Antiemetics: American Society of Clinical Oncology Clinical Practice Guideline Update

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Editor's note: This American Society of Clinical Oncology (ASCO) Clinical Practice Guideline provides recommendations, with comprehensive review and analyses of the relevant literature for each recommendation. Additional information, including a Data Supplement with evidence tables, a Methodology Supplement, slide sets, clinical tools and resources, and links to patient information at www.cancer.net, is available at www.asco.org/supportive-care-guidelines and www.asco.org/guidelineswiki.

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A B S T R A C T

Purpose
To update the ASCO guideline for antiemetics in oncology.

Methods
ASCO convened an Expert Panel and conducted a systematic review of the medical literature for the period of November 2009 to June 2016.

Results
Forty-one publications were included in this systematic review. A phase III randomized controlled trial demonstrated that adding olanzapine to antiemetic prophylaxis reduces the likelihood of nausea among adult patients who are treated with high emetic risk antineoplastic agents. Randomized controlled trials also support an expanded role for neurokinin 1 receptor antagonists in patients who are treated with chemotherapy.

Recommendation
Key updates include the addition of olanzapine to antiemetic regimens for adults who receive high-emetic-risk antineoplastic agents or who experience breakthrough nausea and vomiting; a recommendation to administer dexamethasone on day 1 only for adults who receive anthracycline and cyclophosphamide chemotherapy; and the addition of a neurokinin 1 receptor antagonist for adults who receive carboplatin area under the curve ≥ 4 mg/mL per minute or high-dose chemotherapy, and for pediatric patients who receive high-emetic-risk antineoplastic agents. For radiation-induced nausea and vomiting, adjustments were made to anatomic regions, risk levels, and antiemetic administration schedules. Rescue therapy alone is now recommended for low-emetic-risk radiation therapy. The Expert Panel reiterated the importance of using the most effective antiemetic regimens that are appropriate for antineoplastic agents or radiotherapy being administered. Such regimens should be used with initial treatment, rather than first assessing the patient's emetic response with less-effective treatment. Additional information is available at www.asco.org/supportive-care-guidelines and www.asco.org/guidelineswiki.

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INTRODUCTION

The development of increasingly effective antiemetic regimens over the last quarter century has greatly reduced the incidence of nausea and vomiting due to chemotherapy.[1] The recommended approach to preventing nausea and vomiting varies by the emetic risk of the treatment regimen. Adherence to antiemetic guidelines has been linked to improved control of nausea and vomiting.[2]

This guideline provides updated recommendations to prevent and manage nausea and vomiting caused by antineoplastic agents or radiation therapy for cancer. The first ASCO guideline for antiemetics was published in 1999,[3] with updates in 2006,[4] 2011,[5] and 2015.[6] Important developments that are addressed by the current update include the antiemetic efficacy of olanzapine; evidence to expand the use of neurokinin 1 (NK_1) receptor antagonists; increasing interest in cannabinoids; and refinements in the anatomic regions, risk levels, and antiemetic management recommendations for radiation therapy. This update also adds two new antiemetic medications: rolapitant—an NK_1 receptor antagonist—and a subcutaneously administered form of granisetron.

ASSOCIATED CONTENT

Appendix
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Data Supplement
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THE BOTTOM LINE

Antiemetics: American Society of Clinical Oncology Clinical Practice Guideline Update

Guideline Question

What are the most effective strategies for preventing or managing nausea and vomiting due to antineoplastic agents or radiation therapy?

Target Population

Adults and children who receive antineoplastic agents and adults who undergo radiation therapy for cancer.

Target Audience

Medical and radiation oncologists, oncology nurses, nurse practitioners, physician assistants, oncology pharmacists, and patients with cancer

Methods

An Expert Panel was convened to update clinical practice guideline recommendations on the basis of a systematic review of the medical literature.

Key Recommendations

Adult Patients

High-emetic-risk antineoplastic agents

- **(Updated)** Adult patients who are treated with cisplatin and other high-emetic-risk single agents should be offered a four-drug combination of a neurokinin 1 (NK_1) receptor antagonist, a serotonin (5-HT_3) receptor antagonist, dexamethasone, and olanzapine. Dexamethasone and olanzapine should be continued on days 2 to 4. (Type: evidence based, benefits outweigh harms; quality of evidence: high; strength of recommendation: strong.)

- **(Updated)** Adult patients who are treated with an anthracycline combined with cyclophosphamide should be offered a four-drug combination of an NK_1 receptor antagonist, a 5-HT_3 receptor antagonist, dexamethasone, and olanzapine. Olanzapine should be continued on days 2 to 4. (Type: evidence based, benefits outweigh harms; quality of evidence: high; strength of recommendation: strong.)

Moderate-emetic-risk antineoplastic agents

- **(Updated)** Adult patients who are treated with carboplatin area under the curve (AUC) $\geq$ 4 mg/mL per minute should be offered a three-drug combination of an NK_1 receptor antagonist, a 5-HT_3 receptor antagonist, and dexamethasone. (Type: evidence based, benefits outweigh harms; quality of evidence: high; strength of recommendation: strong.)

- **(Updated)** Adult patients who are treated with moderate-emetic-risk antineoplastic agents, excluding carboplatin AUC $\geq$ 4 mg/mL per minute, should be offered a two-drug combination of a 5-HT_3 receptor antagonist (day 1) and dexamethasone (day 1). (Type: evidence based, benefits outweigh harms; quality of evidence: high; strength of recommendation: strong.)

- **(Updated)** Adult patients who are treated with cyclophosphamide, doxorubicin, oxaliplatin, and other moderate-emetic-risk antineoplastic agents that are known to cause delayed nausea and vomiting may be offered dexamethasone on days 2 to 3. (Type: informal consensus, benefits outweigh harms; quality of evidence: low; strength of recommendation: moderate.)

Low-emetic-risk antineoplastic agents

- **(Updated)** Adult patients who are treated with low-emetic-risk antineoplastic agents should be offered a single dose of a 5-HT_3 receptor antagonist or a single 8-mg dose of dexamethasone before antineoplastic treatment. (Type: informal consensus, benefits outweigh harms; quality of evidence: low; strength of recommendation: moderate.)

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THE BOTTOM LINE (CONTINUED)

Minimal-emetic-risk antineoplastic agents

- (Reworded for clarity) Adult patients who are treated with minimal-emetic-risk antineoplastic agents should not be offered routine antiemetic prophylaxis. (Type: informal consensus, benefits outweigh harms; quality of evidence: low; strength of recommendation: moderate.)

Antineoplastic combinations

- (Reworded for clarity) Adult patients who are treated with antineoplastic combinations should be offered antiemetics that are appropriate for the component antineoplastic agent of greatest emetic risk. (Type: informal consensus, benefits outweigh harms; quality of evidence: intermediate; strength of recommendation: moderate.).

Adjunctive drugs

- **(Updated)** Lorazepam is a useful adjunct to antiemetic drugs, but is not recommended as a single-agent antiemetic. (Type: informal consensus; benefits outweigh harms; quality of evidence: low; strength of recommendation: moderate.)

Cannabinoids

- **(New)** Evidence remains insufficient for a recommendation regarding treatment with medical marijuana for the prevention of nausea and vomiting in patients with cancer who receive chemotherapy or radiation therapy. Evidence is also insufficient for a recommendation regarding the use of medical marijuana in place of the tested and US Food and Drug Administration–approved cannabinoids, dronabinol and nabilone, for the treatment of nausea and vomiting caused by chemotherapy or radiation therapy.

Complementary and alternative therapies

- (Reworded for clarity) Evidence remains insufficient for a recommendation for or against the use of ginger, acupuncture/acupressure, and other complementary or alternative therapies for the prevention of nausea and vomiting in patients with cancer.

High-dose chemotherapy with stem cell or bone marrow transplantation

- **(Updated)** Adult patients who are treated with high-dose chemotherapy and stem cell or bone marrow transplantation should be offered a three-drug combination of an NK_1 receptor antagonist, a 5-HT_3 receptor antagonist, and dexamethasone. (Type: evidence based, benefits outweigh harms; quality of evidence: high; strength of recommendation: strong.)

Multiday antineoplastic therapy

- (Reworded for clarity) Adult patients who are treated with multiday antineoplastic agents should be offered antiemetics before treatment that are appropriate for the emetic risk of the antineoplastic agent administered on each day of the antineoplastic treatment and for 2 days after the completion of the antineoplastic regimen. (Type: evidence based, benefits outweigh harms; quality of evidence: intermediate; strength of recommendation: moderate.)

- **(Strengthened)** Adult patients who are treated with 4- or 5-day cisplatin regimens should be offered a three-drug combination of an NK_1 receptor antagonist, a 5-HT_3 receptor antagonist, and dexamethasone. (Type: evidence based, benefits outweigh harms; quality of evidence: high; strength of recommendation: strong.)

Breakthrough nausea and vomiting

- (No change) For patients with breakthrough nausea or vomiting, clinicians should re-evaluate emetic risk, disease status, concurrent illnesses, and medications, and ascertain that the best regimen is being administered for the emetic risk. (Type: informal consensus, benefits outweigh harms; quality of evidence: low; strength of recommendation: moderate.)

- **(Updated)** Adult patients who experience nausea or vomiting despite optimal prophylaxis, and who did not receive olanzapine prophylactically, should be offered olanzapine in addition to continuing the standard antiemetic regimen. (Type: evidence based, benefits outweigh harms; quality of evidence: intermediate; strength of recommendation: moderate.)

- **(Updated)** Adult patients who experience nausea or vomiting despite optimal prophylaxis, and who have already received olanzapine, may be offered a drug of a different class—for example, an NK_1 receptor antagonist, lorazepam or alprazolam, a dopamine receptor antagonist, dronabinol, or nabilone—in addition to continuing the standard antiemetic regimen. (Type: informal consensus, benefits outweigh harms; quality of evidence: intermediate for dronabinol and nabilone, low otherwise; strength of recommendation: moderate.)

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THE BOTTOM LINE (CONTINUED)

Anticipatory nausea and vomiting

- (Reworded for clarity) All patients should receive the most active antiemetic regimen that is appropriate for the antineoplastic agents being administered. Clinicians should use such regimens with initial antineoplastic treatment, rather than assessing the patient's emetic response with less effective antiemetic treatment. If a patient experiences anticipatory emesis, clinicians may offer behavioral therapy with systematic desensitization. (Type: informal consensus, benefits outweigh harms; quality of evidence: low; strength of recommendation: moderate.)

High emetic risk radiation therapy

- **(Updated)** Adult patients who are treated with high-emetic-risk radiation therapy should be offered a two-drug combination of a 5-HT_3 receptor antagonist and dexamethasone before each fraction and on the day after each fraction if radiation therapy is not planned for that day. (Type: evidence based, benefits outweigh harms; quality of evidence: high; strength of recommendation: strong.)

Moderate-emetic-risk radiation therapy

- (Reworded for clarity) Adult patients who are treated with moderate-emetic-risk radiation therapy should be offered a 5-HT_3 receptor antagonist before each fraction, with or without dexamethasone before the first five fractions. (Type: evidence based, benefits outweigh harms; quality of evidence: high; strength of recommendation: moderate.)

Low-emetic-risk radiation therapy

- **(Updated)** Adult patients who are treated with radiation therapy to the brain should be offered rescue dexamethasone therapy. Patients who are treated with radiation therapy to the head and neck, thorax, or pelvis should be offered rescue therapy with a 5-HT_3 receptor antagonist, dexamethasone, or a dopamine receptor antagonist. (Type: informal consensus, benefits outweigh harms; quality of evidence: low; strength of recommendation: weak.)

