Technology Assessment

Technology Assessment Program

Consideration of Evidence on Antiemetic Drugs for Nausea and Vomiting Associated with Chemotherapy or Radiation Therapy in Adults

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Oregon Evidence-based Practice Center

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Peer Reviewers

We wish to acknowledge individuals listed below for their review of this report. This report has been reviewed in draft form by individuals chosen for their expertise and diverse perspectives. The purpose of the review was to provide candid, objective, and critical comments for consideration by the EPC in preparation of the final report. Synthesis of the scientific literature presented here does not necessarily represent the views of individual reviewers.

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Background

Nausea and vomiting are common symptoms in cancer patients undergoing chemotherapy and radiation therapy. In some cases, failure to control nausea and vomiting in cancer patients may result in reduced nutritional status and quality of life, and may prompt the refusal of continuing chemotherapeutic and radiation therapy cycles. The benefits and harms of antiemetic regimens including a 5-hydroxytryptamine-3 (5-HT3) antagonist and a corticosteroid, with and without aprepitant, have been researched in many clinical studies. However, these antiemetic regimens need to be evaluated in the context of the specific programmatic interests of Centers for Medicare & Medicaid Services in terms of all-oral regimens compared with one another, all-oral regimens compared to all-injectable regimens, and mixed oral compared with injectable regimens. Additionally, the applicability of the evidence to patients age 65 and older needs to be determined.

Methods

This report compares the benefits and harms of antiemetic regimens that consist of a 5-HT3 antagonist plus a corticosteroid, with or without aprepitant, given to prevent and/or treat nausea and/or vomiting caused by emetogenic anticancer chemotherapy and/or radiation, and is based on a systematic review of the literature. The approach, methodology, and criteria used were agreed upon by consensus of staff at the Oregon Evidence-based Practice Center (EPC), Centers for Medicare & Medicaid Services (CMS), and the Agency for Healthcare Research and Quality (AHRQ). We assessed the internal validity (quality) of all studies based on predefined criteria. We graded the overall strength of evidence based on the guidance established for the Evidence-based Practice Center Program of AHRQ. The composite outcomes of total control (no emetic events, no rescue medication, none to mild nausea) and complete response (no emetic events, no rescue medication) were preferred to the individual outcomes of no emesis and no nausea. Applicability of the evidence was considered, with particular attention paid to whether the evidence was applicable to patients 65 years of age and older. Quantitative analyses were conducted where possible using Stats Direct (version 2.7.7, 9/13/2009). Random-effects models were used to estimate pooled relative risks and their 95% confidence intervals.

Results

Key Question 1. What are the comparative overall benefits of antiemetic regimens that consist of a 5-HT3 antagonist plus a corticosteroid, with or without aprepitant, given to prevent and/or treat nausea and/or vomiting caused by emetogenic anticancer chemotherapy and/or radiation? Outcomes of interest include (at least): ability to control nausea and vomiting; ability to tolerate sequential chemotherapy sessions; quality of life measures.

Comparison of oral regimens

Comparison of regimens with and without aprepitant

Evidence consisted of three fair-quality randomized controlled trials (RCTs) in adults undergoing moderately emetogenic chemotherapy. For the optimal patient outcome of total control, there was only low-strength evidence of no significant differences between all-oral regimens, with or without aprepitant, for the overall (RR, 0.84; 95% CI, 0.48 to 1.47), acute (RR, 0.94; 95% CI, 0.68 to 1.30) and delayed (RR, 0.82; 95% CI, 0.57 to 1.17) study periods. For complete response, there was predominantly high-strength evidence indicating a significant increase in benefit with three-drug regimens containing aprepitant compared to two-drug regimens without aprepitant during the overall (RR, 1.22; 95% CI, 1.12 to 1.33; high-strength evidence), acute (RR, 1.11; 95% CI, 1.06 to 1.16; moderate-strength evidence), and delayed periods (RR, 1.15; 95% CI, 1.06 to 1.24; high-strength evidence). There was moderate-strength evidence that an all-oral, three-drug, aprepitant-containing regimen resulted in significantly fewer Chinese women undergoing moderately emetogenic chemotherapy to delay subsequent chemotherapy sessions, but it was unclear how applicable these findings are to broader populations.

Comparison of regimens of a 5-HT3 antagonist plus a corticosteroid, without aprepitant

Evidence consisted of one fair-quality RCT in adults undergoing moderately emetogenic chemotherapy. The strength of the evidence was low that the proportion of patients who experienced total control of nausea and emesis over 24 hours after starting chemotherapy was not statistically significantly different between the group taking oral granisetron plus oral dexamethasone and the group taking ondansetron plus oral dexamethasone (RR, 1.02; 95% CI, 0.58 to 1.76). Evidence was insufficient to draw conclusions about other outcomes (total control during the delayed period, complete response, ability to tolerate sequential chemotherapy sessions, and quality of life).

Comparison of oral regimens to injectable regimens

We did not find any trials that compared an all-oral regimen to an all-injectable regimen, with or without aprepitant.

Comparison of mixed oral and injectable regimens

Comparison of regimens with and without aprepitant

Evidence consisted of eight fair-quality RCTs in adults undergoing primarily highly emetogenic chemotherapy. For the maximal patient outcome of total control (no emesis, no use of rescue medication, no or mild nausea), there was high-strength evidence of a significant increase with mixed oral and injectable three-drug regimens containing aprepitant compared with two-drug regimens without aprepitant during the overall study period (RR, 1.30; 95% CI, 1.10 to 1.54), as well as during both the acute (RR, 1.12; 95% CI, 1.03 to 1.21) and delayed (RR, 1.36; 95% CI, 1.11 to 1.67) treatment periods in adults undergoing highly emetogenic chemotherapy. High-strength evidence also indicated a significant benefit for the three-drug, aprepitant-containing regimen for complete response (no emesis, no use of rescue medication) during the overall (RR, 1.45; 95% CI, 1.32 to 1.60), acute (RR, 1.15; 95% CI, 1.10 to 1.21), and delayed (RR, 1.43; 95%

CI, 1.31 to 1.56) study periods. However, for both outcomes, the benefit of a multi-day, three-drug, aprepitant-containing regimen was minimal during the acute period (a 12% increase) and only became larger in magnitude during the overall and delayed periods when the control group was administered the 5-HT3 antagonist on day 1 only. Greater proportions of patients in the three-drug, aprepitant-containing regimens reported minimal or no impact of chemotherapy-induced nausea and vomiting on quality of life (RR, 1.16; 95% CI, 1.07 to 1.26). Evidence on ability to tolerate sequential chemotherapy sessions was limited to a pooled analysis of data from the extension phases of two short-term trials, which found no significant difference in the rate of study discontinuations between mixed, oral, and injectable three-drug aprepitant-containing regimens and two-drug regimens without aprepitant. However, because the trial discontinuations could have been due to any reason this evidence did not represent a direct link between these treatments and the specific outcome of interest, and the strength of this evidence was low.

