relevant. Reported adverse effects include asthenia/fatigue, constipation, diarrhea, and dizziness.[12]

Dexamethasone is associated with a variety of side effects, usually with repeated dosing over longer periods of time. However, even short-term administration of dexamethasone can be associated with various effects, including cognitive disturbances, increased appetite, stomach upset, and fluid retention. Cannabinoids are used more rarely for nausea and vomiting. The most common adverse event associated with cannabinoids is dizziness.[13] Many older patients

have difficulty tolerating the disorientation that can arise with these agents.

## References


1. Miner WD, Sanger GJ. Inhibition of cisplatin-induced vomiting by selective 5-hydroxytryptamine M-receptor antagonism. *Br J Pharmacol*. 1986;88:497-499.
2. Miller AD, Leslie RA. The area postrema and vomiting. *Front Neuroendocrinol*. 1994;15:301-320.
3. Hargreaves R. Imaging substance P receptors (NK1) in the living human brain using positron emission tomography. *J Clin Psychiatry*. 2002;63 (suppl 11):18-24.
4. Perez EA. Use of dexamethasone with 5-HT3-receptor antagonists for chemotherapy-induced nausea and vomiting. *Cancer J Sci Am*. 1998;4:72-77.
5. Jordan K, Hinke A, Grothey A, et al. A meta-analysis comparing the efficacy of four 5-HT3-receptor antagonists for acute chemotherapy-induced emesis. *Support Care Cancer*. 2007;15:1023-1033.
6. Grunberg SM, Koeller JM. Palonosetron: a unique 5-HT3-receptor antagonist for the prevention of chemotherapy-induced emesis. *Expert Opin Pharmacother*. 2003;4:2297-2303.
7. Eisenberg P, Figueroa-Vadillo J, Zamora R, et al. Improved prevention of moderately emetogenic chemotherapy-induced nausea and vomiting with palonosetron, a pharmacologically novel 5-HT3 receptor antagonist: results of a phase III, single-dose trial versus dolasetron. *Cancer*. 2003;98:2473-2482.
8. De Wit R, Herrstedt J, Rapoport B, et al. The oral NK(1) antagonist, aprepitant, given with standard antiemetics provides protection against nausea and vomiting over multiple cycles of cisplatin-based chemotherapy: a combined analysis of two randomized, placebo-controlled phase III clinical trials. *Eur J Cancer*. 2004;40:403-410.
9. Jantunen I, Kataja V, Muhonen T. An overview of randomised studies comparing 5-HT3 receptor antagonists to conventional anti-emetics in the prophylaxis of acute chemotherapy-induced vomiting. *Eur J Cancer*. 1997;33:66-74.
10. Hainsworth J, Harvey W, Pendergrass K, et al. A single-blind comparison of intravenous ondansetron, a selective serotonin antagonist, with intravenous metoclopramide in the prevention of nausea and vomiting associated with high-dose cisplatin chemotherapy. *J Clin Oncol*. 1991;9:721-728.
11. Aloxi (palonosetron) Full prescribing information. Eisai Inc; USA. Updated March 2008.
12. Emend (aprepitant) Full prescribing information. Merck & Co, Inc., Whitehouse Station, NJ. Updated July 2009.
13. Wang T, Collet JP, Shapiro S, Ware MA. Adverse effects of medical cannabinoids: a systemic review. *CMAJ*. 2008;178:1669.


# Classification of Risk of Chemotherapy-induced Nausea and Vomiting

Lee S. Schwartzberg, MD

Chemotherapeutic agents vary significantly in their emetogenic potential; categorizing the emetogenic risk of chemotherapeutic agents is important for determining the most appropriate prophylactic antiemetic support. Grunberg and colleagues recently updated a 4-level classification of emetogenic potential which categorizes agents based on the percentage of patients who experience acute emesis without the use of antiemetic prophylaxis.[1] This categorization is an important tool for determining the appropriate level of prophylactic antiemetic support.