Minimal-emetic-risk radiation therapy

- **(Updated)** Adult patients who are treated with minimal-emetic-risk radiation therapy should be offered rescue therapy with a 5-HT_3 receptor antagonist, dexamethasone, or a dopamine receptor antagonist. (Type: informal consensus, benefits outweigh harms; quality of evidence: low; strength of recommendation: weak.)

Concurrent radiation and antineoplastic agent therapy

- **(Updated)** Adult patients who are treated with concurrent radiation and antineoplastic agents should receive antiemetic therapy that is appropriate for the emetic risk level of antineoplastic agents, unless the risk level of the radiation therapy is higher. During periods when prophylactic antiemetic therapy for antineoplastic agents has ended and ongoing radiation therapy would normally be managed with its own prophylactic therapy, patients should receive prophylactic therapy that is appropriate for the emetic risk of the radiation therapy until the next period of antineoplastic therapy, rather than receiving rescue therapy for antineoplastic agents as needed. (Type: informal consensus, benefits outweigh harms; quality of evidence: intermediate; strength of recommendation: moderate.)

Pediatric Patients

High-emetic-risk antineoplastic agents

- **(Updated)** Pediatric patients who are treated with high-emetic-risk antineoplastic agents should be offered a three-drug combination of a 5-HT_3 receptor antagonist, dexamethasone, and aprepitant. (Type: evidence based, benefits outweigh harms; quality of evidence: intermediate; strength of recommendation: strong.)

- **(New)** Pediatric patients who are treated with high-emetic-risk antineoplastic agents who are unable to receive aprepitant should be offered a two-drug combination of a 5-HT_3 receptor antagonist and dexamethasone. (Type: evidence based, benefits outweigh harms; quality of evidence: intermediate; strength of recommendation: strong.)

- **(New)** Pediatric patients who are treated with high-emetic-risk antineoplastic agents who are unable to receive dexamethasone should be offered a two-drug combination of palonosetron and aprepitant. (Type: evidence based, benefits outweigh harms; quality of evidence: intermediate; strength of recommendation: strong.)

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THE BOTTOM LINE (CONTINUED)

Moderate-emetic-risk antineoplastic agents

- (Reworded for clarity) Pediatric patients who are treated with moderate-emetic-risk antineoplastic agents should be offered a two-drug combination of a 5-HT_3 receptor antagonist and dexamethasone. (Type: evidence based, benefits outweigh harms; quality of evidence: intermediate; strength of recommendation: strong.)
- **(New)** Pediatric patients who are treated with moderate-emetic-risk antineoplastic agents who are unable to receive dexamethasone should be offered a two-drug combination of a 5-HT_3 receptor antagonist and aprepitant. (Type: evidence based, benefits outweigh harms; quality of evidence: intermediate; strength of recommendation: weak.)

Low-emetic-risk antineoplastic agents

- **(New)** Pediatric patients who are treated with low-emetic-risk antineoplastic agents should be offered ondansetron or granisetron. (Type: informal consensus, benefits outweigh harms; quality of evidence: low; strength of recommendation: strong.)

Minimal emetic risk antineoplastic agents

- **(New)** Pediatric patients who are treated with minimal-emetic-risk antineoplastic agents should not be offered routine antiemetic prophylaxis. (Type: informal consensus, benefits outweigh harms; quality of evidence: low; strength of recommendation: strong.)

Additional Resources

More information, including a Data Supplement with additional evidence tables, a Methodology Supplement with information about evidence quality and strength of recommendations, slide sets, and clinical tools and resources, is available at www.asco.org/supportive-care-guidelines and www.asco.org/guidelineswiki. Patient information is available at www.cancer.net.

ASCO believes that cancer clinical trials are vital to inform medical decisions and improve cancer care, and that all patients should have the opportunity to participate.

Although this guideline provides estimates of the emetic risk of both intravenous (IV) and oral antineoplastic agents, emetic risk information is limited and variable for many of the oral agents. As a result, the recommendations in this guideline for antineoplastic-related nausea and vomiting are most definitive for adults who are treated with single-day IV chemotherapy.

GUIDELINE QUESTIONS

This guideline addresses the prevention and management and nausea and vomiting due to antineoplastic agents and/or radiation therapy in patients with cancer. The full list of clinical questions is provided in the Data Supplement.

METHODS

Guideline Update Development Process

ASCO convened an Expert Panel (Appendix Table A1, online only) to consider the evidence and formulate the recommendations. Members of the Expert Panel were drawn from both community and academic settings and have expertise in medical oncology, radiation oncology, nursing, pharmacy, and health services research. The panel also included a patient representative. The Expert Panel met via teleconference and in person and corresponded through e-mail. On the basis of a consideration of the evidence, the authors were asked to contribute to the development of the guideline, provide critical review, and finalize guideline recommendations. Members of the Expert Panel were responsible for reviewing and approving the penultimate version of guideline, which was then circulated for external review and submitted to *Journal of Clinical Oncology* for editorial review and consideration for publication. All ASCO guidelines are ultimately reviewed and approved by the Expert Panel and the ASCO Clinical Practice Guideline Committee before publication.

Recommendations developed by the Expert Panel are based on a systematic review of the medical literature and clinical experience. PubMed and the Cochrane Library were searched from November 1, 2009, to June 1, 2016. The updated search was restricted to articles that were published in English and to randomized controlled trials (RCTs) and meta-analyses of RCTs. Search terms are listed in the Data Supplement. RCTs were required to have at least 25 patients per arm and at least 5 days—120 hours—of follow-up. The updated search was guided by the signals[7] approach that is designed to identify only new, potentially practice-changing data—signals—that might translate into revised practice recommendations. This approach relies on targeted routine literature searching and the expertise of ASCO Expert Panel members to help identify potential signals. The Methodology Supplement (available at www.asco.org/supportive-care-guidelines) provides additional information on the signals approach.

Guideline recommendations were crafted, in part, by using the Guidelines Into Decision Support methodology.[8] In addition, a review of the ability to implement the guideline was conducted. Ratings for the type and strength of recommendation and the quality of the evidence are provided with each recommendation. In selected cases in which evidence was lacking—but there was a high level of agreement among Expert Panel members—informal consensus was used.

As in the 2011 ASCO guideline, the emetic risk of antineoplastic mediations was classified by using four levels based on the likelihood of emesis in the absence of antiemetic prophylaxis: high ($>$ 90%), moderate (30% to 90%), low (10% to 30%), and minimal ($<$ 10%).[9] The 2011

ASCO guideline only addressed the emetic risk of IV antineoplastic agents. To update that list as well as to add information about the emetic risk of oral antineoplastic agents, the Expert Panel incorporated information from a 2016 publication by the Multinational Association of Supportive Care in Cancer (MASCC) and the European Society of Medical Oncology (ESMO).[10] The Expert Panel also updated the MASCC/ESMO search to identify drugs that had been approved since their review. For these additional drugs, the Expert Panel collected information and classified emetic risk according to methods developed by MASCC/ESMO.[10]

Radiation treatments were also classified as posing a high, moderate, low, or minimal risk of inducing nausea and vomiting, depending on the anatomic region being irradiated. No other patient-, tumor-, or treatment-related factors presently inform this classification. The incidence of radiation-induced nausea and vomiting after radiation therapy to many anatomic regions remains unclear as a result of heterogeneity among study patient populations, designs, outcome measures, total doses, doses per fraction, doses administered to individual organs, target volumes, and radiation therapy techniques. The Expert Panel supports the four-level risk classification for radiation-induced nausea and vomiting but notes that evidence for radiation-induced nausea and vomiting and its relationship to discrete irradiated anatomic regions is limited, especially for low- and minimal-emetic-risk radiation therapy. In addition, most of the evidence for radiation-induced nausea and vomiting was collected before the widespread implementation of highly conformal radiation therapy techniques that likely modulate the risk of radiation-induced nausea and vomiting.

Additional information about the methods used to develop this guideline update is available in the Methodology Supplement at www.asco.org/supportive-care-guidelines.

The ASCO Expert Panel and guidelines staff will work with the Expert Panel co-chairs to keep abreast of new evidence related to this guideline topic. On the basis of a formal review of the emerging literature, ASCO will determine the need to update.

This is the most recent information as of the publication date. Visit the ASCO Guidelines Wiki at www.asco.org/guidelineswiki to submit new evidence.

Guideline Disclaimer

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Guideline and Conflicts of Interest

The Expert Panel was assembled in accordance with ASCO's Conflict of Interest Policy Implementation for Clinical Practice Guidelines ("Policy," found at http://www.asco.org/rwc). All members of the Expert Panel completed ASCO's disclosure form, which requires disclosure of financial and other interests, including relationships with commercial entities that are reasonably likely to experience direct regulatory or commercial impact as a result of promulgation of the guideline. Categories for disclosure include employment; leadership; stock or other ownership; honoraria, consulting or advisory role; speaker's bureau; research funding; patents, royalties, other intellectual property; expert testimony; travel, accommodations, expenses; and other relationships. In accordance with the Policy, the majority of the members of the Expert Panel did not disclose any relationships constituting a conflict under the Policy.

RESULTS

A total of 41 publications were included in the systematic review: 35 RCTs[11-45] and six meta-analyses.[46-51] A majority of the studies addressed chemotherapy-induced nausea and vomiting. Four studies addressed radiation therapy.[15,22,26,36] Evidence tables, RCT quality assessments, and a QUOROM diagram are provided in the Data Supplement.

Emetic risk information for 19 new antineoplastic agents was abstracted from a total of 36 clinical trials.[52-87] An evidence table is provided in the Data Supplement.

RECOMMENDATIONS

ANTINEOPLASTIC AGENT–INDUCED NAUSEA AND VOMITING IN ADULTS

Tables 1 and 2 list IV and oral antineoplastic agents by emetic risk. Adult antiemetic dosing schedules for each risk class are listed in Table 3.

CLINICAL QUESTION 1. What is the optimal treatment to prevent nausea and vomiting as a result of high-emetic-risk antineoplastic agents in adults who receive single-day antineoplastic agent therapy?

Recommendation 1.1. Adult patients who are treated with cisplatin and other high-emetic-risk single agents should be offered a four-drug combination of a NK_1 receptor antagonist, a serotonin ($5\text{-}HT_3$) receptor antagonist, dexamethasone, and olanzapine. Dexamethasone and olanzapine should be continued on days 2 to 4. (Type: evidence based, benefits outweigh harms; quality of evidence: high; strength of recommendation: strong.)

Recommendation 1.2. Adult patients who are treated with an anthracycline combined with cyclophosphamide (AC) should be offered a four-drug combination of an NK_1 receptor antagonist, a $5\text{-}HT_3$ receptor antagonist, dexamethasone, and olanzapine. Olanzapine should be continued on days 2 to 4. (Type: evidence based, benefits outweigh harms; quality of evidence: high; strength of recommendation: strong.)