Comparison of regimens of a 5-HT3 antagonist plus a corticosteroid, without aprepitant
Evidence consisted of three fair-quality RCTs in adults undergoing moderate to highly emetogenic chemotherapies. The outcomes of total control and ability to tolerate sequential chemotherapy sessions were not found in any trials. Low-strength evidence found no statistically significant differences in complete response between different mixed oral and intravenous regimens of a 5-HT3 antagonist and dexamethasone in the overall study period (RR, 0.97; 95% CI, 0.88 to 1.07), the acute period (RR, 0.97; 95% CI, 0.88 to 1.07), or the delayed period (RR, 1.00; 95% CI, 0.60 to 1.66).

Comparison of regimens given immediately prior to and/or for 48 hours after initiation of chemotherapy with those regimens given for longer periods of time

We did not find any evidence relating to formulations of included drugs approved by the US Food and Drug Administration (FDA).

Key Question 2. What are the harms of antiemetic regimens that consist of a 5-HT3 antagonist plus a corticosteroid, with or without aprepitant, given to prevent and/or treat nausea and/or vomiting caused by emetogenic anticancer chemotherapy and/or radiation?

Comparison of regimens with and without aprepitant

No significant differences were found between any regimens in incidences of overall adverse events for three-drug, aprepitant-containing regimens compared with two-drug regimens without aprepitant, both when all-oral regimens were compared in patients undergoing moderately emetogenic chemotherapy (RR, 0.93; 95% CI, 0.85 to 1.03; moderate-strength evidence) and when mixed oral and intravenous regimens were compared in patients undergoing highly emetogenic chemotherapy (RR, 1.03; 95% CI, 0.97 to 1.10; high-strength evidence).

Comparison of regimens of a 5-HT3 antagonist plus a corticosteroid, without aprepitant

There was only low-strength evidence of no significant differences in incidence of overall adverse events between different two-drug regimens, without aprepitant, regardless of whether

they were all given orally (RR, 1.40; 95% CI, 0.9 to 2.21) or using a mixed oral and intravenous regimen (RR, 0.85; 95% CI, 0.42 to 1.68).

Key Question 3. Are there subgroups of patients based on demographics (age, race, gender), socioeconomic status, other medications, or comorbidities, for which one of these antiemetic regimens is more effective or associated with fewer adverse events in the context of emetogenic anticancer chemotherapy and/or radiation?

Applicability of the evidence to patients age 65 and older?

While older age has been shown to be associated with lower rates of nausea and vomiting associated with highly or moderately emetogenic chemotherapy, the likelihood that the findings reported above – directly comparing antiemetic regimens – are broadly applicable to patients age 65 and older is still somewhat limited. The mean or median ages in the studies ranged from a low of 47 years to a high of 62 years, with less than one-third of enrolled patients being age 65 and over.

For comparisons of all-oral regimens, evidence (based on our analysis of published an unpublished data from a single study) indicated no significant difference in patients age 65 and over (RR, 1.11; 95% CI, 0.82 to 1.51), whereas the difference was significant in younger patients (RR, 1.21; 95% CI, 1.03 to 1.43). However, findings presented in the published paper, based on multiple logistic regression analyses, indicated that the three-drug regimen was superior to the two-drug regimen when age > 55 was taken into account. Analysis of patients over age 65 and taking drug regimen into account was not presented. The strength of this evidence to answer the question posed here was low.

For comparisons of mixed oral and intravenous regimens, four randomized controlled trials (RCTs) reported subgroup analyses based on age and we found the strength of this evidence to be moderate. When compared to a two-drug regimen where the 5-HT3 antagonist is administered on day one only, a mixed oral and injectable three-drug regimen containing aprepitant was superior in rates of complete response across the five-day period from start of chemotherapy (RR, 1.39; 95% CI, 1.17 to 1.64). These findings were limited in that they only related to this specific comparison and to only one outcome measure, did not include evidence on comparative harms, and some of the data were unpublished. Based on a single trial, comparison of a mixed oral and injectable three-drug regimen containing aprepitant with a two-drug regimen that continued administration of the 5-HT3 antagonists beyond day one found no statistically significant difference between regimens in complete response over the entire treatment period (RR, 1.13; 95% CI, 0.94 to 1.38), while the analysis of data for younger patients indicated a statistically significant benefit for the three-drug regimen (RR, 1.22; 95% CI, 1.03 to 1.45).

Future research is needed to clarify the benefits of three-drug regimens compared with various two-drug regimens in patients over age 65. Trials enrolling older patients, assessing more outcomes (for example patient-relevant outcomes such as total control and ability to tolerate sequential chemotherapy), and clearly assessing potential differences in adverse effects are needed.

Is there evidence of disparate effects on age, gender, socioeconomic status, or ethnicity/race?

The evidence base had strong applicability to women, with approximately 60% of all enrolled patients across the studies being female. While women experience higher rates of chemotherapy-induced nausea and vomiting than men, it appeared that both oral and mixed oral and injectable three-drug regimens were superior to two-drug regimens in women, with women achieving a slightly higher rate of complete response compared with men. In pooled analysis of data from two RCTs comparing a mixed oral and injectable three-drug regimen containing aprepitant with a two-drug regimen not containing aprepitant, 42% (435/1043) of the patients were women and the rate of complete response across both treatments was higher among men (61%) than women (53%). In comparison to the two-drug regimen, the aprepitant-containing regimen resulted in a difference of 25% in complete response over five days in women (our calculation of unadjusted relative risk, 1.65; 95% CI, 1.37 to 2.00) while the difference among men was 16% (our calculation of unadjusted relative risk, 1.30; 95% CI, 1.14 to 1.48). The strength of this evidence was moderate, largely because of the risk of bias resulting from a pooled analysis including data from two of eleven possible RCTs making comparisons of *mixed* oral and intravenous regimens, no regimens given by the same route, and no evidence on comparative harms. Further research may change our confidence in the estimate of effect and may change the estimate. However, there was inadequate evidence on any differences in harms to make conclusions.

Insufficient evidence was available for evaluating disparate effects on socioeconomic status or ethnicity/race.

Are certain groups more likely to receive one treatment over another, due to prescription trends in a geographic region, socioeconomic status, health insurance coverage, etc.?

No evidence on prescription trends based on geographic region, socioeconomic status, or health insurance coverage was found. The only relevant studies we found provided low-strength evidence that, among patients receiving primarily moderate to highly emetogenic single-day chemotherapy regimens, the choice of antiemetic regimen was not associated significantly with the patient's prior experience with chemotherapy-induced nausea and vomiting or the patient's age, sex, alcohol use, or baseline Eastern Cooperative Oncology Group performance status.

Conclusions

For the maximal patient outcome of total control (no emesis, no use of rescue medication, no or only mild nausea), the evidence was strongest in support of a significant increase with mixed oral and injectable three-drug regimens containing aprepitant compared with two-drug regimens without aprepitant during the overall study period, as well as during both the acute and delayed treatment periods in adults undergoing highly emetogenic chemotherapy. However, the benefit of a multi-day, three-drug, aprepitant-containing regimen was minimal during the acute period and only became larger in magnitude during the overall and delayed periods when the control group was administered the 5-HT3 antagonist on day one only. For all-oral regimens, comparisons of regimens with or without aprepitant, or comparisons between two-drug regimens without aprepitant, there was low-strength evidence of no significant differences for the outcome of total control. No conclusions could be reached about total control for the comparison among

different mixed two-drug regimens, without aprepitant, as evidence was unavailable for this outcome.