## Emetogenic Risk Classifications

The highly emetogenic agents include agents that cause emesis in 90% or more of patients (Tables 1 and 2). The most classic highly emetogenic regimen, which originally led to the development of antiemetic therapy, is the use of relatively high doses of cisplatin (≥50 mg/m$^2$), either as a single agent or in combination with other agents of equal or lesser emetogenic risk.[2]

Other highly emetogenic agents are not frequently used today with the exception of dacarbazine, a component of the ABVD (doxorubicin, bleomycin, vinblastine, and dacarbazine) regimen, which remains a standard treatment for Hodgkin's disease. Another notable exception is the combination of doxorubicin and cyclophosphamide (AC), which was reclassified as a highly emetogenic regimen in both the 2006 ASCO guidelines and in recent NCCN guidelines.[2,3] This reclassification is relevant for patients who receive AC alone or as part of a combination regimen, such as the cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) regimen commonly used in the treatment of lymphoma.

Moderately emetogenic chemotherapy includes the agents that cause emesis in 30–90% of patients. Many commonly used chemotherapeutic agents fall into this category, including carboplatin, irinotecan, oxaliplatin, high-dose methotrexate, doxorubicin, and other anthracyclines.

Patient factors also contribute to emetogenic risk. Risk factors for CINV include female gender, younger age, a history of hyperemesis during pregnancy, motion sickness, or anxiety; and low prior alcohol use.[4,5] The contribution of patient factors, combined with the wide range of emetogenic potential within the moderately emetogenic group, can lead to significant variability in emetogenic risk among patients receiving these agents.

**Table 1.** NCCN Guidelines 2009: Anticancer Therapy Emetic Risk Groups

| Level | Agent | |
|---|---|---|
| High emetic risk (>90% frequency of emesis) | AC combination defined as either doxorubicin or epirubicin with cyclophosphamide | Dacarbazine |
| | Altretamine | Mechlorethamine |
| | Carmustine >250 mg/m$^2$ | Procarbazine (oral) |
| | Cisplatin ≥50 mg/m$^2$ | Streptozocin |
| | Cyclophosphamide > 1,500 mg/m$^2$ | |
| Moderate emetic risk (30–90% frequency of emesis) | Aldesleukin >12–15 million units/m$^2$ | Doxorubicin |
| | Amifostine >300 mg/m$^2$ | Epirubicin |
| | Arsenic trioxide | Etoposide (oral) |
| | Azacitidine | Idarubicin |
| | Bendamustine | Ifosfamide |
| | Busulfan >4 mg/d | Imatinib (oral) |
| | Carboplatin | Irinotecan |
| | Carmustine ≤250 mg/m$^2$ | Lomustine |
| | Cisplatin <50 mg/m$^2$ | Melphalan > 50 mg/m$^2$ |
| | Cyclophosphamide ≤1,500 mg/m$^2$ | Methotrexate 250–>1,000 mg/m$^2$ |
| | Cyclophosphamide (oral) | Oxaliplatin >75 mg/m$^2$ |
| | Cytarabine >1 g/m$^2$ | Temozolomide (oral) |
| | Dactinomycin | Vomprelbine (oral) |
| | Daunorubicin | |

### *CINV Prophylaxis for High-risk Emetogenic Chemotherapy*

The most appropriate CINV prophylaxis will depend on the intrinsic emetogenic risk of the drug in addition to patient factors. For agents with high emetogenic risk, the NCCN guidelines recommend triple-therapy on day 1 consisting of a 5-HT$_3$ receptor antagonist plus corticosteroids (typically dexamethasone) plus an NK-1 receptor antagonist.[2] Dexamethasone is recommended on days 2–4 and aprepitant on days 2–3, based on clinical trial data.

Each of these components of antiemetic prophylaxis is available in both intravenous and oral formulations. These formulations have equivalent efficacy. However, patients unable to take tablets orally due to emesis require intravenous antiemetics; in selected patients, a transdermal 5-HT$_3$ receptor antagonist may be an alternative choice.