Literature review update and analysis. Changes to the previous ASCO recommendation for high-emetic-risk chemotherapy[6]

Table 1. Emetic Risk of Single Intravenous Antineoplastic Agents in Adults

Risk Level	Agent
High (> 90%)	Anthracycline/cyclophosphamide combination
	Carmustine
	Cisplatin
	Cyclophosphamide ≥ 1,500 mg/m^2
	Dacarbazine
	Mechlorethamine
	Streptozocin
Moderate (30%-90%)	Alemtuzumab
	Azacitidine
	Bendamustine
	Busulfan
	Carboplatin
	Clofarabine
	Cyclophosphamide < 1,500 mg/m^2
	Cytarabine > 1,000 mg/m^2
	Daunorubicin
	Doxorubicin
	Epirubicin
	Idarubicin
	Ifosfamide
	Irinotecan
	Irinotecan liposomal injection
	Oxaliplatin
	Romidepsin
	Temozolomide*
	Thiotepa†
	Trabectedin
Low (10%-30%)	Aflibercept
	Atezolizumab
	Belinostat
	Blinatumomab
	Bortezomib
	Brentuximab
	Cabazitaxel
	Carfilzomib
	Catumaxumab
	Cetuximab
	Cytarabine ≤ 1,000 mg/m^2
	Docetaxel
	Elotuzumab
	Eribulin
	Etoposide
	Fluorouracil
	Gemcitabine
	Ipilimumab
	Ixabepilone
	Methotrexate
	Mitomycin
	Mitoxantrone
	Nab-paclitaxel
	Necitumumab
	Paclitaxel
	Panitumumab
	Pemetrexed
	Pegylated liposomal doxorubicin
	Pertuzumab
	Temsirolimus
	Topotecan
	Trastuzumab-emtansine
	Vinflunine
Minimal (< 10%)	Bevacizumab
	Bleomycin
	2-Chlorodeoxyadenosine
	Cladribine
	Daratumumab
	Fludarabine

(continued in next column)

Table 1. Emetic Risk of Single Intravenous Antineoplastic Agents in Adults (continued)

Risk Level	Agent
	Nivolumab
	Obinutuzumab
	Ofatumumab
	Pembrolizumab
	Pixantrone
	Pralatrexate
	Ramucirumab
	Rituximab
	Trastuzumab
	Vinblastine
	Vincristine
	Vinorelbine

*No direct evidence found for intravenous temozolomide; as all sources indicate a similar safety profile to the oral formulation; the classification was based on oral temozolomide.
†Classification refers to individual evidence from pediatric trials.

are the addition of olanzapine, the addition of rolapitant to the list of available NK_1 receptor antagonists, and use of dexamethasone on day 1 only for patients who are treated with AC combinations.

The decision to add olanzapine to the antiemetic regimen for high-emetic-risk chemotherapy was driven by a phase III RCT.[27] Patients who received cisplatin-based chemotherapy or an AC combination were randomly assigned to receive either olanzapine 10 mg or placebo on days 1 to 4. All patients also received an NK_1 receptor antagonist (either aprepitant or fosaprepitant), a 5-HT_3 receptor antagonist, and dexamethasone. The proportion of patients who reported no nausea was significantly higher in those who received olanzapine compared with the placebo from 0 to 24 hours (74% *v* 45%), 24 to 120 hours, (42% *v* 25%), and 0 to 120 hours (37% *v* 22%) after chemotherapy. Olanzapine also improved complete response during each time interval but increased sedation on day 2. A 2016 meta-analysis of olanzapine used in a variety of ways and settings also suggested that olanzapine reduces chemotherapy-induced nausea and vomiting, but did not report on adverse effects.[46]

Rolapitant—an NK_1 receptor antagonist that was approved by the US Food and Drug Administration in 2015—was evaluated in four RCTs[30,32,40] and a post-hoc analysis across multiple cycles of chemotherapy[31] and added to the guideline as one of the NK_1 receptor antagonist options. In a randomized dose-ranging study that evaluated four doses of rolapitant, the highest dose of rolapitant (180 mg), plus ondansetron and dexamethasone, produced statistically significantly higher complete response rates than did ondansetron and dexamethasone.[30] The overall no emesis and no rescue medication rate was 63% in the rolapitant 180 mg arm compared with 47% in the control arm. Fifty-two patients (11%) experienced a serious adverse event, with incidence ranging from 9% to 14% across study arms.

Two international phase III trials (HEC-1 and HEC-2) that were reported in a single publication compared rolapitant 180 mg with placebo among patients who were treated with cisplatin-based chemotherapy.[32] Patients in each study arm also received granisetron and dexamethasone. In both trials, addition of rolapitant improved the rate of no vomiting and no use of rescue medication in the time from 24 to 120 hours. In a pooled analysis, complete response was 71% with

Table 2. Emetic Risk of Single Oral Antineoplastic Agents in Adults

Risk Level	Agent
High (> 90%)	Hexamethylmelamine
	Procarbazine
Moderate (30%-90%)	Bosutinib
	Cabozantinib
	Ceritinib
	Crizotinib
	Cyclophosphamide
	Imatinib
	Lenvatinib
	TAS-102 (trifluridine-tipiracil)
	Temozolomide
	Vinorelbine
Low (10%-30%)	Afatinib
	Alectinib
	Axatinib
	Capecitabine
	Cobimetinib
	Dabrafenib
	Dasatinib
	Everolimus
	Etoposide
	Fludarabine
	Ibrutinib
	Idelalisib
	Ixazomib
	Lapatinib
	Lenalidomide
	Olaparib
	Osimertinib
	Nilotinib
	Palbociclib
	Pazopanib
	Ponatinib
	Panobinostat
	Regorafenib
	Sonidegib
	Sunitinib
	Tegafur-uracil
	Thalidomide
	Trametinib
	Vandetanib
	Venetoclax
	Vorinostat
Minimal (< 10%)	Busulfan
	Chlorambucil
	Erlotinib
	Gefitinib
	Hydroxyurea
	Melphalan
	Methotrexate
	Pomalidomide
	Ruxolitinib
	Sorafenib
	6-Thioguanine
	Vemurafenib
	Vismodegib

NOTE. Classified emetic potential of oral agents based on a full course of therapy and not a single dose. Adapted from Jordan K et al: 2016 Updated MASCC/ESMO consensus recommendations: Emetic risk classification and evaluation of the emetogenicity of antineoplastic agents. Support Care Cancer 25:271-275, 2017. With permission of Springer.

rolapitant and 60% with placebo. Complete response was also higher with rolapitant in the 0- to 24-hour and 0- to 120-hour periods, but these results were statistically significant in only one of the trials.

Addition of rolapitant to granisetron and dexamethasone was also evaluated in patients who were treated with AC or moderate-emetic-risk chemotherapy.[40] Among patients who were treated with moderate-emetic-risk chemotherapy, addition of rolapitant improved complete response ($P < .05$) during all time points. Among patients who were treated with AC, the only statistically significant improvement in complete response was for the overall phase (63% with rolapitant *v* 55% with placebo; $P = .03$).

Use of dexamethasone on day 1 only in patients who were treated with AC—and for a longer duration in patients who were treated with cisplatin and other high-emetic-risk agents—is consistent with how dexamethasone was administered in the phase III trials of rolapitant[32] and earlier trials of netupitant-palonosetron[88] and aprepitant.[89]

Two phase III trials have tested subcutaneous extended-release granisetron. One trial demonstrated that subcutaneous extended-release granisetron was noninferior to IV palonosetron in patients who received high- or moderate-emetic-risk chemotherapy.[29] Patients in this trial did not receive an NK_1 receptor antagonist. The other trial compared subcutaneous extended-release granisetron with ondansetron in patients who were treated with high-emetic-risk chemotherapy.[39] All patients in the trial also received fosaprepitant. Subcutaneous extended-related granisetron provided superior control of delayed emesis compared with ondansetron, but did not significantly improve complete emesis control for the entire period at risk.

Clinical interpretation. Chemotherapy-induced nausea has remained a challenge, even as control of emesis has improved via use of NK_1 receptor antagonists. The beneficial effect of olanzapine on nausea and the low incidence of additional adverse effects in the trial by Navari et al[27] drove the Expert Panel's recommendation to add olanzapine to antiemetic prophylaxis for patients who were treated with high-emetic-risk chemotherapy. The dose recommended by the Expert Panel (10 mg) was the dose evaluated in the trail by Navari et al. Results from a randomized phase II study, which were presented at the 2016 ASCO Annual Meeting, suggest that a 5-mg dose may also be effective.[90]

The recommendation for antiemetic prophylaxis in patients who were treated with the AC combination is based largely on studies of patients with breast cancer. Less-intensive antiemetic therapy may be an option for AC-treated patients with other types of cancers, such as non-Hodgkin lymphoma, although evidence to support this is limited. A nonrandomized phase II trial that did not meet the criteria for inclusion in the systematic review evaluated a single dose of IV palonosetron among 86 patients who were treated for non-Hodgkin lymphoma.[91] Complete response during the overall phase was 86%, and none of the patients had severe nausea, which suggests that palonosetron in combination with prednisolone as part of the cyclophosphamide, doxorubicin, vincristine, and prednisone regimen may be effective in these patients.

CLINICAL QUESTION 2. What is the optimal treatment to prevent nausea and vomiting from moderate-emetic-risk antineoplastic agents in adults who receive single-day antineoplastic agent therapy?

Recommendation 2.1. Adult patients who are treated with carboplatin area under the curve (AUC) $\geq$ 4 mg/mL per minute should be offered a three-drug combination of an NK_1 receptor antagonist, a $5\text{-}HT_3$ receptor antagonist, and dexamethasone.

Table 3. Antiemetic Dosing for Adults by Chemotherapy Risk Category

Emetic Risk Category	Dose on Day of Chemotherapy	Dose on Subsequent Days
High: Cisplatin and other agents		
NK_1 receptor antagonist		
Aprepitant	125 mg oral	80 mg oral on days 2 and 3
Fosaprepitant	150 mg IV	
Netupitant-palonosetron	300 mg netupitant/0.5 mg palonosetron oral in single capsule (NEPA)	
Rolapitant	180 mg oral	
5-HT_3 receptor antagonist*		
Granisetron	2 mg oral or 1 mg or 0.01 mg/kg IV or 1 transdermal patch or 10 mg subcutaneous	
Ondansetron	8 mg oral twice daily or 8 mg oral dissolving tablet twice daily or three 8 mg oral soluble films or 8 mg or 0.15 mg/kg IV	
Palonosetron	0.50 mg oral or 0.25 mg IV	
Dolasetron	100 mg oral only	
Tropisetron	5 mg oral or 5 mg IV	
Ramosetron	0.3 mg IV	
Dexamethasone		
If aprepitant is used †	12 mg oral or IV	8 mg oral or IV once daily on days 2-4
If fosaprepitant is used†	12 mg oral or IV	8 mg oral or IV on day 2; 8 mg oral or IV twice daily on days 3 and 4
If netupitant-palonosetron is used†	12 mg oral or IV	8 mg oral or IV once daily on days 2-4
If rolapitant is used	20 mg oral or IV	8 mg oral or IV twice daily on days 2-4
Olanzapine	10 mg oral	10 mg oral on days 2-4
High: Anthracycline combined with cyclophosphamide‡		
NK_1 receptor antagonist		
Aprepitant	125 mg oral	80 mg oral; days 2 and 3
Fosaprepitant	150 mg IV	
Netupitant-palonosetron	300 mg netupitant/0.5 mg palonosetron oral in single capsule (NEPA)	
Rolapitant	180 mg oral	
5-HT_3 receptor antagonist*		
Granisetron	2 mg oral or 1 mg or 0.01 mg/kg IV or 1 transdermal patch or 10 mg subcutaneous	
Ondansetron	8 mg oral twice daily or 8 mg oral dissolving tablet twice daily or three 8 mg oral soluble films or 8 mg or 0.15 mg/kg IV	
Palonosetron	0.50 mg oral or 0.25 mg IV	
Dolasetron	100 mg oral only	
Tropisetron	5 mg oral or 5 mg IV	
Ramosetron	0.3 mg IV	
Dexamethasone		
If aprepitant is used†	12 mg oral or IV	
If fosaprepitant is used†	12 mg oral or IV	
If netupitant-palonosetron is used†	12 mg oral or IV	
If rolapitant is used	20 mg oral or IV	
Olanzapine	10 mg oral	10 mg oral on days 2-4
Moderate§		
5-HT_3 receptor antagonist		
Granisetron	2 mg oral or 1 mg or 0.01 mg/kg IV or 1 transdermal patch or 10 mg subcutaneous	
Ondansetron	8 mg oral twice daily or 8 mg oral dissolving tablet twice daily or 8 mg oral soluble film twice daily or 8 mg or 0.15 mg/kg IV	
Palonosetron	0.50 mg oral or 0.25 mg IV	
Dolasetron	100 mg oral only	
Tropisetron	5 mg oral or 5 mg IV	
Ramosetron	0.3 mg IV	
Dexamethasone	8 mg oral or IV	8 mg oral or IV on days 2 and 3‖