For complete response (no emesis, no use of rescue medication), there was predominantly high-strength evidence indicating a significant increase in benefit with three-drug regimens containing aprepitant compared with two-drug regimens without aprepitant during all study periods, regardless of whether the antiemetics were all given by an oral route or mixed oral and intravenous routes. Again, however, in the case where mixed routes were used in patients undergoing primarily highly emetogenic chemotherapy, the benefit of a multi-day, three-drug, aprepitant-containing regimen was minimal during the acute period and only became larger in magnitude during the overall and delayed periods when the control group was administered the 5-HT3 antagonist on day one only. There was only low-strength evidence of no significant differences in complete response between different mixed oral and intravenous route two-drug regimens, without aprepitant. No conclusions could be reached about complete response for the comparison among different all-oral, two-drug regimens, without aprepitant, as evidence was unavailable for this outcome.

Overall, comparative evidence on the impact of antiemetic regimens on the patient's ability to tolerate subsequent chemotherapy sessions was low strength. Based on a single study of Chinese women undergoing moderately emetogenic chemotherapy, an all-oral, three-drug, aprepitant-containing regimen resulted in significantly fewer patients needing to delay subsequent chemotherapy sessions compared with an all-oral two-drug regimen not containing aprepitant. Applicability of these findings to a broader population was not clear. For mixed oral and intravenous regimens, no difference in the rate of completion of six cycles of chemotherapy was found between three-drug aprepitant-containing regimens and two-drug regimens, based on a pooled analysis of data from extensions phases of two short-term trials. Further studies designed with this primary outcome are needed to reliably answer this question.

There were no significant differences found between any regimens in incidence of overall adverse events for three-drug, aprepitant-containing regimens compared with two-drug regimens without aprepitant both when all-oral regimens were compared in patients undergoing moderately emetogenic chemotherapy (moderate-strength evidence) and when mixed oral and intravenous regimens were compared in patients undergoing highly emetogenic chemotherapy (high-strength evidence). There was only low-strength evidence of no significant differences in incidence of overall adverse events between different two-drug regimens without aprepitant, regardless of whether they were all given orally or using a mixed oral and intravenous regimen.

The applicability of this evidence to patients age 65 and older was still somewhat limited, with only four studies reporting subgroup analyses. When compared to a two-drug regimen where the 5-HT3 antagonist was administered on day one only, a mixed oral and intravenous three-drug regimen containing aprepitant was superior in rates of complete response across the five-day period from start of chemotherapy. These findings were limited in that they only related to this specific comparison and to only one outcome measure, did not include evidence on comparative harms, and some of the data are unpublished. The evidence base had strong applicability to women, with approximately 60% of all enrolled patients across the studies being female. While women experienced higher rates of chemotherapy-induced nausea and vomiting than men, it appeared that both oral and mixed intravenous/oral three-drug regimens were superior to two-drug regimens in women, with women achieving a slightly higher rate of complete response compared to men. However, there was inadequate evidence on any differences in harms to make conclusions.

Insufficient evidence was available for evaluating disparate effects on socioeconomic status or ethnicity/race. Although we attempted to identify studies in patients undergoing radiation, only one study was available and it was rated poor quality.

INTRODUCTION

Nausea and vomiting are common symptoms in cancer patients undergoing chemotherapy and radiation therapy. In some cases, failure to control nausea and vomiting in cancer patients may result in reduced nutritional status and quality of life and may prompt refusal for continuation of chemotherapeutic and radiation therapy cycles.[1, 2]

Many types of neuroreceptors are believed to be involved in the development of nausea and vomiting, including serotonin (5-hydroxytryptamine-3 [5-HT3]), dopamine, corticosteroid, and substance P/neurokinin 1 (NK1).[2] Although a variety of older drugs have been used to prevent and treat chemotherapy induced nausea and vomiting in the past (for example, metoclopramide), these drugs were less selective for the receptors found to be involved in nausea and vomiting, resulting in lower than acceptable response and higher than acceptable rates of side effects. Therefore, antiemetic agents have been developed to target specific neuroreceptors and can be used in combination with one another. The 5-HT3 antagonists (e.g., dolasetron, granisetron, ondansetron, or palonosetron) and aprepitant (a neurokinin 1 receptor antagonist) were developed specifically to treat and prevent nausea and vomiting and are the most commonly used drugs today.

The intravenous dosage form of ondansetron was the first 5-HT3 antagonist to be approved by the US Food and Drug Administration (FDA) in 1991, and oral aprepitant was approved in 2003. The two-drug combination of a 5-HT3 antagonist plus dexamethasone (a corticosteroid) and the three-drug combination of aprepitant, a 5-HT3 antagonist, and dexamethasone are now the most commonly used regimens and are supported by the current American Society of Clinical Oncology guideline for antiemetics in oncology.[3] Table 1 outlines the FDA-approval status of these drugs for use in managing nausea and vomiting in cancer patients and Appendix A provides dosages recommended by the FDA.

Table 1. Antiemetic drug indications approved by the US Food and Drug Administration

Drug (brand name)	Dosage form[a]	Moderately and highly emetogenic chemotherapy	Radiation
Aprepitant/ Fosaprepitant (Emend)	Oral capsule	X	
	Injection	X	
Dolasetron (Anzemet)	Oral tablet	X[a]	
	Injection	X	
Granisetron (Kytril) (Sancuso)	Oral tablet	X	X
	Injection	X	
	Film, extended release, transdermal	X	
Ondansetron (Zofran)	Injection	X	
	Oral tablet, solution	X	X
	Oral solution	X	X
Palonosetron (Aloxi)	Injection	X	

[a] Only approved by the FDA for moderately emetic chemotherapy.

Purpose of the Report

The Social Security Act sets forth specific statutory requirements under which oral aprepitant and 5-HT3 antagonist drugs are a benefit in the fee-for-service Medicare program. Medicare may provide coverage for oral aprepitant and 5-HT3 antagonists (1) when used as a full therapeutic replacement for intravenous dosage forms and (2) when administered immediately before, at, or within 48 hours after the time of administration of the chemotherapeutic agent or the radiation therapy. Medicare has received comments suggesting changes to the policy regarding the coverage for these oral antiemetic drugs. This led to interest in a Technology Assessment of the comparative benefits and harms between and among oral and intravenous treatment regimens of antiemetics, specifically two-drug and three-drug regimens consisting of a 5-HT3 antagonist and a corticosteroid, with or without aprepitant. Therefore, the Coverage and Analysis Group at the Centers for Medicare and Medicaid Services (CMS) requested this report from The Technology Assessment Program (TAP) at the Agency for Healthcare Research and Quality (AHRQ). AHRQ assigned this report to the Oregon Evidence-based Practice Center (Oregon EPC) (Contract #I HHSA 290-2007-10057-1).

The objective of the report is to evaluate the comparative overall benefits and harms of antiemetic regimens that consist of a 5-HT3 antagonist plus a corticosteroid, with or without aprepitant, given to prevent and/or treat nausea and/or vomiting caused by emetogenic chemotherapy and/or radiation. Special attention will be given to how they affect outcomes in the Medicare population (i.e., people at least 65 years old). The main focus is on comparing regimens given by all-oral or all-intravenous routes and all-oral regimens compared to each other. The specific questions addressed are described at the end of the Introduction section.