The NCCN antiemetic guidelines include 4 available choices for 5-HT$_3$ receptor antagonists: ondansetron, granisetron, dolasetron, and palonosetron. In the 2009 guidelines, intravenous palonosetron is recommended (category 2B; some disagreement) as a preferred agent over the other agents.[2] Dexamethasone can be administered intravenously or orally. NK-1 antagonists include the oral agent aprepitant or the intravenous agent fosaprepitant. If aprepitant is used, the dexamethasone dose given prior to chemotherapy should be reduced from 20 to 12 mg. More recently, the NK-1 receptor antagonist casopitant has demonstrated efficacy in patients receiving moderately or highly emetogenic chemotherapy.[6,7]

The NCCN guidelines strongly recommend the use of an anti-anxiety agent such as lorazepam before, during, and after therapy for patients at risk for anticipatory nausea and vomiting, particularly for patients with anxiety. Lorazepam can also be administered orally or intravenously before chemotherapy and potentially after therapy. An agent to reduce reflux symptoms, either an H2 receptor antagonist or a proton pump inhibitor, may also be appropriate.

### *CINV Prophylaxis for Moderate-risk Emetogenic Chemotherapy*

For moderately emetogenic drugs, NCCN guidelines recommend day 1 prophylaxis consisting of dexamethasone

**Table 2.** MASCC Guidelines: Anticancer Therapy Emetic Risk Groups

| | | |
|---|---|---|
| **Intravenous Agents** | | |
| High | Cisplatin<br>Mechlorethamine<br>Streptozocin<br>Cyclophosphamide >1,500 mg/m$^2$<br>Carmustine<br>Dacarbazine | |
| Moderate | Oxaliplatin<br>Cytarabine >1 gm/m$^2$<br>Carboplatin<br>Ifosfamide<br>Cyclophosphamide <1,500 mg/m$^2$ | Doxorubicin<br>Daunorubicin<br>Epirubicin<br>Idarubicin<br>Irinotecan |
| **Oral Agents** | | |
| High | Hexamethylmelamine<br>Procarbazine | |
| Moderate | Cyclophosphamide<br>Etoposide<br>Temozolomide | Vinorelbine<br>Imatinib |
| Low | Capecitabine<br>Tegafururacil | |
| Minimal | Chlorambucil<br>Hydroxyurea<br>L-Phenylalanine mustard | 6-Thioguanine<br>Methotrexate<br>Gefitinib |

and a 5-HT$_3$ receptor antagonist with or without lorazepam and/or an H2 receptor antagonist or a proton pump inhibitor.[1] For patients receiving chemotherapeutic agents towards the more emetogenic end of the moderately emetogenic range, an NK-1 antagonist should be added. Options for prophylaxis on days 2–3 include: aprepitant with or without dexamethasone; dexamethasone alone; or a 5-HT$_3$ antagonist. Palonosetron should not be administered beyond day 1 per cycle due to its long half-life. Lorazepam and/or an H2 blocker or a proton pump inhibitor can be added to any of the day 2–3 regimens as needed.

### *CINV Prophylaxis for Low-risk Emetogenic Drugs*

Antiemetic prophylaxis for patients receiving chemotherapy with low emetogenic potential can include dexamethasone, prochlorperazine, or metoclopramide, with or without lorazepam and/or an H2 receptor antagonist or a proton pump inhibitor. Clinicians should be aware of the risk for dystonic reactions with proclorperazine or metoclopramide and monitor patients appropriately.

## References

1. Grunberg SM, Osoba D, Hesketh PJ, et al. Evaluation of new antiemetic agents and definition of antineoplastic agent emetogenicity: an update. *Support Care Cancer* 2005;13:80-84.
2. National Comprehensive Cancer Network. *Clinical Practice Guidelines in Oncology: antiemesis*. V.4.2009. December 15, 2009.
3. Gralla RJ, Osoba D, Kris MG, et al. Recommendations for the use of antiemetics: Evidence-based, clinical practice guidelines. American Society of Clinical Oncology. *J Clin Oncol* 1999;17:2971-2994.
4. Osoba D, Zee B, Pater J, Warr D, Latreille J, Kaizer L. Determinants of postchemotherapy nausea and vomiting in patients with cancer. Quality of Life and Symptom Control Committees of the National Cancer Institute of Canada Clinical Trials Group. *J Clin Oncol*. 1997;15:116-123.
5. Lohr L. Chemotherapy-induced nausea and vomiting. *Cancer J*. 2008;14:85-93.
6. Grunberg SM, Rolski J, Strausz J, et al. Efficacy and safety of casopitant mesylate, a neurokinin 1 (NK1)-receptor antagonist, in prevention of chemotherapy-induced nausea and vomiting in patients receiving cisplatin-based highly emetogenic chemotherapy: a randomised, double-blind, placebo-controlled trial. *Lancet Oncol*. 2009;10:549-558.
7. Herrstedt J, Apornwirat W, Shaharyar A, et al. Phase III trial of casopitant, a novel neurokinin-1 receptor antagonist, for the prevention of nausea and vomiting in patients receiving moderately emetogenic chemotherapy. *J Clin Oncol*. 2009;27:5363-5369.