(continued on following page)

Table 3. Antiemetic Dosing for Adults by Chemotherapy Risk Category (continued)

Emetic Risk Category	Dose on Day of Chemotherapy	Dose on Subsequent Days
Low¶		
5-HT_3 receptor antagonist		
Granisetron	2 mg oral or 1 mg or 0.01 mg/kg IV or 1 transdermal patch or 10 mg subcutaneous	
Ondansetron	8 mg oral twice daily or 8 mg oral dissolving tablet twice daily or 8 mg oral soluble film twice daily or 8 mg or 0.15 mg/kg IV	
Palonosetron	0.50 mg oral or 0.25 mg IV	
Dolasetron	100 mg oral only	
Tropisetron	5 mg oral or 5 mg IV	
Ramosetron	0.3 mg IV	
Dexamethasone	8 mg oral or IV	

NOTE. For patients who receive multiday chemotherapy, clinicians must first determine the emetic risk of the agent(s) included in the regimen. Patients should receive the agent of the highest therapeutic index daily during chemotherapy and for 2 days thereafter. Patients can also be offered the granisetron transdermal patch or granisetron extended-release injection that deliver therapy over multiple days rather than taking a 5-HT_3 receptor antagonist daily.

Abbreviations: 5-HT_3, 5-hydroxytryptamine-3; IV, intravenous; NK_1, neurokinin 1.

*If netupitant-palonosetron is used, no additional 5-HT_3 receptor antagonist is needed.

†The dexamethasone dose is for patients who are receiving the recommended four-drug regimen for highly emetic chemotherapy. If patients do not receive an NK_1 receptor antagonist, the dexamethasone dose should be adjusted to 20 mg on day 1 and to 16 mg on days 2-4.

‡In non–breast cancer populations—for example, non-Hodgkin lymphoma—receiving a combination of an anthracycline and cyclophosphamide with treatment regimens incorporating corticosteroids, the addition of palonosetron without the use of an NK_1 receptor antagonist, and olanzapine is an option.

§If carboplatin area under the curve is ≥ 4 mg/mL per minute, add an NK_1 receptor antagonist to the 5-HT_3 receptor antagonist and dexamethasone. Dexamethasone dosing is day 1 only: 20 mg with rolapitant, and 12 mg with aprepitant, fosaprepitant, or netupitant-palonosetron.

‖For moderate-emetic-risk agents with a known risk for delayed nausea and vomiting.

¶Patients who are treated with low-emetic-risk antineoplastic therapy should be offered a 5-HT_3 receptor antagonist or dexamethasone.

(Type: evidence based, benefits outweigh harms; quality of evidence: high; strength of recommendation: strong.)

Recommendation 2.2. Adult patients who are treated with moderate-emetic-risk antineoplastic agents—excluding carboplatin AUC ≥ 4 mg/mL per minute—should be offered a two-drug combination of a 5-HT_3 receptor antagonist (day 1) and dexamethasone (day 1). (Type: evidence based, benefits outweigh harms; quality of evidence: high; strength of recommendation: strong.)

Recommendation 2.3. Adult patients who are treated with cyclophosphamide, doxorubicin, oxaliplatin, and other moderate-emetic-risk antineoplastic agents that are known to cause delayed nausea and vomiting may be offered dexamethasone on days 2 to 3. (Type: informal consensus, benefits outweigh harms; quality of evidence: low; strength of recommendation: moderate.)

Literature review update and analysis. Changes to the previous ASCO recommendation for moderate-emetic-risk chemotherapy[5] are the addition of an NK_1 inhibitor for patients who are treated with carboplatin AUC ≥ 4 mg/mL per minute, support for the use of any of the available 5-HT_3 receptor antagonists (the previous version of the guideline specified palonosetron as the preferred option), and the use of dexamethasone on day 1 only unless patients receive a drug with known potential for causing delayed nausea and vomiting.

Use of an NK_1 receptor antagonist in patients who were treated with carboplatin was evaluated in two phase III trials.[17,45] A post hoc analysis compared rolapitant with placebo among 401 carboplatin-treated patients with a range of cancer types.[17] All patients also received oral granisetron (2 mg) on days 1 to 3 and oral dexamethasone (20 mg) on day 1. Patients in the rolapitant arm had higher rates of complete response from 0 to 120 hours (80% *v* 65%; $P < .001$). From 0 to 24 hours, nausea and vomiting were uncommon and the difference in complete response between treatment arms was not significant (92% *v* 88%; $P = .23$).

The efficacy of aprepitant was evaluated in a placebo-controlled trial of 297 patients with gynecologic cancers that were treated with paclitaxel (175 to 180 mg/m^2) and carboplatin (AUC 5 to 6 mg/mL per minute) every 3 weeks.[45] Patients also received granisetron or ondansetron and dexamethasone (20 mg IV) on day 1. Patients in the aprepitant arm had higher rates of no vomiting and no significant nausea and were more likely to achieve a complete response (62% *v* 47%; $P = .007$).

The efficacy of palonosetron relative to other 5-HT_3 receptor antagonists was evaluated in a 2014 meta-analysis.[50] Three of 16 studies focused only on moderate-emetic-risk antineoplastic therapy, but two of these three studies included patients who were treated with the AC combination (now considered high-emetic-risk chemotherapy), and the third study enrolled only 30 patients. It remains uncertain, therefore, whether palonosetron is superior to the other 5-HT_3 receptor antagonists among patients who are treated with moderate-emetic-risk antineoplastic agents.

Use of single-day dexamethasone among patients who receive moderate-emetic-risk antineoplastic agents was evaluated in a randomized trial by Komatsu et al.[20] Palonosetron plus a single day of dexamethasone was noninferior to palonosetron plus 3 days of dexamethasone. These findings are consistent with those of two earlier trials.[92,93]

Evidence is sparse regarding the use of olanzapine in moderate-emetic-risk chemotherapy. Olanzapine is not recommended for routine prophylaxis in this setting. Chiu et al[46] evaluated 10 trials in the preventive setting; six focused only on high-emetic-risk chemotherapy, and four included a mix of high- and moderate-risk chemotherapies. Because only one study provided results that were stratified by emetic risk, the meta-analysis

by Chiu et al did not evaluate emetic risk subgroups in the preventive setting.

Clinical interpretation. The emetic risk of carboplatin (AUC $\geq$ 4 mg/mL per minute) is at the higher end of the moderate-emetic-risk category. Results from studies that incorporated carboplatin in the evaluation of NK_1 receptor antagonists demonstrate significant improvement in the control of nausea and vomiting with the addition of an NK_1 receptor antagonist and justify its use in this setting. The carboplatin dose cutoff (AUC $\geq$ 4 mg/mL per minute) reflects doses used in the clinical trials. The potential value of routinely incorporating an NK_1 receptor antagonist with lower carboplatin doses, such as the commonly used weekly dose of AUC 2 mg/mL per minute, remains unknown and cannot be recommended at this time.

The 2011 recommendation of palonosetron as the preferred 5-HT_3 receptor antagonist in this setting was based on evidence that no longer applies: the recommendation was derived primarily from studies of AC regimens that are now considered to confer high emetic risk. As a result, the Expert Panel changed the 2011 recommendation to allow the use of any of the available 5-HT_3 receptor antagonists.

The change in dexamethasone dose to day 1 only—unless administering an agent with potential to cause delayed nausea and vomiting—reflects the absence of high-quality evidence that dexamethasone is needed for delayed emesis prophylaxis with all moderate-emetic-risk agents. Administration of cyclophosphamide, doxorubicin, and oxaliplatin still justifies dexamethasone on days 2 to 3.

CLINICAL QUESTION 3. What is the optimal treatment to prevent nausea and vomiting from low-emetic-risk antineoplastic agents in adults who receive single-day antineoplastic agent therapy?

Recommendation 3. Adult patients who are treated with low-emetic-risk antineoplastic agents should be offered a single dose of a 5-HT_3 receptor antagonist or a single 8-mg dose of dexamethasone before antineoplastic treatment. (Type: informal consensus, benefits outweigh harms; quality of evidence: low; strength of recommendation: moderate.)

Literature review update and analysis. The change to the previous ASCO recommendation is the addition of a 5-HT_3 receptor antagonist as an option. This was based on the consensus of the Expert Panel. There was no new evidence to inform this recommendation.

Clinical interpretation. Evidence to guide the prevention of nausea and vomiting in this setting remains limited. The decision by the Expert Panel to add a 5-HT_3 receptor antagonist as an option for patients who are treated with low-emetic-risk antineoplastic agents is based on the fact that these agents are an effective and safe standard to prevent emesis caused by high- and moderate-risk anticancer therapies and meets the need of clinicians who have concerns about adverse effects of corticosteroids.

CLINICAL QUESTION 4. What is the optimal treatment to prevent nausea and vomiting from minimal-emetic-risk antineoplastic agents in adults who receive single-day antineoplastic agent therapy?

Recommendation 4. Adult patients who are treated with minimal-emetic-risk antineoplastic agents should not be offered routine antiemetic prophylaxis. (Type: informal consensus, benefits outweigh harms; quality of evidence: low; strength of recommendation: moderate.)

Literature review update and analysis. There was no new evidence that would prompt a change to the recommendation.

CLINICAL QUESTION 5. What is the optimal treatment to prevent nausea and vomiting in adults who receive single-day combination antineoplastic agent therapy?

Recommendation 5. Adult patients who are treated with antineoplastic combinations should be offered antiemetics that are appropriate for the component antineoplastic agent of greatest emetic risk. (Type: informal consensus, benefits outweigh harms; quality of evidence: intermediate; strength of recommendation: moderate.)

Literature review update and analysis. There was no new evidence that would prompt a change to the recommendation.

CLINICAL QUESTION 6. What is the role of adjunctive drugs for nausea and vomiting after cancer treatments?

Recommendation 6. Lorazepam is a useful adjunct to antiemetic drugs but is not recommended as a single-agent antiemetic. (Type: informal consensus; benefits outweigh harms; quality of evidence: low; strength of recommendation: moderate.)