This technology assessment report builds upon portions of previous work conducted by the Oregon EPC; a systematic review of the comparative effectiveness and harms of 5-HT3 antagonists and aprepitant in children and adults for prevention/treatment of nausea and vomiting associated with surgical procedures, chemotherapeutic agents, radiation therapy, and pregnancy, for the Drug Effectiveness Review Project (DERP) (http://derp.ohsu.edu/final/Antiemetics_final_report_update%201_JAN_091.pdf).

Key Questions

CMS requested an evaluation of the comparative overall benefits of antiemetic regimens that consisted of a 5-HT3 antagonist plus a corticosteroid, with or without aprepitant, given to prevent and/or treat nausea and/or vomiting caused by emetogenic anticancer chemotherapy and/or radiation. Specifically, they posed the following questions for review:

1. What are the comparative overall benefits of antiemetic regimens that consist of a 5-HT3 antagonist plus a corticosteroid, with or without aprepitant, given to prevent and/or treat nausea and/or vomiting caused by emetogenic anticancer chemotherapy and/or radiation? Outcomes of interest include (at least): ability to control nausea and vomiting; ability to tolerate sequential chemotherapy sessions; quality of life measures
    a. How do all-oral regimens compare to each other?
    b. How do all-oral regimens compare to all-injectable regimens?
    c. How do mixed oral and injectable regimens compare?

    d. How do regimens given immediately prior to and/or for 48 hours after initiation of chemotherapy compare to those regimens given for longer periods of time?

2. What are the harms of antiemetic regimens that consist of a 5-HT3 antagonist plus a corticosteroid, with or without aprepitant, given to prevent and/or treat nausea and/or vomiting caused by emetogenic anticancer chemotherapy and/or radiation?
    a. How do all-oral regimens compare to each other?
    b. How do all-oral regimens compare to all-injectable regimens?
    c. How do mixed oral and injectable regimens compare?
    d. How do regimens given immediately prior to and/or for 48 hours after initiation of starting the chemotherapy regimen compare to those regimens given for longer periods of time?
3. Are there subgroups of patients based on demographics (age, race, gender), socioeconomic status, other medications, or comorbidities for which one of these antiemetic regimens is more effective or associated with fewer adverse events in the context of emetogenic anticancer chemotherapy and/or radiation?
    a. What is the applicability of the evidence to patients age 65 and older?
    b. Is there evidence of disparate effects based on age, gender, socioeconomic status, or ethnicity/race?
    c. Are certain groups more likely to receive one treatment over another, due to prescription trends in a geographic region, socioeconomic status, health insurance coverage, etc.?

Purpose and Limitations of Systematic Reviews

Systematic reviews, also called evidence reviews, are the foundation of evidence-based practice. They focus on the strength and limits of evidence from studies about the effectiveness of a clinical intervention. Systematic reviews begin with careful formulation of research questions. The goal is to select questions that are important to patients and clinicians then to examine how well the scientific literature answers those questions. Terms commonly used in systematic reviews, such as statistical terms, are provided in Appendix B.

Systematic reviews emphasize the patient's perspective in the choice of outcome measures used to answer research questions. Studies that measure health outcomes (events or conditions that the patient can feel, such as fractures, functional status, and quality-of-life) are preferred over studies of intermediate outcomes (such as change in bone density). Reviews also emphasize measures that are easily interpreted in a clinical context. Specifically, measures of *absolute risk* or the probability of disease are preferred to measures such as relative risk. The difference in absolute risk between interventions depends on the number of events in each group, such that the difference (absolute risk reduction) is smaller when there are fewer events. In contrast, the difference in relative risk is fairly constant between groups with different baseline risks for the event, such that the difference (relative risk reduction) is similar across these groups. Relative risk reduction is often more impressive than absolute risk reduction. Another useful measure is the *number needed to treat* (or harm). The number needed to treat is the number of

patients who would need be treated with an intervention for one additional patient to benefit (experience a positive outcome or avoid a negative outcome). The absolute risk reduction is used to calculate the number needed to treat.

Systematic reviews weigh the quality of the evidence, allowing a greater contribution from studies that meet high methodological standards and, thereby, reducing the likelihood of biased results. In general, for questions about the relative benefit of a drug, the results of well-executed randomized controlled trials are considered better evidence than results of cohort, case-control, and cross-sectional studies. In turn, these studies provide better evidence than uncontrolled trials and case series. For questions about tolerability and harms, observational study designs may provide important information that is not available from controlled trials. Within the hierarchy of observational studies, well-conducted cohort designs are preferred for assessing a common outcome. Case-control studies are preferred only when the outcome measure is rare and the study is well conducted.

Systematic reviews pay particular attention to whether results of *efficacy studies* can be generalized to broader applications. Efficacy studies provide the best information about how a drug performs in a controlled setting. These studies attempt to tightly control potential confounding factors and bias; however, for this reason the results of efficacy studies may not be applicable to many, and sometimes to most, patients seen in everyday practice. Most efficacy studies use strict eligibility criteria that may exclude patients based on their age, sex, adherence to treatment, or severity of illness. For many drug classes, including the antipsychotics, unstable or severely impaired patients are often excluded from trials. In addition, efficacy studies frequently exclude patients who have comorbid disease, meaning disease other than the one under study. Efficacy studies may also use dosing regimens and follow-up protocols that are impractical in typical practice settings. These studies often restrict options that are of value in actual practice, such as combination therapies and switching to other drugs. Efficacy studies also often examine the short-term effects of drugs that in practice are used for much longer periods. Finally, efficacy studies tend to assess effects by using objective measures that do not capture all of the benefits and harms of a drug or do not reflect the outcomes that are most important to patients and their families.

Systematic reviews highlight studies that reflect actual clinical *effectiveness* in unselected patients and community practice settings. Effectiveness studies conducted in primary care or office-based settings use less stringent eligibility criteria, more often assess health outcomes, and have longer follow-up periods than most efficacy studies. The results of effectiveness studies are more applicable to the “average” patient than results from the highly selected populations in efficacy studies. Examples of effectiveness outcomes include quality-of-life, frequency or duration of hospitalizations, social function, and the ability to work. These outcomes are more important to patients, family, and care providers than surrogate or intermediate measures, such as scores based on psychometric scales.

Efficacy and effectiveness studies overlap. For example, a study might use very narrow inclusion criteria like an efficacy study, but, like an effectiveness study, might examine flexible dosing regimens, have a long follow-up period, and measure quality-of-life and functional outcomes. For this report we sought evidence about outcomes that are important to patients and would normally be considered appropriate for an effectiveness study. However, many of the studies that reported these outcomes were short term and used strict inclusion criteria to select eligible patients. For these reasons, it was neither possible nor desirable to exclude evidence based on these characteristics. Labeling a study as either an efficacy or an effectiveness study,

although convenient, is of limited value; it is more useful to consider whether the patient population, interventions, time frame, and outcomes are relevant to one's practice or to a particular patient.