# Question and Answer Forum

**What factors should clinicians consider when evaluating the choice between oral and intravenous antiemetic agents?**

**Dr. Susan Urba** Oral agents are generally simpler, less expensive, and more convenient. Therefore, if a patient is able to swallow, oral administration is preferable. However, not all agents are available in both oral and intravenous formulations.

**Dr. Gary Morrow** There are some other considerations as well. From a practical perspective, once patients have experienced emesis, oral medication is of no use whatsoever. Another consideration, unfortunately, is differences in reimbursement schedules for oral agents, which can be taken at home, versus intravenous agents, which require an in-office procedure.

**How readily have new antiemetic agents been incorporated into formularies and guidelines?**

**GM** In general, there has been some reluctance to adopt new classes of agents. The thinking has been to start with agents that are in the armamentarium at the time, reserving newer agents for cases of inadequate control. However, clinical trials and clinical experience clearly showed that this was not the proper approach to attain control of CINV; that the emphasis should be on prevention, not treatment. In the long-term, these agents have all been shown to conserve resources, increase patient satisfaction, and, in many cases, allow a different aggressiveness in the chemotherapy treatments.

**SU** Physicians sometimes have to step in to advocate for new agents to be added to the formulary at their hospital, to ensure that their patients are receiving optimal care. They may need to write letters, summarize clinical trial data, or take other steps to ensure that their Pharmacy and Therapeutics Committee understands the clinical importance of these new agents. These committees are interested in whether an agent is considered part of the standard of care, and of course cost is always a major consideration. In the case of CINV, guideline panels are clear that a combination of drugs is necessary for ensuring optimal prophylaxis.

In regards to guidelines, the NCCN guidelines are reviewed each year to ensure they are up-to-date. Prior to this review, the current guidelines are circulated to liaisons from all participating institutions. The liaisons then circulate the guidelines among their colleagues to elicit their input regarding the guidelines. Clinicians may make suggestions based on clinical experience, or they may draw attention to new evidence in the literature that should be considered. These suggestions are then compiled and discussed by the Committee. Therefore, while NCCN institutions may only have one or two representatives in the review discussion, each liaison has previously solicited input from all the physicians on staff. This ensures that the guidelines incorporate the latest evidence from the literature as well as the perspectives of practicing oncologists who are using these agents on a regular basis.

**What are some important areas for further research in CINV?**

**Dr. Lee Schwartzberg** Although we have made progress, CINV remains an important issue that is not completely solved. When the optimal CINV prophylaxis regimen is used, we can prevent emesis in the majority of patients. However, we have not done as well in preventing nausea, particularly in the delayed phase. Whether defined by visual scales or using patient-reported outcomes (subjective symptoms or the use of breakthrough medicine), nausea is often not completely controlled in the days following administration of chemotherapy. This delayed CINV has substantial consequences in terms of quality-of-life, loss of productivity in the work force, and inability to perform activities of daily living. While this period may be relatively brief, it can occur repeatedly with each course of chemotherapy, making a significant cumulative impact.

**GM** We now realize that nausea and vomiting are not the same in terms of biology or clinical significance. Emesis is much more easily measured as it is a behavioral response with a defined outcome. There is very little question whether or not a patient has experienced emesis. Furthermore, there are reasonable animal models that allow exploration of neural pathways and an understanding of which neural structures and body systems are involved. So we know a lot more of the biology of vomiting than of nausea since nausea is an entirely self-reported symptom. As a patient-reported outcome, it does not have reliable or well-agreed–upon animal models that would allow the same degree of biological exploration that has been possible with animal models of vomiting.