Literature review update and analysis. The change to the previous recommendation is the deletion of diphenhydramine as an adjunctive drug. There was no new evidence regarding lorazepam or diphenhydramine as adjuncts to antiemetics.

Clinical interpretation. Diphenhydramine was incorporated into antiemetic regimens primarily to prevent the adverse effects from dopaminergic blockade—for example, akasthisia—that were anticipated with the use of high-dose metoclopramide before the introduction of selective 5-HT_3 receptor antagonists. With high doses of metoclopramide rarely used for the prevention of antineoplastic agent-induced nausea and vomiting, the rationale for the inclusion of diphenhydramine no longer exists.

CLINICAL QUESTION 7. What is the role of cannabinoids in the prevention or treatment of nausea and vomiting induced by antineoplastic agents or radiation?

Recommendation 7. Evidence remains insufficient for a recommendation regarding medical marijuana for the prevention of nausea and vomiting in patients with cancer who receive chemotherapy or radiation therapy. Evidence is also insufficient for a recommendation regarding the use of medical marijuana in place of the tested and US Food and Drug Administration–approved cannabinoids, dronabinol and nabilone, for the treatment of nausea and vomiting caused by chemotherapy or radiation therapy.

Literature review update and analysis. The cannabinoid receptor plays a role in human physiology. A 2015 meta-analysis evaluated the role of cannabinoids in chemotherapy-induced nausea and vomiting.[51] Trials included in the analysis were conducted between 1975 and 1991 and none involved comparisons with current antiemetic regimens. The authors concluded, "Cannabis-based medications may be useful for treating refractory chemotherapy-induced nausea and vomiting. However, methodological limitations of the trials limit our conclusions and further research reflecting current chemotherapy regimens and newer anti-emetic drugs is likely to modify these conclusions."[51](p 2)

Clinical interpretation. As of this writing, 29 states, the District of Columbia, Guam, and Puerto Rico have sanctioned the use of medical marijuana. In contrast to US Food and Drug

Administration–approved cannabinoids, dronabinol and nabilone, for which doses and schedules have been precisely defined, this information is not available for the various preparations of medical marijuana. The exact mechanisms by which marijuana may prevent or treat nausea and vomiting remain uncertain, although mechanisms have been proposed.[94] 5-HT_3 receptor antagonists, dexamethasone, NK_1 receptor antagonists, and olanzapine are recommended for the prevention of nausea and vomiting after chemotherapy and radiation as outlined in other recommendations. When a cannabinoid is chosen for rescue and refractory use, the Expert Panel recommends dronabinol or nabilone.

CLINICAL QUESTION 8. What is the role of complementary and alternative therapies in the prevention or treatment of nausea and vomiting induced by antineoplastic agents or radiation?

Recommendation 8. Evidence remains insufficient for a recommendation for or against the use of ginger, acupuncture/acupressure, and other complementary or alternative therapies for the prevention of nausea and vomiting in patients with cancer.

Literature review update and analysis. The wording of the recommendation has changed, but the content remains the same: The Expert Panel made no recommendation for or against complementary or alternative therapies for the prevention of nausea and vomiting.

The role of ginger in the prevention of chemotherapy-induced nausea and vomiting was evaluated in two trials[12,37] and a meta-analysis.[48] A 2015 trial enrolled 60 women who were treated with anthracycline-based chemotherapy.[12] All women were receiving at least their second cycle of chemotherapy and had experienced chemotherapy-induced nausea with a severity of grade ≥ 3 during previous cycles. Patients were randomly assigned to receive powdered ginger plus standard of care or standard of care alone. Ginger was administered orally, twice a day, for the first 3 days of chemotherapy. Standard care included an NK_1 receptor antagonist, a 5-HT_3 receptor antagonist, and dexamethasone. Patients in the ginger arm reported less severe nausea and fewer vomiting episodes on days 2, 3, and 5. Detailed safety information was not provided, but the authors noted that no adverse events that were attributable to ginger were recorded. A second trial analyzed 576 patients—of 744 randomly assigned patients—who received one of three doses of ginger or a placebo.[37] All patients received a 5-HT_3 inhibitor and dexamethasone during study treatment, but information was not provided about type of chemotherapy. Ginger or placebo was administered three times a day for 6 days, starting 3 days before chemotherapy. On day 1 of chemotherapy, average and maximum nausea were lower in the ginger arms than in the placebo arm. The two lower doses of ginger (0.5 g and 1.0 g) produced the largest reductions in nausea intensity.

A 2013 systematic review evaluated five trials, four of which were included in a meta-analysis.[48] The trial by Ryan et al,[37] described above, was identified by the review but was not included in the meta-analysis because it did not provide data on the incidence of nausea and vomiting. In the meta-analysis, ginger did not have a significant effect on the incidence of acute nausea, acute vomiting, or delayed vomiting.

Two trials evaluated acupuncture for the prevention of nausea and vomiting[15,33] and two evaluated acupressure.[16,24] A crossover trial of acupuncture enrolled 70 patients with gynecologic cancers who were receiving platinum-based chemotherapy.[33] Patients were randomly assigned to receive acupuncture in cycle 1 and ondansetron in cycle 2, or the reverse. All patients also received dexamethasone for 3 days. Ondansetron was administered for breakthrough emesis to patients in both arms. Complete response from 0 to 24 hours was similar with the two treatments, but acupuncture produced higher complete response rates from 24 to 120 hours (53% *v* 36%; $P = .02$). Constipation and insomnia were less common with acupuncture than with ondansetron. A second trial compared acupuncture with sham acupuncture among 215 patients who received radiotherapy for gynecologic, anal, colorectal, stomach, pancreatic, or testicular cancers.[15] Seventy percent of patients in the true acupuncture arm experienced nausea at least once compared with 62% of patients in the sham acupuncture arm; this difference was not statistically significant. The two trials of acupressure wristbands found no significant benefit against nausea and vomiting when wristbands were added to standard antiemetic treatment among patients who were treated with chemotherapy.[16,24]

Clinical interpretation. The ability of ginger to control antineoplastic agent–induced nausea and vomiting is still not confirmed and evidence is conflicting. Evidence regarding acupuncture and acupressure is also conflicting and is inadequate to make a recommendation regarding routine use. There is no increase in adverse effects associated with the use of ginger, acupuncture, or acupressure.

CLINICAL QUESTION 9. What is the optimal treatment for the prevention of nausea and vomiting in patients who are undergoing high-dose chemotherapy for stem cell or bone marrow transplantation conditioning?

Recommendation 9. Adult patients who are treated with high-dose chemotherapy and stem cell or bone marrow transplantation should be offered a three-drug combination of an NK_1 receptor antagonist, 5-HT_3 receptor antagonist, and dexamethasone. (Type: evidence based, benefits outweigh harms; quality of evidence: high; strength of recommendation: strong.)

Literature review update and analysis. The change to the previous recommendation is the addition of an NK_1 receptor antagonist. Three trials evaluated aprepitant among patients who were undergoing high-dose chemotherapy and stem cell or bone marrow transplantation. Schmitt et al[38] evaluated 364 adults with multiple myeloma who were undergoing autologous stem cell transplantation after high-dose melphalan conditioning. Patients were randomly assigned to receive either aprepitant or placebo on days 1 to 4. All patients also received granisetron on days 1 to 4 and dexamethasone on days 1 to 3. Overall complete response—no emesis and no rescue medication within 120 hours of melphalan administration—was 58% in the aprepitant arm and 41% in the placebo arm ($P = .004$). Rates of adverse events were similar in the two treatment arms. Stiff et al[41] evaluated 179 adult patients who were scheduled to receive high-dose cyclophosphamide preparative regimens before stem cell transplantation. Patients were randomly assigned to receive either aprepitant or placebo during and for 3 days after the preparative regimen. All patients also received ondansetron and dexamethasone on each day of the preparative regimen and for 1 additional day. Complete control of vomiting occurred in 73% of patients in the aprepitant arm and in 23% of patients in the placebo arm ($P = .001$). Average nausea scores were not statistically significantly different between arms.

Regimen-related toxicity, engraftment, and transplantation outcomes were similar in the two groups. In the first 30 days, five patients died in the aprepitant arm—three from sepsis, one from toxic epidermal necrolysis and sepsis, and one from veno-occlusive disease of the liver—and two died in the placebo arm—one from viral pneumonia/encephalitis and one from fungal pneumonia. Finally, Svanberg et al[42] evaluated prolonged aprepitant treatment in 96 patients who received high-dose chemotherapy before undergoing autologous stem cell transplantation. Patients in the aprepitant arm were more likely to experience no vomiting than patients in the placebo arm. There was no statistically significant difference between treatment arms in the number of days with nausea or the use of rescue medication.

Clinical interpretation. In each of the trials described above, addition of aprepitant to a 5-HT_3 receptor antagonist and dexamethasone resulted in significantly less vomiting.

CLINICAL QUESTION 10. What is the optimal treatment for the prevention of nausea and vomiting for adults who receive multiday antineoplastic agent therapy?

Recommendation 10.1. Adult patients who are treated with multiday antineoplastic agents should be offered antiemetics before treatment that are appropriate for the emetic risk of the antineoplastic agent administered on each day of the antineoplastic treatment and for 2 days after completion of the antineoplastic regimen. (Type: evidence based, benefits outweigh harms; quality of evidence: intermediate; strength of recommendation: moderate.)

Recommendation 10.2. Adult patients who are treated with 4- or 5-day cisplatin regimens should be offered a three-drug combination of an NK_1 receptor antagonist, a 5-HT_3 receptor antagonist, and dexamethasone. (Type: evidence based, benefits outweigh harms; quality of evidence: high; strength of recommendation: strong.)

Literature review update and analysis. Recommendation 10.2 strengthens the previous recommendation regarding antiemetic prophylaxis among patients who are treated with 4- or 5-day cisplatin regimens.

One trial in patients who received a 5-day cisplatin regimen for testicular cancer demonstrated improved outcomes with no increase in adverse effect after the addition of an NK_1 receptor antagonist to the combination of dexamethasone and a 5-HT_3 receptor antagonist.[11] Aprepitant was administered on days 3 to 7. Complete response was higher in the aprepitant arm than in the placebo arm in both the acute phase (days 1 to 5; 47% *v* 15%; $P < .001$) and the delayed phase (days 6 to 8; 63% *v* 35%; $P < .001$). In a meta-analysis of this trial and a 2007 trial, addition of an NK_1 receptor antagonist resulted in a more than three-fold increase in the odds of no emesis among patients who were treated with 5-day cisplatin (risk difference, 28%; odds ratio, 3.56; 95% CI, 1.77 to 7.15).[10]

Clinical interpretation. All studies support the use of a three-drug antiemetic regimen for patients who are treated with 5-day cisplatin.[95,96]

CLINICAL QUESTION 11. What is the optimal antiemetic regimen for adults who experience nausea and vomiting secondary to therapy with an antineoplastic agent despite optimal prophylaxis (breakthrough)?

Recommendation 11.1. For patients with breakthrough nausea or vomiting, clinicians should re-evaluate emetic risk, disease status, concurrent illnesses, and medications and ascertain that the best regimen is being administered for the emetic risk. (Type: informal consensus, benefits outweigh harms; quality of evidence: low; strength of recommendation: moderate.)

Recommendation 11.2. Adult patients who experience nausea or vomiting despite optimal prophylaxis, and who did not receive olanzapine prophylactically, should be offered olanzapine in addition to continuing the standard antiemetic regimen. (Type: evidence based; benefits outweigh harms, quality of evidence: intermediate; strength of recommendation: moderate.)