Studies anywhere on the continuum from efficacy to effectiveness can be useful in comparing the clinical value of different drugs. Effectiveness studies are more applicable to practice, but efficacy studies are a useful scientific standard for determining whether characteristics of different drugs are related to their effects on disease. Systematic reviews thoroughly cover the efficacy data in order to ensure that decision makers can assess the scope, quality, and relevance of the available data. This thoroughness is not intended to obscure the fact that efficacy data, no matter how large the quantity, may have limited applicability to practice. Clinicians can judge the relevance of studies' results to their practice and should note where there are gaps in the available scientific information.

Unfortunately, for many drugs there exist few or no effectiveness studies and many efficacy studies. Yet clinicians must decide on treatment for patients who would not have been included in controlled trials and for whom the effectiveness and tolerability of the different drugs are uncertain. Systematic reviews indicate whether or not there exists evidence that drugs differ in their effects in various subgroups of patients, but they do not attempt to set a standard for how results of controlled trials should be applied to patients who would not have been eligible for them. With or without an evidence report, these decisions must be informed by clinical judgment.

In the context of development of recommendations for clinical practice, systematic reviews are useful because they define the strengths and limits of the evidence, clarifying whether assertions about the value of an intervention are based on strong evidence from clinical studies. By themselves, they do not say what to do. Judgment, reasoning, and applying one's values under conditions of uncertainty must also play a role in decision making. Users of an evidence report must also keep in mind that *not proven* does not mean *proven not*; that is, if the evidence supporting an assertion is insufficient, it does not mean the assertion is untrue. The quality of the evidence on effectiveness is a key component, but not the only component, in making decisions about clinical policy. Additional criteria include acceptability to physicians and patients, potential for unrecognized harm, applicability of the evidence to practice, and consideration of equity and justice.

METHODS

This report on the comparative benefits and harms of antiemetic regimens that consist of a 5-hydroxytryptamine-3 (5-HT3) antagonist plus a corticosteroid, with or without aprepitant, given to prevent and/or treat nausea and/or vomiting caused by emetogenic anticancer chemotherapy and/or radiation, was based on a systematic review of the literature. The approach, methodology, and criteria used were agreed upon by consensus of staff at the Oregon Evidence-based Practice Center (Oregon EPC), Centers for Medicare & Medicaid Services (CMS), and the Agency for Healthcare Research and Quality (AHRQ).

Search Strategy

In October 2009, in consultation with a medical librarian, we conducted a comprehensive search of the scientific literature to identify relevant citations addressing the Key Questions of this technology assessment. For Key Questions 1a through 3b, we searched MEDLINE® and the third Quarter 2009 Cochrane databases (Central Register of Controlled Trials, Database of Systematic Reviews, Database of Abstracts of Reviews of Effects) from October 2009 back to October 2008 using included drugs, indications, and study designs as search terms (see Appendix C for complete search strategies). For identification of citations between 1966 and October 2008, we relied on the previous searches done for the Drug Effectiveness Review Project (DERP) Drug Class Review on Newer Antiemetics. For Key Question 3c, which was not included in the scope of the DERP Drug Class Review on Newer Antiemetics, we conducted a new search of MEDLINE® (1966 through January 2010) and the first Quarter 2010 Cochrane databases (Central Register of Controlled Trials, Database of Systematic Reviews, and Database of Abstracts of Reviews of Effects). References of included studies were screened for any studies that may have met inclusion but were not identified through other means.

Study Selection

Using the criteria listed below, two reviewers assessed abstracts of citations identified from literature searches for inclusion. Full-text articles of potentially relevant abstracts were retrieved, and a second review for inclusion was conducted by two reviewers reapplying the inclusion criteria. Disagreements in inclusion decisions were resolved through consensus.

Populations

Adults at risk for or with nausea, vomiting (including retching), or both, related to the following therapies and conditions:

- Chemotherapy of various emetogenicity
- Radiation therapy

For classification of chemotherapy emetic risk, we used the descriptions as reported in the individual trial publications (e.g., high, moderate, etc.). When the emetogenic potential was not explicitly stated, we referred to the four-level classification system revised by the Multinational Association of Supportive Care in Cancer (MASCC) in 2009 (high, moderate, low, minimal).[4] In this system, for example, chemotherapeutic agents rated as having a "high" degree of emetogenicity have a 90% incidence of emesis (i.e., cisplatin) and those rated as "moderate" have a 30% to 90% incidence of emesis (i.e., carboplatin).

Interventions

In accordance with the specific programmatic interests of CMS, eligibility of interventions was assessed based the antiemetic regimen in its entirety. Included studies involved either a three-drug regimen including aprepitant, a 5-HT3 antagonist (e.g., dolasetron, granisetron, ondansetron, palonosetron), and a corticosteroid (e.g., dexamethasone, prednisone), or a two-

drug regimen including a 5-HT3 antagonist and a corticosteroid. The primary focus of the report is to compare all oral regimens to each other, to compare all oral regimens to all intravenous regimens, and to compare mixed oral and intravenous regimens. Studies comparing two regimens in which all drugs are given intravenously were excluded. Formulations of aprepitant and the 5-HT3 antagonists are shown in Table 1. Based on consideration of the collective form and routs of all the drugs combined, regimens were classified as either all-oral, all-intravenous, or containing mixed oral and intravenous drugs. We excluded studies that used a 5-HT3 antagonist alone or in combination with another non-corticosteroid drug (e.g., metoclopramide, lorazepam, etc.) and in which the dosage form or route of the corticosteroid was variable, unclear, or both.

Effectiveness outcomes

The following outcomes were evaluated during the acute (during the first 24 hours of chemotherapy administration) or delayed phases (after the first 24 hours of chemotherapy administration):

- Total control (e.g., no emesis, no use of rescue medication, no or mild nausea)
- Complete response (e.g., no emesis, no use of rescue medication)
- No emesis
- No nausea
- Ability to tolerate sequential chemotherapy sessions
- Quality-of-life measures

Wherever possible, data on effective dose range, dose response, and duration of therapy (time to success) was evaluated within the context of comparative effectiveness.

Harms

- Overall adverse events
- Specific adverse events (headache, constipation, dizziness, sedation, etc)
- Withdrawals due to adverse events
- Serious adverse events

Study designs

For effectiveness: controlled clinical trials and good-quality systematic reviews.
For harms: controlled clinical trials and observational studies.

Data Abstraction

The following data were abstracted from included trials: study design; setting; population characteristics including sex, age, ethnicity, and diagnosis; eligibility and exclusion criteria; interventions (dose and duration); comparisons; numbers screened, eligible, enrolled, and lost to follow-up; method of outcome ascertainment; and results for each outcome. We recorded intention-to-treat results when reported. If true intention-to-treat results were not reported, but

loss to follow-up was very small (≤ 5%), we considered these results to be intention-to-treat results. In cases where only per protocol results were reported, we calculated intention-to-treat results if the data for these calculations were available. If such calculations were made, they were noted. Data abstraction was performed by one reviewer and independently checked by a second reviewer.