Although clinicians often rank vomiting above nausea in regards to concerning side effects, patients are more bothered by nausea. As Dr. Schwartzberg mentioned, there is little evidence of the efficacy of 5-$HT_3$ receptor antagonists and NK-1 receptor antagonists in the control of nausea. Because of this lack of evidence, separate guidelines have not been developed for controlling nausea. However, nausea is not well controlled with current approaches. Thus, the difference between nausea and vomiting is a wide open area for research. This could include development of new agents or improvements in the assessment of current agents. Better control of nausea should be an important goal for the future.

Marijuana and its derivatives have demonstrated reasonable control in nausea, though of course there are legal and political issues with medical marijuana.[1] Another alternative approach is ginger, which recently showed a beneficial effect against chemotherapy-induced nausea in a large, multicenter phase III trial.[2]

One limitation in determining the efficacy of antiemetic agents for controlling nausea is that nausea has not been assessed as a phenomenon separate from vomiting. However, a variety of well respected scales for measuring nausea have been developed. Thus, future trials and guidelines will hopefully delineate nausea and vomiting as 2 separate phenomena.

**LS** Breakthrough CINV is another area in need of further improvements in therapy. For these patients who develop CINV despite current optimal therapy, regaining control of symptoms is challenging.

We could also benefit by further defining patient factors that contribute to the likelihood of CINV within the broad range of moderately emetogenic chemotherapy. This way, we could identify patients receiving moderately emetogenic chemotherapy who would benefit from more aggressive antiemetic prophylaxis involving triple combination therapy.

Other steps to improving prophylaxis for moderately emetogenic chemotherapy could include comparing the efficacy of double regimens versus triple regimens. There is still an unanswered question regarding the value of first-generation oral 5-$HT_3$ receptor antagonists after an intravenous or oral dose is administered for prechemotherapy prophylaxis. Concerns remain with the use of dexamethasone on a regular basis, given the risk of adverse effects.

A need still exists for new classes of agents, or, failing that, better agents of the existing classes, to improve further the overall prophylactic effect. Our goal is to prevent the development of any nausea or vomiting in any patient. Although we have made significant progress toward that goal, room for improvement remains.

## References

1. Machado Rocha FC, Stéfano SC, De Cássia Haiek R, Rosa Oliveira LM, Da Silveira DX. Therapeutic use of Cannabis sativa on chemotherapy-induced nausea and vomiting among cancer patients: systematic review and meta-analysis. *Eur J Cancer Care*. 2008;17:431-443.

2. Ryan JL, Heckler C, Dakhil SR, et al. Ginger for chemotherapy-related nausea in cancer patients: A URCC CCOP randomized, double-blind, placebo-controlled clinical trial of 644 cancer patients. *J Clin Oncol* (ASCO Annual Meeting Abstracts).2009; 27: Abstract 9511.

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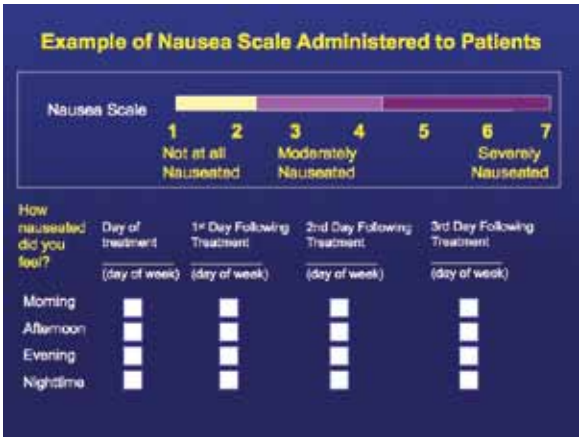