Recommendation 11.3. Adult patients who experience nausea or vomiting despite optimal prophylaxis, and who have already received olanzapine, may be offered a drug of a different class—for example, an NK_1 receptor antagonist, lorazepam or alprazolam, a dopamine receptor antagonist, dronabinol, or nabilone—in addition to continuing the standard antiemetic regimen. (Type: informal consensus, benefits outweigh harms; quality of evidence: intermediate for dronabinol and nabilone, low otherwise; strength of recommendation: moderate.)

Literature review update and analysis. Recommendation 11.2—the addition of olanzapine for patients who have not received it previously—is a new recommendation. A 2013 trial compared olanzapine with metoclopramide for breakthrough nausea and vomiting among patients who were treated with high-emetic-risk chemotherapy who did not receive prophylactic olanzapine.[25] All patients received initial prophylaxis with dexamethasone, palonosetron, and fosaprepitant. Of 276 patients enrolled, 112 developed breakthrough nausea and vomiting and 108 were included in the analysis—56 in the olanzapine arm and 52 in the metoclopramide arm. During the 72-hour observation period after breakthrough nausea and vomiting, patients who were treated with olanzapine were more likely than patients who were treated with metoclopramide to have no emesis (70% *v* 31%; $P < .01$) and no nausea (68% *v* 23%; $P < .01$). There were no grade 3 or 4 adverse events. Scores for symptoms, such as sedation, as measured by the MD Anderson Symptom Inventory, did not differ significantly between the two study arms.

Clinical interpretation. Olanzapine provides a benefit in the breakthrough nausea setting for patients who did not receive it prophylactically.

CLINICAL QUESTION 12. What treatment options are available for adults who experience anticipatory nausea and vomiting?

Recommendation 12. All patients should receive the most active antiemetic regimen appropriate for the antineoplastic agents being administered. Clinicians should use such regimens with initial antineoplastic treatment, rather than assessing the patient's emetic response with less effective antiemetic treatment. If a patient experiences anticipatory emesis, clinicians may offer behavioral therapy with systematic desensitization. (Type: informal consensus, benefits outweigh harms; quality of evidence: low; strength of recommendation: moderate.)

Literature review update and analysis. There was no new evidence that would prompt a change to the recommendation.

RADIATION-INDUCED NAUSEA AND VOMITING IN ADULTS

Updated risk stratification according to site of radiation treatment is provided in Table 4. Dosing schedules according to risk are listed in Table 5.

CLINICAL QUESTION 13. What is the optimal prophylaxis for nausea and vomiting caused by high-emetic-risk radiation?

Recommendation 13. Adult patients who are treated with high-emetic-risk radiation therapy should be offered a two-drug combination of a 5-HT_3 receptor antagonist and dexamethasone before each fraction and on the day after each fraction if radiation therapy is not planned for that day. (Type: evidence based, benefits outweigh harms; quality of evidence: high; strength of recommendation: strong.)

Literature review update and analysis. The 2011 recommendation specified a 5-day course of dexamethasone; the updated recommendation allows the duration of dexamethasone to match the duration of 5-HT_3 receptor antagonist use. No new evidence was identified.

Clinical interpretation. Total nodal irradiation has been removed from the 2017 guideline as it is now seldom used. Nodal subsites of total nodal irradiation can be managed with the appropriate recommendations for moderate- or low-emetic-risk radiation.

High-emetic-risk, multiple-fraction radiation therapy schedules vary. Fractions may be administered once or multiple times per day, during sequential or staggered days. Optimal frequency and duration of prophylactic 5-HT_3 receptor antagonist therapy for high-emetic-risk single-fraction or multiple-fraction radiation are unclear. Previous studies administered prophylactic 5-HT_3 receptor antagonist therapy for durations longer than, equal to, and shorter than the duration of radiation therapy.[97] Randomized studies that have compared these approaches are lacking. On the basis of consensus, the Expert Panel favors extending the duration of prophylaxis to include the day after each fraction to address the risk of delayed radiation-induced nausea and vomiting.

Optimal frequency and duration of prophylactic dexamethasone therapy when administered with prophylactic 5-HT_3 receptor antagonist therapy for high-emetic-risk single-fraction or multiple-fraction radiation therapy are unclear. Previous studies administered prophylactic dexamethasone therapy in this setting for durations longer than[98] and shorter than[99] the duration of radiation therapy. Randomized studies that have compared these approaches are lacking. A study that involved moderate-emetic-risk radiation therapy demonstrated a benefit for a number of secondary end points by adding prophylactic dexamethasone to prophylactic 5-HT_3 receptor antagonist therapy before the first five fractions.[100] The 2011 recommendation for prophylactic dexamethasone therapy before the first five fractions did not ensure prophylaxis for patients who received more than five fractions. The Expert Panel favors extending the duration of prophylaxis to include the day after each fraction, which is in line with the administration of prophylactic 5-HT_3 receptor antagonist therapy.

Table 4. Emetic Risk in Adults by Site of Radiation Therapy

Risk Level	Site
High (> 90%)	Total body irradiation
Moderate (30%-90%)	Upper abdomen, craniospinal irradiation
Low (10%-30%)	Brain, head and neck, thorax, pelvis
Minimal (< 10%)	Extremities, breast

CLINICAL QUESTION 14. What is the optimal prophylaxis for nausea and vomiting caused by moderate-emetic-risk radiation therapy?

Recommendation 14. Adult patients who are treated with moderate-emetic-risk radiation therapy should be offered a 5-HT_3 receptor antagonist before each fraction, with or without dexamethasone before the first five fractions. (Type: evidence based, benefits outweigh harms; quality of evidence: high; strength of recommendation: moderate.)

Literature review update and analysis. The 2011 recommendation was reworded for clarity. Studies of acupuncture[15] and berberine[22] have been identified since the 2011 update but did not change the previous recommendation.

Clinical interpretation. Upper-body irradiation and half-body irradiation have been removed from the 2017 guideline, as they are variably defined and now seldom used. Upper abdomen subsites of upper- and half-body irradiation can be managed with the recommendation for moderate-emetic-risk radiation therapy. Craniospinal irradiation has been reclassified as moderate emetic risk rather than low emetic risk to acknowledge the involvement of the upper abdomen with this technique.

The Expert Panel suggests that upper abdomen be operationally defined as the anatomic region that extends from the superior border of the 11th thoracic vertebra to the inferior border of the third lumbar vertebra. Radiation therapy that involves this region, at least in part, would be considered moderate emetic risk. This definition is consistent with that from more contemporary studies of radiation-induced nausea and vomiting.[100,101]

Optimal frequency and duration of prophylactic 5-HT_3 receptor antagonist therapy for moderate-emetic-risk, single-fraction or multiple-fraction radiation therapy are unclear. Previous studies administered prophylactic 5-HT_3 receptor antagonist therapy for durations longer than, equal to, and shorter than the duration of radiation therapy.[97] Randomized studies that have compared these approaches are lacking. On the basis of informal consensus, the Expert Panel favors prophylaxis before each fraction but recommends careful monitoring of patients during radiation therapy schedules that span multiple weeks to detect symptoms experienced during interspersed days when radiation therapy and prophylaxis are not administered—for example, weekends—and to balance the benefits and toxicities of prolonged 5-HT_3 receptor antagonist therapy. A study that involved moderate-emetic-risk radiation therapy demonstrated a benefit for a number of secondary end points by adding prophylactic dexamethasone therapy to prophylactic 5-HT_3 receptor antagonist therapy before the first five fractions.[100]

CLINICAL QUESTION 15. What is the optimal treatment to manage nausea and vomiting associated with low-emetic-risk radiation therapy?

Recommendation 15. Adult patients who are treated with radiation therapy to the brain should be offered rescue dexamethasone therapy. Adult patients who are treated with radiation therapy to the head and neck, thorax, or pelvis should be offered

Table 5. Antiemetic Administration in Adults by Radiation Therapy Risk Category

Risk Category	Dose	Schedule
High: Total body irradiation		
5-HT_3 receptor antagonist[a]		
Ondansetron	8 mg oral or 8 mg oral dissolving tablet, or 8 mg oral soluble film or 8 mg or 0.15 mg/kg IV	Use as prophylactic therapy—once daily to twice daily on days of radiation therapy, with first dose administered before radiation therapy; once daily to twice daily on the day after each day of radiation therapy, if radiation therapy is not planned for that day
Granisetron	2 mg oral or 1 mg or 0.01 mg/kg IV	Use as prophylactic therapy—once daily on days of radiation therapy, before radiation therapy; once daily on the day after each day of radiation therapy, if radiation therapy is not planned for that day
Corticosteroid		
Dexamethasone	4 mg oral or IV	Use as prophylactic therapy—once daily on days of radiation therapy, before radiation therapy; once daily on the day after each day of radiation therapy, if radiation therapy is not planned for that day
Moderate: Upper abdomen,[b] craniospinal irradiation		
5-HT_3 receptor antagonist[c]		
Ondansetron	8 mg oral or 8 mg oral dissolving tablet, or 8 mg oral soluble film or 8 mg or 0.15 mg/kg IV	Use as prophylactic therapy—once daily to twice daily on days of radiation therapy, with the first dose administered before radiation therapy [d]
Granisetron	2 mg oral or 1 mg or 0.01 mg/kg IV	Use as prophylactic therapy—once daily on days of radiation therapy, before radiation therapy[d]
Tropisetron	5 mg oral or IV	Use as prophylactic therapy—once daily on days of radiation therapy, before radiation therapy[d]
Corticosteroid		
Dexamethasone	4 mg oral or IV	Use as prophylactic therapy—once daily on the days of first five radiation therapy fractions, before radiation therapy
Low: Brain, head and neck, thorax, pelvis[e]		
5-HT_3 receptor antagonist[f]		
Ondansetron	8 mg oral or 8 mg oral dissolving tablet, or 8 mg oral soluble film or 8 mg or 0.15 mg/kg IV	Use as rescue therapy[g]
Granisetron	2 mg oral or 1 mg or 0.01 mg/kg IV	Use as rescue therapy[g]
Corticosteroid		
Dexamethasone	For brain, if not already taking corticosteroid, 4 mg oral or IV; for other anatomic regions, 4 mg oral or IV	Use as rescue therapy—titrate up as needed to a maximum of 16 mg oral or IV daily[g]
Dopamine receptor antagonist[h]		
Prochlorperazine	5-10 mg oral or IV	Use as rescue therapy—titrate up as needed to maximum of 3-4 administrations daily[g]
Metoclopramide	5-20 mg oral or IV	Use as rescue therapy—titrate up as needed to maximum of 3-4 administrations daily[g]
Minimal: Extremities, breast		
5-HT_3 receptor antagonist[i]		
Ondansetron	8 mg oral 8 mg oral dissolving tablet, or 8 mg oral soluble film or 8 mg or 0.15 mg/kg IV	Use as rescue therapy[j]
Granisetron	2 mg oral or 1 mg or 0.01 mg/kg IV	Use as rescue therapy[j]
Corticosteroid		
Dexamethasone	4 mg oral or IV	Use as rescue therapy[j]
Dopamine receptor antagonist[h]		
Prochlorperazine	5-10 mg oral or IV	Use as rescue therapy[j]
Metoclopramide	5-20 mg oral or IV	Use as rescue therapy[j]

Abbreviations: 5-HT_3, 5-hydroxytryptamine-3; IV, intravenous; NK_1, neurokinin 1.