Validity Assessment

We assessed the internal validity (quality) of trials based on the predefined criteria listed in Appendix D. These criteria are based on the US Preventive Services Task Force and the National Health Service Centre for Reviews and Dissemination (United Kingdom) criteria.[5, 6] We rated the internal validity of each trial based on the methods used for randomization, allocation concealment, and blinding; the similarity of compared groups at baseline; maintenance of comparable groups; adequate reporting of dropouts, attrition, crossover, adherence, and contamination; loss to follow-up; and the use of intention-to-treat analysis. Trials that had a fatal flaw were rated poor quality, trials that met all criteria were rated good quality, and the remainder were rated fair quality. As the fair-quality category is broad, studies with this rating vary in their strengths and weaknesses. The results of some fair-quality studies are *likely* to be valid, while others are only *possibly* valid. A poor-quality trial is not valid; the results are at least as likely to reflect flaws in the study design as a true difference between the compared drugs. A fatal flaw is reflected by failure to meet combinations of items of the quality assessment checklist. A particular randomized trial might receive two different ratings, one for effectiveness and another for adverse events.

Appendix D also shows the criteria we used to rate observational studies of adverse events. These criteria reflect aspects of the study design that are particularly important for assessing adverse event rates. We rated observational studies as good quality for adverse event assessment if they adequately met six or more of the seven predefined criteria, fair quality if they met three to five criteria, and poor quality if they met two or fewer criteria.

Included systematic reviews were also rated for quality (Appendix D). We rated the internal validity based a clear statement of the questions(s); reporting of inclusion criteria; methods used for identifying literature (the search strategy), validity assessment, and synthesis of evidence; and details provided about included studies. Again, these studies were categorized as good when all criteria were met.

Grading Strength of Evidence

We graded strength of evidence based on the guidance established for the Evidence-based Practice Center Program of the Agency for Healthcare Research and Quality.[7] Developed to grade the overall strength of a body of evidence, this approach incorporates four key domains: risk of bias (including study design and aggregate quality), consistency, directness, and precision of the evidence. It also considers other optional domains that may be relevant for some scenarios, such as a dose-response association, plausible confounding that would decrease the observed effect, strength of association (magnitude of effect), and publication bias.

Table 2 describes the grades of evidence that can be assigned. Grades reflect the strength of the body of evidence to answer key questions on the comparative efficacy, effectiveness, and

harms of 5-HT3 antagonists, with or without aprepitant. Grades do not refer to the general efficacy or effectiveness of pharmaceuticals.

Among the multitude of outcomes assessed in trials of antiemetics, we focused on rating the strength of evidence for only a subset of four that we judged to represent the most clinically important and reliable: total control, complete response, ability to tolerate sequential chemotherapy sessions, and overall adverse events. Complete response was the most commonly reported composite outcome and is typically defined as no emetic episodes and no use of rescue medication. Complete response was used by the American Society of Clinical Oncology in their 2006 update of their guideline for antiemetics in oncology and was recommended as a standard primary endpoint for clinical trials.[3] Total control is typically defined as no vomiting, no use of rescue medication, and none to mild nausea. Although total control is a less commonly reported outcome and includes patient subjectivity with regard to the component of nausea, we emphasize its importance in this review as we believe the fewest number of overall symptoms represents the maximal patient outcome and optimal goal of antiemetic therapy. We agree, however, that as an individual outcome, the subjective perception of nausea as judged only by the patient is, by nature, less reliable, and we have not discussed the results of this outcome in this report.

Table 2. Definitions of the grades of overall strength of evidence

Grade	Definition
High	High confidence that the evidence reflects the true effect. Further research is very unlikely to change our confidence in the estimate of effect.
Moderate	Moderate confidence that the evidence reflects the true effect. Further research may change our confidence in the estimate of the effect and may change the estimate.
Low	Low confidence that the evidence reflects the true effect. Further research is likely to change our confidence in the estimate of the effect and is likely to change the estimate.
Insufficient	Evidence either is unavailable or does not permit estimation of an effect.
Sources: [8]	

Applicability

The applicability of each body of evidence considered in this report was discussed. Particular attention was paid to whether the evidence was applicable to patients 65 years of age and older.

Data Synthesis

We constructed evidence tables showing the study characteristics, quality ratings, and results for all included studies. We reviewed studies using a hierarchy of evidence approach, and the best evidence was the focus of our synthesis for each question, population, intervention, and outcome addressed. Studies that evaluated one antiemetic regimen against another provided direct evidence of comparative effectiveness and adverse event rates and were the focus of this review. As discussed in more detail above under “Grading Strength of Evidence”, the composite outcomes of total control (no emetic events, no rescue medication, none to mild nausea) and complete response (no emetic events, no rescue medication) were preferred to the individual outcomes of no emesis and no nausea.

Quantitative analyses were conducted where possible. We used Stats Direct (version 2.7.7, 9/13/2009) to perform meta-analyses of outcomes reported by a sufficient number of studies that were homogeneous enough that combining their results could be justified. In order to determine whether meta-analysis could be meaningfully performed, we considered the quality of the studies and the heterogeneity among studies in design, patient population, interventions, and outcomes. When meta-analysis could not be performed, the data were summarized qualitatively.

Random-effects models[9] were used to estimate pooled relative risks and their 95% confidence intervals. We used Forest plots to graphically summarize results of individual studies and of the pooled analysis.[10] The Q statistic and the I^2 statistic (the proportion of variation in study estimates due to heterogeneity) were calculated to assess heterogeneity in effects between studies.[11, 12] Potential sources of heterogeneity were examined by analysis of subgroups of study design, study quality, patient population, and variation in interventions.

Peer Review and Public Comment

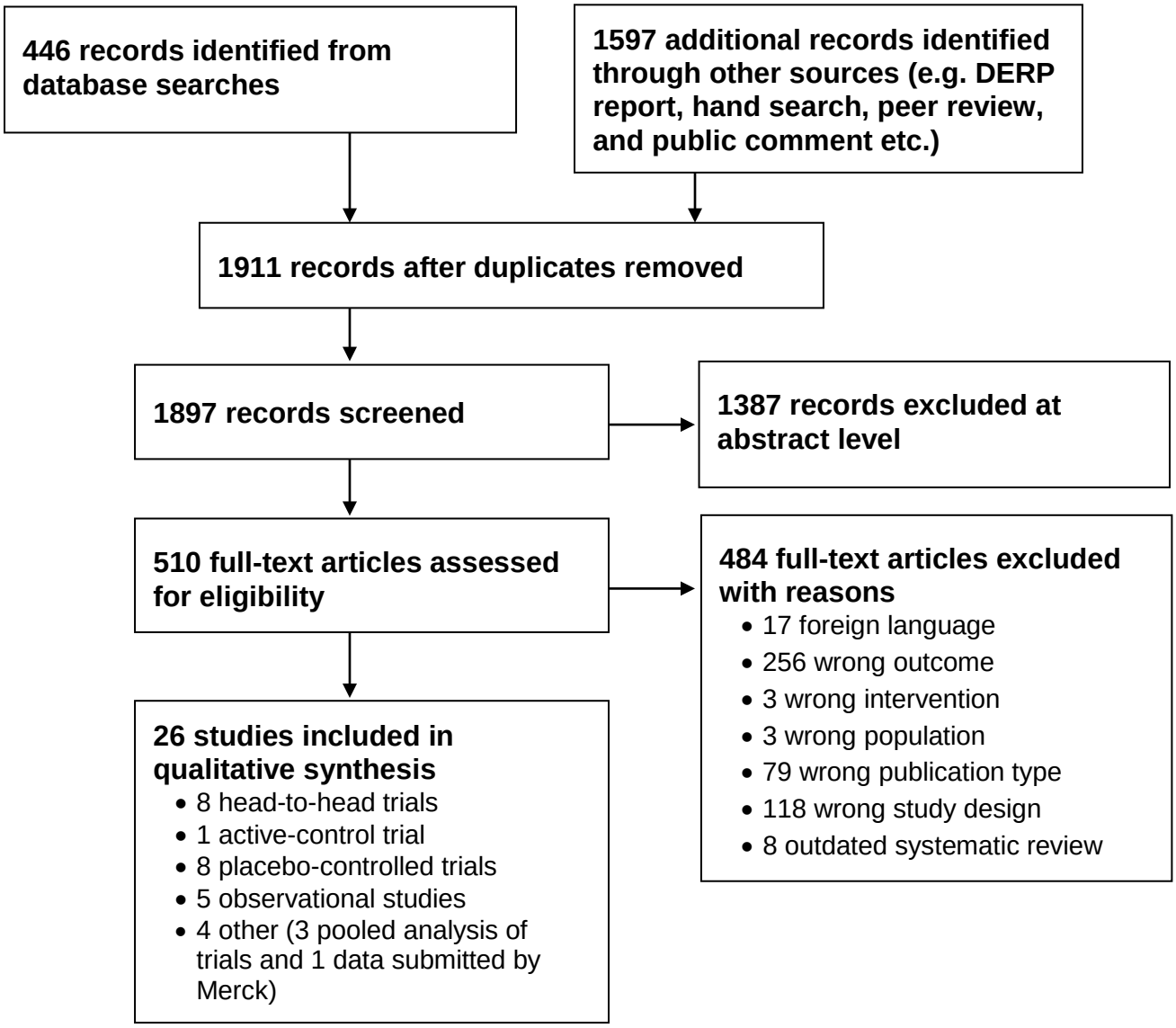
We requested and received peer review of the report from three sources. Comments were reviewed, and where possible, incorporated into the final document. The draft report was also posted to the AHRQ website for public comment. We received comments from one pharmaceutical company and one professional organization.