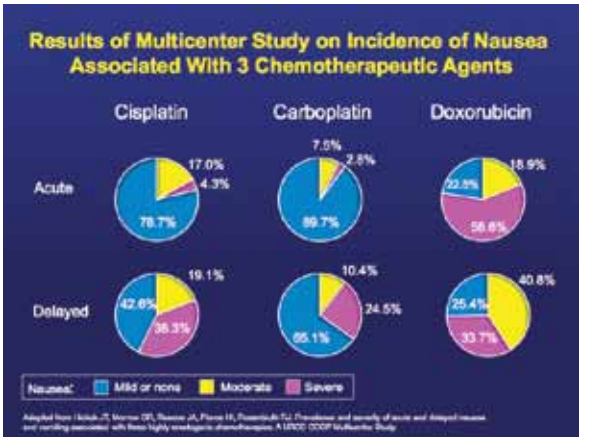


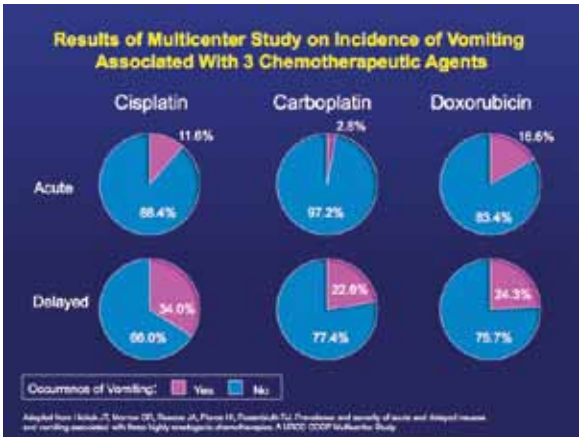




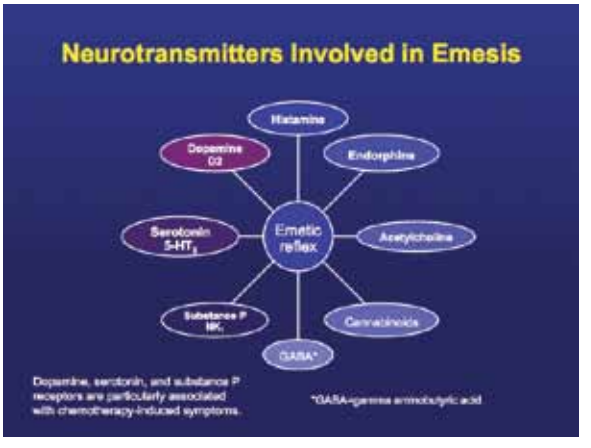

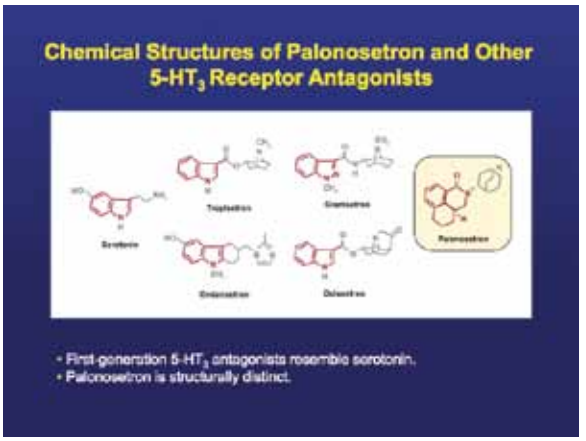


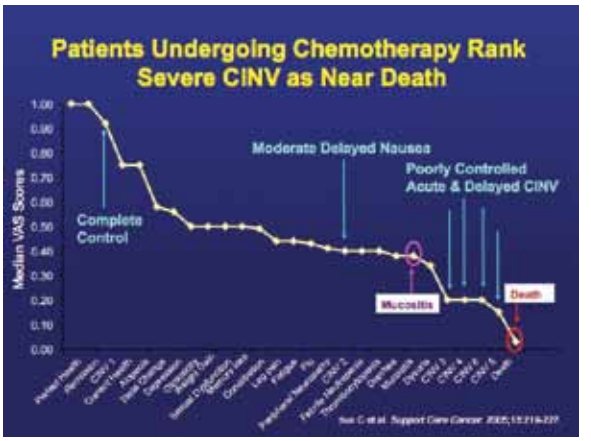


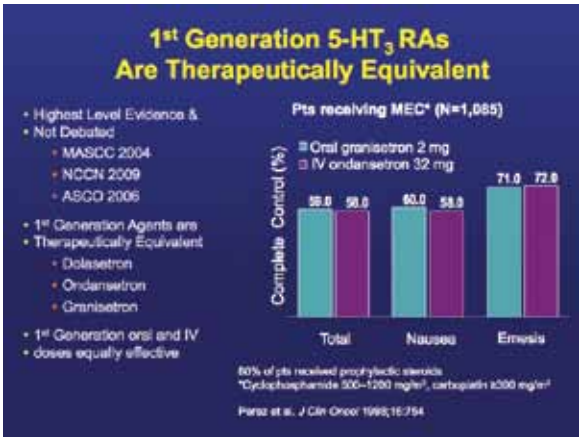


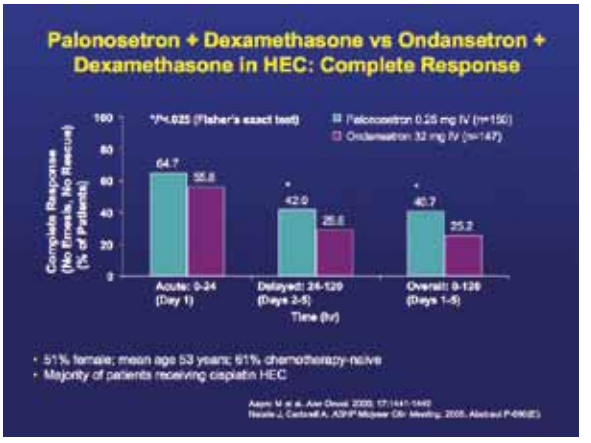


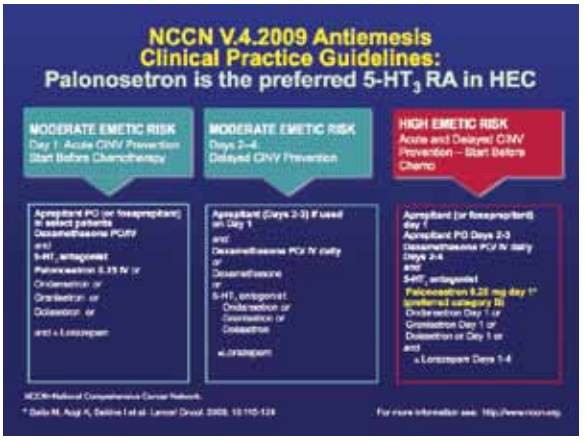


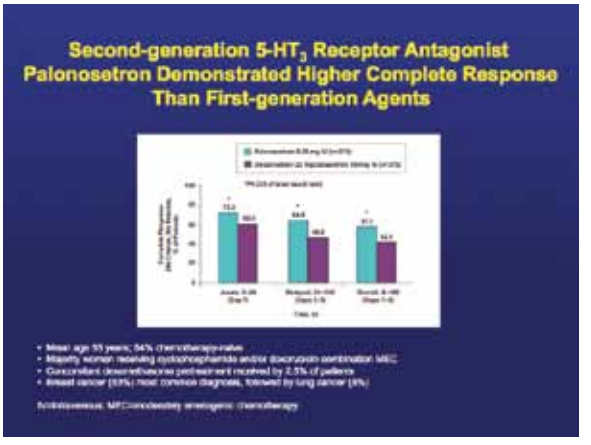


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# Notes

# Recent Advances in the Management of Chemotherapy-induced Nausea and Vomiting: A Post-MASCC 2009 Discussion

**CME Post-Test:** *Circle the correct answer for each question below.*

1. Which of the following chemotherapy side effects do patients rank as most distressing?

   a. Nausea
   b. Hair loss
   c. Fatigue
   d. Vomiting

2. Which of the following ligands binds to NK-1 receptors?

   a. Dopamine
   b. Serotonin
   c. Substance P
   d. Cannabinoids

3. According to the 2009 NCCN guidelines for antiemesis, AC is classified into what emetogenic risk category?

   a. Highly emetogenic chemotherapy
   b. Moderately emetogenic chemotherapy
   c. Low emetogenic chemotherapy
   d. AC is not addressed as a combination in the guidelines

4. Which of the following patient factors is NOT associated with an increased risk of CINV?

   a. History of anxiety
   b. Female gender
   c. Older age
   d. Prior alcohol use

5. Which of the following 5-$HT_3$ receptor antagonists is recommended as a preferred agent by NCCN guidelines for day 1 antiemetic therapy?