[a]Either 5-HT_3 receptor antagonist is appropriate. Palonosetron, dolasetron, and tropisetron have been removed from the 2017 guideline as data on their use in high-emetic-risk radiation therapy are lacking.

[b]Radiation therapy involving, at least in part, the anatomic region from the superior border of the 11th thoracic vertebra to the inferior border of the third lumbar vertebra.

[c]Ondansetron or granisetron preferred due to a larger body of evidence for these agents. Palonosetron and dolasetron have been removed from the 2017 guideline as sufficient data on their use in moderate-emetic-risk radiation therapy are lacking.

[d]Monitor patients during radiation therapy schedules that span multiple weeks to detect symptoms experienced during interspersed days when radiation therapy and prophylaxis are not administered—for example, weekends—and to balance benefits and toxicities of prolonged 5-HT_3 receptor antagonist therapy.

[e]Corticosteroid is the preferred first agent for the brain. Any antiemetic class is appropriate for head and neck, thorax, and pelvis.

[f]Either 5-HT_3 receptor antagonist is appropriate. Palonosetron, dolasetron, and tropisetron have been removed from the 2017 guideline as sufficient data on their use in low-emetic-risk radiation therapy are lacking

[g]Depending on the severity of symptoms and the remaining duration of radiation therapy, patients can receive subsequent rescue therapy as needed or begin receiving prophylactic therapy for the remainder of radiation therapy.

[h]Either dopamine receptor antagonist is appropriate.

[i]Either 5-HT_3 receptor antagonist is appropriate. Palonosetron, dolasetron, and tropisetron have been removed from the 2017 guideline as sufficient data on their use in minimal-emetic-risk radiation therapy are lacking.

[j]Patients can receive rescue therapy as needed. Alternative explanations for symptoms should be investigated to avoid the need for prophylactic therapy for the remainder of radiation therapy.

rescue therapy with a 5-HT_3 receptor antagonist, dexamethasone, or a dopamine receptor antagonist. (Type: informal consensus, benefits outweigh harms; quality of evidence: low; strength of recommendation: weak.)

Literature review update and analysis. The 2011 recommendation advised either prophylactic or rescue 5-HT_3 receptor antagonist therapy for low-emetic-risk radiation therapy. The updated recommendation advises rescue therapy only, with the type of rescue therapy varying by the site of radiation. Studies of acupuncture[15] and berberine[22] have been identified since the 2011 update but did not change the previous recommendation.

Clinical interpretation. In this update, cranium has been renamed as brain to reflect the intended underlying anatomic site and to avoid redundancy with head and neck. Lower thorax region has been renamed as thorax; evidence to support differentiating between the lower thorax region and other thoracic regions with respect to radiation-induced nausea and vomiting is lacking.

The Expert Panel notes that, compared with high- and moderate-emetic-risk radiation therapy, radiation-induced nausea and vomiting incidence data and data from randomized intervention trials for low-emetic-risk radiation therapy are lacking. Given the absence of evidence to support prophylactic therapy, as well as the potential toxicities of prolonged prophylactic therapy, prophylaxis for low-emetic-risk radiation has been removed from the 2017 guideline, and the Expert Panel favors a recommendation for rescue therapy alone. Depending on the severity of symptoms and the remaining duration of radiation therapy, patients can receive either subsequent rescue therapy as needed or may begin receiving prophylactic therapy for the remainder of radiation therapy. The Expert Panel favors rescue dexamethasone therapy for radiation therapy to the brain as it reflects typical practice patterns.[102] Furthermore, patients who begin radiation therapy to the brain while already taking dexamethasone often have the dexamethasone dose increased as an initial intervention. Rescue dexamethasone therapy and rescue dopamine receptor antagonist therapy were added to rescue 5-HT_3 receptor antagonist therapy so as not to restrict options within the low-emetic-risk category, which includes a heterogeneous group of anatomic sites. Optimal frequency and duration of rescue therapy for these agents for low-emetic-risk, single-fraction or multiple-fraction radiation therapy are unclear.

CLINICAL QUESTION 16. What is the optimal treatment to manage nausea and vomiting associated with minimal-emetic-risk radiation therapy?

Recommendation 16. Adult patients who are treated with minimal-emetic-risk radiation therapy should be offered rescue therapy with a 5-HT_3 receptor antagonist, dexamethasone, or a dopamine receptor antagonist. (Type: informal consensus, benefits outweigh harms; quality of evidence: low; strength of recommendation: weak.)

Literature review update and analysis. The updated recommendation adds dexamethasone as a rescue therapy option. No new evidence was identified.

Clinical interpretation. Rescue dexamethasone therapy was added to rescue 5-HT_3 receptor antagonist therapy and rescue dopamine receptor antagonist therapy recommendations so as not to restrict options. Patients can receive rescue therapy as needed. Alternative explanations for symptoms should be investigated to avoid the need for prophylactic therapy for the remainder of radiation therapy.

CLINICAL QUESTION 17. What is the optimal treatment for the management of nausea and vomiting during concurrent radiation and antineoplastic agent therapy?

Recommendation 17. Adult patients who are treated with concurrent radiation and antineoplastic agents should receive antiemetic therapy that is appropriate for the emetic risk level of the antineoplastic agents, unless the risk level of the radiation therapy is higher. During periods when prophylactic antiemetic therapy for the antineoplastic agents has ended and ongoing radiation therapy would normally be managed with its own prophylactic therapy, patients should receive prophylactic therapy that is appropriate for the emetic risk of the radiation therapy until the next period of antineoplastic therapy, rather than receiving rescue therapy for the antineoplastic agents as needed. (Type: informal consensus, benefits outweigh harms; quality of evidence: intermediate; strength of recommendation: moderate.)

Literature review update and analysis. The second sentence of the updated recommendation is new. Two trials were identified but did not alter the recommendations. One trial evaluated the addition of fosaprepitant to palonosetron and dexamethasone among women who received low-emetic-risk pelvic radiation and concurrent weekly cisplatin.[36] The other trial compared fosaprepitant with olanzapine—each given with palonosetron and dexamethasone—among patients with head and neck or esophageal cancers who received radiation therapy and concurrent cisplatin and fluorouracil.[26]

Clinical interpretation. The 2011 recommendation did not address the period after the end of prophylaxis for antineoplastic agent–induced nausea and vomiting. The updated recommendation addresses this gap.

ANTINEOPLASTIC AGENT–INDUCED NAUSEA AND VOMITING IN PEDIATRIC PATIENTS

Pediatric clinicians should consult recognized pediatric drug formularies for information regarding appropriate pediatric dosing of antiemetic agents.

CLINICAL QUESTION 18. What is the optimal treatment to prevent nausea and vomiting from high-emetic-risk antineoplastic agents in pediatric patients?

Recommendation 18.1. Pediatric patients who are treated with high-emetic-risk antineoplastic agents should be offered a three-drug combination of a 5-HT_3 receptor antagonist, dexamethasone, and aprepitant. (Type: evidence based, benefits outweigh harms; quality of evidence: intermediate; strength of recommendation: strong.)

Recommendation 18.2. Pediatric patients who are treated with high-emetic-risk antineoplastic agents who are unable to receive aprepitant should be offered a two-drug combination of a 5-HT_3 receptor antagonist and dexamethasone. (Type: evidence based, benefits outweigh harms; quality of evidence: intermediate; strength of recommendation: strong.)

Recommendation 18.3. Pediatric patients who are treated with high-emetic-risk antineoplastic agents who are unable to receive dexamethasone should be offered a two-drug combination of palonosetron and aprepitant. (Type: evidence based, benefits

outweigh harms; quality of evidence: intermediate; strength of recommendation: strong.)

Literature review update and analysis. Changes to the previous recommendations are the addition of aprepitant for pediatric patients who receive high-emetic-risk chemotherapy and the addition of recommendations for children who cannot receive aprepitant or dexamethasone.

The addition of aprepitant to a 5-HT_3 receptor antagonist in pediatric patients was evaluated in two studies. Bakhshi et al[13] analyzed 93 patients age 5 to 18 years who received 1-day or 3-day high-emetic-risk chemotherapy. In addition to aprepitant or placebo, all patients received ondansetron and dexamethasone. From 0 to 24 hours, moderate-to-severe vomiting occurred in 38% of patients in the aprepitant arm and 72% of patients in the placebo arm ($P = .001$). Moderate-to-severe vomiting was also less common among patients in the aprepitant arm during the period from 24 to 120 hours (42% *v.* 56%), but this result was not statistically significant ($P = .18$). No grade 3 or 4 adverse events were reported. In a second trial, Kang et al[18] analyzed 302 children age 6 months to 17 years who received single-day or multiple-day, moderate or high-emetic-risk chemotherapy. All patients received ondansetron and 28% received dexamethasone. Addition of aprepitant improved complete response rates during both the 0- to 24-hour and 24- to 120-hour periods after chemotherapy. The most common serious adverse event was febrile neutropenia, which occurred in 15% of patients in both study arms.

A noninferiority trial by Kovacs et al[21] contributed to the US Food and Drug Administration approval of palonosetron for use in children during initial and repeat courses of emetogenic chemotherapy, including high-emetic-risk chemotherapy. The study compared two doses of palonosetron (10 μg/kg and 20 μg/kg) with ondansetron among children who received either high- or moderate-emetic-risk chemotherapy. The higher dose of palonosetron was noninferior to ondansetron with respect to complete response in the 0- to 24-hour period and potentially superior to ondansetron from 0 to 120 hours.

A 2016 Cochrane review evaluated a range of different antiemetics in children.[49] The review supports the efficacy of 5-HT_3 receptor antagonists in patients who receive chemotherapy and notes that granisetron and palonosetron may be more effective than ondansetron. The review also notes that the addition of dexamethasone improves the control of nausea and vomiting, albeit with an uncertain risk-benefit profile.

Clinical interpretation. For aprepitant, the phase III trial by Bakhshi et al[13] is the most comprehensive and clinically useful trial in children who receive multiple-day chemotherapy and a standard antiemetic backbone. Aprepitant is the only NK_1 receptor antagonist that has been recommended for children and adolescents, as published pediatric experience with other agents within this class either did not meet the criteria for inclusion in the evidence base of this guideline update or does not exist. Evidence gaps in the treatment of children include the dosing of palonosetron and aprepitant in multiday chemotherapy.

CLINICAL QUESTION 19. What is the optimal treatment to prevent nausea and vomiting from moderate-emetic-risk antineoplastic agents in pediatric patients?

Recommendation 19.1. Pediatric patients who are treated with moderate-emetic-risk antineoplastic agents should be offered a two-drug combination of a 5-HT_3 receptor antagonist and dexamethasone. (Type: evidence based, benefits outweigh harms; quality of evidence: intermediate; strength of recommendation: strong.)

Recommendation 19.2. Pediatric patients who are treated with moderate-emetic-risk antineoplastic agents and who are unable to receive dexamethasone should be offered a two-drug combination of a 5-HT_3 receptor antagonist and aprepitant. (Type: evidence based, benefits outweigh harms; quality of evidence: intermediate; strength of recommendation: weak.)

Literature review update and analysis. The recommendation for children who cannot receive dexamethasone is new. Results of the updated literature review in pediatric patients are described in Clinical Question 18.