RESULTS

Overview

Literature searches identified 1897 unique citations. By applying the eligibility and exclusion criteria to titles and abstracts of all identified citations, we obtained full-text copies of 510 citations. After re-applying the criteria for inclusion, we ultimately included 26 publications. See Appendix E for a list of excluded studies and reasons for exclusion at this stage. We excluded studies that used a 5-HT3 antagonist alone,[13-18] in combination with another, non-corticosteroid drug (e.g., metoclopramide, lorazepam, etc.),[19, 20] and in which the dosage form or route of the corticosteroid was variable, unclear, or both.[18, 21-26] Figure 1 shows the flow of study selection.

Figure 1. Results of literature search



Key Question 1. What are the comparative overall benefits of antiemetic regimens that consist of a 5-HT3 antagonist plus a corticosteroid, with or without aprepitant given to prevent and/or treat nausea and/or vomiting caused by emetogenic anticancer chemotherapy and/or radiation? Outcomes of interest include (at least): ability to control nausea and vomiting; ability to tolerate sequential chemotherapy sessions; quality of life measures

A. How do all-oral regimens compare to each other?

Comparison of regimens with and without aprepitant

We included three fair-quality randomized controlled trials (RCTs) that compared an all-oral, three-drug regimen of aprepitant, ondansetron, and dexamethasone to an all-oral, two-drug regimen of ondansetron plus dexamethasone.[13-15] Two of the trials were conducted in a total of 946 patients with breast cancer undergoing moderately emetogenic chemotherapy based on an anthracycline (i.e., doxorubicin, epirubicin) and cyclophosphamide.[13, 14] The first of these was a multi-center, international trial in primarily white females with a mean age of 53 years.[13] The second trial[14] evaluated 124 women of ethnic Chinese origin who were enrolled from a single-center in Hong Kong (mean age of 47.5 years), 44 of which had taken part in the earlier multi-center trial.[13]

The third trial was conducted in a broader population of 848 patients (77% female, mean age of 56 years) with various malignancies (51% breast cancer, 20% colon cancer, 12% lung cancer, 4% ovarian cancer) and undergoing moderately emetogenic chemotherapy based on either an anthracycline and cyclophosphamide (48%) or a non-anthracycline and cyclophosphamide regimen (52%).[15]

In all three RCTs, treatment was administered according to the treatment regimens listed in Table 3.

Table 3. Oral antiemetic regimens in randomized controlled trials of 5-HT3 antagonist plus a corticosteroid, used with or without aprepitant

Regimen type	Drugs (oral)	Day 1	Day 2	Day 3
Three-drug regimen	Aprepitant	125 mg, 1 hour before chemotherapy	80 mg qd	80 mg qd
	Ondansetron	8 mg, 30 to 60 minutes before chemotherapy 8 mg, 8 hours after first dose	None	None
	Dexamethasone	12 mg, 30 minutes before chemotherapy	None	None
Two-drug regimen	Ondansetron	8 mg, 30 to 60 minutes before chemotherapy 8 mg, 8 hours after first dose	8 mg bid	8 mg bid
	Dexamethasone	20 mg, 30 minutes before chemotherapy	None	None

Abbreviations: bid, twice daily; qd, once daily.

Compared to an all-oral, two-drug regimen of ondansetron and dexamethasone, there was moderate-strength evidence that an all-oral, three-drug regimen with aprepitant, ondansetron, and dexamethasone did not significantly increase the proportion of women of ethnic Chinese origin undergoing moderately emetogenic chemotherapy that reported total control during the overall trial period (26% compared with 31%; RR, 0.84; 95% CI, 0.48 to 1.47), or during the acute (54% compared to 56%; RR, 0.94; 95% CI, 0.68 to 1.30) or delayed periods (56% compared with 58%; RR, 0.82; 95% CI, 0.57 to 1.17).[14] However, this same trial also provided low-strength evidence of a significantly lower rate of delay in subsequent cycle of chemotherapy for the aprepitant group (8% compared with 27%; RR, 0.29; 95% CI, 0.12 to 0.71), likely due in part to the significantly higher rate of neutropenia in the two-drug regimen group (53% compared with 35%; P=0.0468).[14] The outcomes of total control and delay in subsequent chemotherapy sessions were not reported in the other two trials.[13, 15]

For complete response, although this outcome was reported in all three trials, our pooled analysis did not include data from the trial of Chinese women[14] due to the overlap of 44 patients also included in the trial by Warr et al (2009).[13]

Compared to an all-oral, two-drug regimen without aprepitant, there was high-strength evidence from two trials that an all-oral, three-drug regimen with aprepitant significantly increased the proportion of patients reporting a complete response 0 to 120 hours (overall phase) following initiation of chemotherapy (pooled rates, 60% compared with 49%; RR, 1.22; 95% CI, 1.12 to 1.33).[13, 15] The difference between groups in the smaller trial of Chinese women was not significant (47% compared with 42%; P=0.58).[14] Pooled rates of complete response were also significantly greater with the all-oral, three-drug regimen with aprepitant during the acute (82% compared with 74%; RR, 1.11; 95% CI, 1.06 to 1.16) and delayed periods (63% compared with 55%; RR, 1.15; 95% CI, 1.06 to 1.24) in the larger trials, but not in the smaller trial of Chinese women (acute: 72.1% compared with 72.6%; P=0.95; delayed: 64% compared with 58%; P=0.51).[14]

Quality-of-life assessment was conducted in two of three trials using the Functional Living Index-Emesis (FLIE) questionnaire.[13, 14] The FLIE questionnaire contains nine items in each of two domains, nausea and vomiting, and involves rating each item on a 100-mm visual analog scale with higher scores indicating a worse quality of life. In the first trial, a significantly greater proportion of patients in the aprepitant group reported minimal or no impact on daily living of the combined domains (63% compared with 56%; P=0.019).[13] However, in the second trial, there was no significant difference between the all-oral, three-drug regimen with aprepitant and the all-oral, two-drug regimen without aprepitant when the mean total scores were compared (11.24 compared with 23.12; P=0.45).[14] Again, sample size may have been inadequate to find a statistically significant difference.