   a. Dolasetron
   b. Granisetron
   c. Ondansetron
   d. Palonosetron

6. Which of the following agents are associated with high risk of emesis according to the MASCC guidelines?

   a. Cyclophosphamide and Etoposide
   b. Hexamethylmelamine and Procarbazine
   c. Chlorambucil and Hydroxyurea
   d. None of the above

7. The addition of palonosetron to dexamethasone and aprepitant on days 2-3 is recommended for improving protection against delayed CINV.

   a. True
   b. False

8. Which of the following agents is recommended to manage anticipatory nausea and vomiting?

   a. Dexamethasone
   b. Lorazepam
   c. 5-$HT_3$ receptor antagonist
   d. NK-1 receptor antagonist

9. What is the most common side effect of 5-$HT_3$ receptor antagonists?

   a. Headache
   b. Dizziness
   c. Disorientation
   d. Stomach upset

10. Which of the following CINV symptoms is least well controlled with current therapies?

    a. Acute nausea
    b. Acute vomiting
    c. Delayed nausea
    d. Delayed vomiting

Project ID: 6825

Evaluation Form: Recent Advances in the Management of Chemotherapy-induced Nausea and Vomiting: A Post-MASCC 2009 Discussion

PIM is committed to excellence in continuing education, and your opinions are critical to us in this effort. To assist us in evaluating the effectiveness of this activity and to make recommendations for future educational offerings, please take a few minutes to complete this evaluation form. You must complete this evaluation form to receive acknowledgment for completing this activity.

**Please rate your level of agreement by circling the appropriate rating:**
1 = Strongly Disagree 2 = Disagree 3 = Neutral 4 = Agree 5 = Strongly Agree

**Learning Objectives**
After participating in this activity, I am now better able to:

| | |
|---|---|
| 1. Describe the importance of new study findings and clinical trial data in the treatment of chemotherapy-induced nausea & vomiting (CINV) in cancer patients. | 1 2 3 4 5 |
| 2. Assess the results of these new study findings including updates on guidelines for highly and moderate emetogenic chemotherapy and radiotherapy. | 1 2 3 4 5 |
| 3. Discuss how to integrate the latest knowledge and methods for treating cancer patients with CINV into clinical practice in an effort to improve current quality of life. | 1 2 3 4 5 |
| 4. Identify future research directions for all therapies in CINV in cancer patients. | 1 2 3 4 5 |

**Based upon your participation in this activity, choose the statement(s) that apply:**
❒ I gained new strategies/skills/information that I can apply to my area of practice.
❒ I plan to implement new strategies/skills/information into my practice.

**What strategies/changes do you plan to implement into your practice?** _____

**What barriers do you see to making a change in your practice?** _____

**Which of the following best describes the impact of this activity on your performance?**
❒ I will implement the information in my area of practice.
❒ I need more information before I can change my practice behavior.
❒ This activity will not change my practice, as my current practice is consistent with the information presented.
❒ This activity will not change my practice, as I do not agree with the information presented.

**Please rate your level of agreement by circling the appropriate rating:**
1 = Strongly Disagree 2 = Disagree 3 = Neutral 4 = Agree 5 = Strongly Agree

**The content presented:**

| | |
|---|---|
| Enhanced my current knowledge base | 1 2 3 4 5 |
| Addressed my most pressing questions | 1 2 3 4 5 |
| Promoted improvements or quality in health care | 1 2 3 4 5 |
| Was scientifically rigorous and evidence-based | 1 2 3 4 5 |
| Avoided commercial bias or influence | 1 2 3 4 5 |

**Would you be willing to participate in a post-activity follow-up survey?** ❒ Yes ❒ No

**Please list any topics you would like to see addressed in future educational activities:** _____

If you wish to receive acknowledgment for completing this activity, please complete the post-test by selecting the best answer to each question, complete this evaluation verification of participation, and fax to: (303) 790-4876. You may also complete the post-test online at www.cmeuniversity.com. On the navigation menu, click on "Find Post-tests by Course" and search by **project ID 6825**. Upon successfully completing the post-test and evaluation, your certificate will be made available immediately.

## Post-test Answer Key

| 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 |
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