CLINICAL QUESTION 20. What is the optimal treatment to prevent nausea and vomiting from low-emetic-risk antineoplastic agents in pediatric patients?

Recommendation 20. Pediatric patients who are treated with low-emetic-risk antineoplastic agents should be offered ondansetron or granisetron. (Type: informal consensus, benefits outweigh harms; quality of evidence: low; strength of recommendation: strong.)

Literature review update and analysis. This is a new recommendation. No new evidence was identified to address this question.

Clinical interpretation. The recommendation is generalized from evidence in adults.

CLINICAL QUESTION 21. What is the optimal treatment to prevent nausea and vomiting from minimal-emetic-risk antineoplastic agents in pediatric patients?

Recommendation 21. Pediatric patients who are treated with minimal-emetic-risk antineoplastic agents should not be offered routine antiemetic prophylaxis. (Type: informal consensus, benefits outweigh harms; quality of evidence: low; strength of recommendation: strong.)

Literature review update and analysis. This is a new recommendation. No new evidence was identified to address this question.

Clinical interpretation. The recommendation is generalized from evidence in adults.

NEW AGENTS AND FORMULATIONS

New antiemetic medications that have become available since the previous update are rolapitant—an NK_1 receptor antagonist—and granisetron—a 5-HT_3 receptor antagonist—extended-release injection. The dosing of these agents is provided in Table 3.

PATIENT AND CLINICIAN COMMUNICATION

Health care providers frequently underestimate the incidence and severity of nausea and vomiting caused by radiation therapy and chemotherapy.[103] To ensure optimal symptom management, clinicians should assess symptoms throughout therapy. Patient

response to antiemetic therapy may change over time, requiring reassessments and modifications to antiemetic strategies as warranted. Clinicians are encouraged to provide patients with a prescription for a rescue antiemetic before the patient begins the first day of treatment.

Checklists can facilitate the collection of direct patient reporting of symptom severity and persistence. For adults, assessment tools that are similar to the Multinational Association for Supportive Care in Cancer Antiemesis Tool (http://www.mascc.org/mat), which assesses nausea and vomiting within 24 hours of treatment as well as delayed onset, and the National Cancer Institute Patient-Reported Outcomes Version of the Common Terminology Criteria for Adverse Events (https://healthcaredelivery.cancer.gov/pro-ctcae/) nausea items may be helpful to clinicians. In addition, mobile chemotherapy diaries and symptom tracker applications may be helpful to patients and health care providers. Tools that have been validated for use in children include the Pediatric Nausea Assessment Tool[104] and the Symptom Screening in Pediatrics Tool.[105]

Table 6. Estimated Costs for Antiemetic Products

Agent	Dose	Schedule	Price Per Dose (USD)	Total Cost Per Treatment Cycle (USD)
5-HT_3 receptor antagonists				
Ondansetron IV	8 mg/0.15 mg/kg	Prechemotherapy, one dose	1.10	1.10
Ondansetron oral (generic)	8 mg	Twice daily on days 1-3	6.50	6.50
Ondansetron oral (brand)	8 mg	Twice daily on days 1-3	45.55	268.28
Ondansetron oral dissolving tablet (generic)	8 mg	Every 12 hours as needed, days 1-3	6.50	6.50
Ondansetron oral dissolving tablet (brand)	8 mg	Every 12 hours as needed, days 1-3	85.05	253.14
Ondansetron oral soluble film (brand)	8 mg	Every 12 hours as needed, days 1-3	75.82	225.46
Granisetron IV	1 mg or 0.01 mg/kg IV	Prechemotherapy, one dose	3.13	3.13
Granisetron oral	1 mg	Once (2 mg) on day 1, 1 mg twice daily on days 2 and 3	6.50	14.36
Granisetron transdermal	3.1 mg	Prechemotherapy, up to 7 days	467.00	467.00
Granisetron extended-release injection, for subcutaneous use*	10 mg	Prechemotherapy, and not more frequently than once every 7 days		
Dolasetron oral	100 mg	Once daily on days 1-3	100.83	330.50
Palonosetron IV	0.25 mg	Prechemotherapy, one dose	228.80	228.80
NK_1 receptor antagonists				
Aprepitant oral	125 mg	Prechemotherapy, one dose	284.01	284.01
Aprepitant oral	80 mg	Once daily on days 2, 3	182.14	364.28
Fosaprepitant IV	150 mg	Prechemotherapy, one dose	299.87	299.87
Rolapitant	180 mg	Prechemotherapy, one dose	610.50	610.50
Combination products				
Netupitant/palonsetron)	300 mg/0.5 mg	Prechemotherapy, one dose	632.35	632.35
Antipsychotics				
Olanzapine (generic)	5 mg	Once daily on days 1-3	6.50	6.50
Olanzapine (generic)	10 mg	Once daily on days 1-3	6.50	6.50
Olanzapine (brand)	5 mg	Once daily on days 1-3	15.07	43.22
Olanzapine (brand)	10 mg	Once daily on days 1-3	22.21	64.62
Dopaminergic antagonists				
Metoclopramide IV	1 to 2 mg/kg	Prechemotherapy, one dose	99.50	99.50
Metoclopramide oral (generic)	0.5 mg/kg	Every 6 hours, days 2-4	6.50	6.50
Metoclopramide oral (brand)	0.5 mg/kg	Every 6 hours, days 2-4	65.00	192.99
Prochlorperazine IV	5-10 mg	Prechemotherapy, every 6-8 hours, maximum 40 mg	11.93	11.93
Prochlorperazine oral	10 mg	Every 6 to 8 hours as needed	6.50	6.50
Cannabinoids				
Nabilone oral	1-2 mg	Twice daily, days 1-3	75.38	249.63
Dronabinol oral (generic)	5 mg/m^2	Every 2-4 hours as needed	184.70	223.94†
Dronabinol oral (brand)	5 mg/m^2	Every 2-4 hours as needed	314.60	941.80†

NOTE. Schedules were those recommended as antiemetic drug doses as of October 4, 2016. Prices per dose were for a single infusion or per pill for orally administered medications. Prices for infused drugs reimbursed through Medicare Part B only were identified from the 2016 Medicare Part B Drug average sales price data.[117] Prices for orally administered drugs reimbursed through Medicare Part D were identified in the PlanFinder for a beneficiary living within ZIP code 10065.[118] To remain as consistent as possible with prior methodology, we selected a Humana PDP plan with the lowest cost for beneficiaries to identify the full cost of each drug.[119,120] Drug costs may vary by plan and by pharmacy where a prescription is filled—for example, preferred or nonpreferred pharmacies. In some cases, antiemetic coverage for orally administered drugs may be covered by either Part B or Part D. We have selected the Medicare Part D price in these cases. Of note, drug prices are dynamic and the prices listed in the table may not reflect current prices. In some cases, the recorded out-of-pocket price per dose is equivalent to the price per cycle. This may represent a minimum price per fill set by the health plan. Brand products with generic substitutes may not be covered by some insurance plans and prices may differ from those noted.

Abbreviations: 5-HT_3, 5-hydroxytryptamine-3; IV, intravenous; NK_1, neurokinin 1.

*Price information not yet available through Medicare.

†Assume 3 days' use, 12 pills per day.

HEALTH DISPARITIES

Although ASCO clinical practice guidelines represent expert recommendations on the best practices in disease management, it is important to note that many patients have limited access to medical care. Racial and ethnic disparities in health care contribute significantly to this problem in the United States. Patients with cancer who are members of racial and/or ethnic minorities suffer disproportionately from comorbidities, experience more substantial obstacles to receiving care, are more likely to be uninsured, and are at greater risk of receiving care of poor quality than other Americans.[106-109] Many other patients lack access to care because of their distance from appropriate treatment facilities.

Several studies have suggested that the use of recommended antiemetic drugs varies by race. By using SEER-Medicare data, Check et al[110] analyzed NK_1 receptor antagonist use among women who received high-emetic-risk chemotherapy for early-stage breast cancer. Overall, black women were 32% less likely to receive an NK_1 receptor antagonist than white women (risk ratio [RR], 0.68; 95% CI, 0.51 to 0.91). Use of IV fosaprepitant did not vary statistically significantly by race (RR, 0.82; 95% CI, 0.51 to 1.33), but use of oral aprepitant did (RR, 0.54; 95% CI, 0.35 to 0.83). The authors note that the different findings for fosaprepitant and aprepitant could be due to drug cost and availability. In contrast to fosaprepitant, which is administered in the clinic and covered under Medicare Part B, with aprepitant, many patients are required to fill a prescription at a pharmacy, often at higher out-of-pocket costs.

A study of cancer disparities within the Veterans Affairs health care system collected information about more than 76,000 veterans with lung, colorectal, or prostate cancer during the period from 2001 to 2005.[111] Among patients who received high-emetic-risk chemotherapy, black patients were 13% less likely than white patients to receive a 5-HT_3 receptor antagonist (odds ratio, 0.87; 95% CI, 0.78 to 0.98). Adjustment for hospital fixed effects weakened this association, which suggests that site of care—rather than differential care within a site—may have contributed to the disparity. Black patients were also less likely than white patients to receive recommended treatment with a 5-HT_3 receptor antagonist and dexamethasone in an analysis of the Texas Cancer Registry-Medicare linked database.[112]

COST IMPLICATIONS

Increasingly, individuals with cancer are required to pay a larger proportion of their treatment costs through deductibles and coinsurance.[113,114] Higher patient out-of-pocket costs have been shown to be a barrier to initiating and adhering to recommended cancer treatments.[115,116]

Table 6 shows estimated costs for antiemetic products. Of note, medication prices may vary markedly, depending on negotiated discounts and rebates. Discussion of cost can be an important part of shared decision-making.[121] Clinicians should exercise judgment and—whenever it is practical and feasible—discuss with patients the use of less expensive alternatives when considering two or more treatment options that are comparable in terms of benefits and harms.[121]

Depending on a patient's particular insurance coverage, reimbursement may originate in his or her medical or pharmacy benefit, which may have different cost-sharing arrangements. Patients should be aware that different products may be preferred or covered by their particular insurance plan. Even with the same insurance plan, the price may vary between different pharmacies. When discussing financial issues and concerns, patients should be made aware of any financial counseling services that are available to address this complex and heterogeneous landscape.[121]

As part of the guideline development process, ASCO may opt to search the literature for published cost-effectiveness analyses that might inform the relative value of available treatment options. Excluded from consideration are cost-effective analyses that lack contemporary cost data and agents that are not currently available in either the United States or Canada and/or are industry sponsored.

EXTERNAL REVIEW

The draft was submitted to two external reviewers with content expertise. Based on the reviews, revisions were made by co-chairs and shared with the Expert Panel for approval.

ADDITIONAL RESOURCES

More information, including a Data Supplement with evidence tables, a Methodology Supplement with information about evidence quality and strength of recommendations, slide sets, and clinical tools and resources, is available at www.asco.org/supportive-care-guidelines. Patient information is available at www.cancer.net. Visit www.asco.org/guidelineswiki to provide comments on the guideline or to submit new evidence.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at jco.org.

AUTHOR CONTRIBUTIONS

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Final approval of manuscript: All authors
Accountable for all aspects of the work: All authors

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Antiemetics: American Society of Clinical Oncology Clinical Practice Guideline Update

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Appendix

Table A1. Antiemetics: American Society of Clinical Oncology Clinical Practice Guideline Update Expert Panel Membership

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Abbreviation: PGIN, Practice Guidelines Implementation Network.