Comparison of regimens of a 5-HT3 antagonist plus a corticosteroid, without aprepitant

We included one fair-quality RCT that compared two all-oral regimens of a 5-HT3 antagonist plus a corticosteroid.[16] A total of 65 chemotherapy-naïve patients were randomized to receive either a single dose of oral granisetron 1 mg or oral ondansetron 16 mg, both in combination with oral dexamethasone 12 mg, and administered within 30 minutes of moderately emetogenic chemotherapy. The study sample was comprised of mostly women (75%) with breast cancer (62%). The median age was 62.5 years in the granisetron group (range 25 to 84) and 59 years in the ondansetron group (range 20 to 91). This trial only evaluated outcomes over 24 hours after

starting chemotherapy and did not report complete response, quality of life, or ability to tolerate sequential chemotherapy sessions. There was no significant difference between the granisetron and ondansetron groups in the proportion of patients who experienced total control of nausea and emesis over 24 hours after starting chemotherapy (46% compared with 45%; P=0.94). Overall, this trial provided a low strength of evidence that there was no significant difference between all-oral regimens for the outcome of 24-hour total control (RR, 1.02; 95% CI, 0.58 to 1.76) (Appendix F).

B. How do all-oral regimens compare to all-injectable regimens?

We did not find any trials that compared an all-oral regimen to an all-injectable regimen, with or without aprepitant.

C. How do mixed oral and injectable regimens compare?

Comparison of mixed oral and injectable regimens with and without aprepitant

We included eight RCTs that compared mixed oral and injectable regimens with and without aprepitant (Evidence Table 1).[17-24] All RCTs were rated fair quality due to insufficient detail provided for verification of adequate allocation concealment methods (Evidence Table 2).

Two trials evaluated regimens including aprepitant in an older formulation and dose that is now unavailable in the United States (400 mg on day 1 and 300 mg on days 2 through 5).[21, 24] Because of the difference in aprepitant formulation and dose, these trials were not included in any meta-analyses. In the remaining six trials,[17-20, 22, 23] on the first day of treatment, the three-drug regimen was comprised of oral aprepitant 125 mg, an intravenous 5-HT3 antagonist (ondansetron 32 mg or palonosetron 0.25 mg), and oral dexamethasone 12 to 20 mg, and the two-drug regimen was comprised of the same dosage of the intravenous 5-HT3 antagonist and the same or a slightly higher[19, 22, 23] dosage of oral dexamethasone. On subsequent days, the aprepitant-based and control group regimens varied and are listed in Table 4. Two trials included a third treatment arm in which aprepitant was administered only on day 1 and was compared to the multi-day aprepitant regimen.[19, 21] Results of those comparisons will be discussed under Key Question 3d below. Another two trials included a third treatment arm in which aprepitant was administered at 375 mg on day 1 and 250 mg on subsequent days.[17, 18] However, during the conduct of these trials, new data became available suggesting a pharmacokinetic interaction between the higher dosages of aprepitant and dexamethasone, in which the dexamethasone levels were increased by approximately two-fold. Therefore, those treatment arms were discontinued in both trials and results will not be discussed here.

In all trials, patients were undergoing highly emetic chemotherapy. In all but one trial, there were more males than females, with primarily respiratory and urogenital malignancies. In the remaining trial, patients were primarily female with breast cancer.[19] Mean ages ranged from 53 years to 64 years.

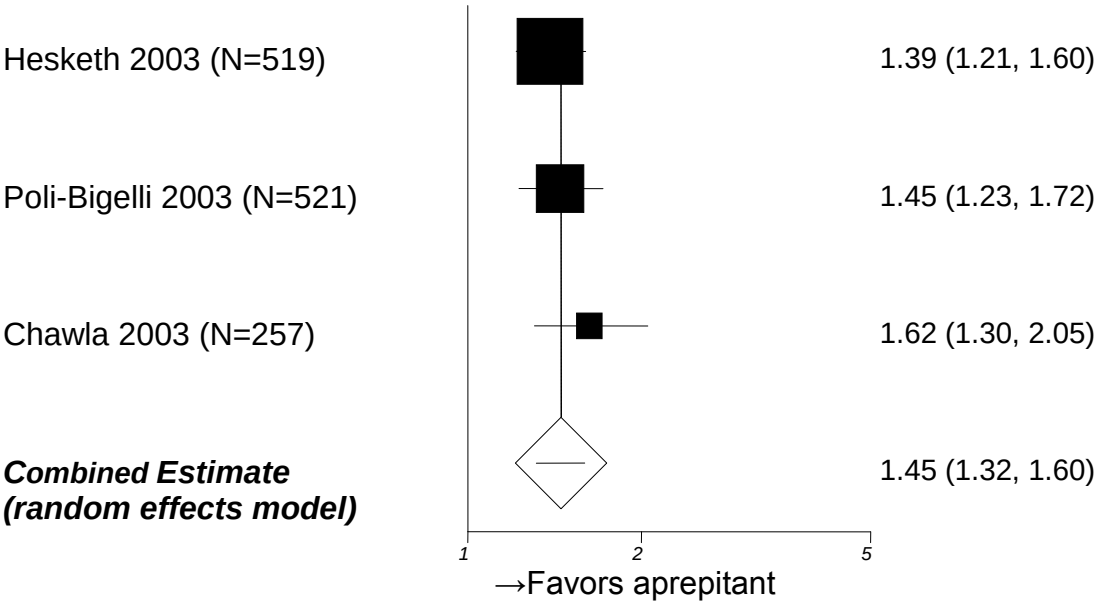
Table 4. Treatment regimens on days two to five

Author Year	Aprepitant group	Control group
Hesketh 2003,[20] Poli-Bigelli 2003,[22] Herrington 2008,[19]	Aprepitant 80 mg qd on days 2-3 Dexamethasone 8 mg bid on days 2-4	Dexamethasone 8 mg bid on days 2-4
de Wit 2003,[18] Chawla 2003[17]	Aprepitant 80 mg qd on days 2-5 Dexamethasone 8 mg qd on days 2-5	Dexamethasone 8 mg qd on days 2-5
Schmoll 2006[23]	Aprepitant 80 mg qd on days 2-3 Dexamethasone 80 mg qd on days 2-4	Ondansetron 8 mg plus dexamethasone 8 mg, both bid on days 2-4

Abbreviations: bid, twice daily; qd, once daily.

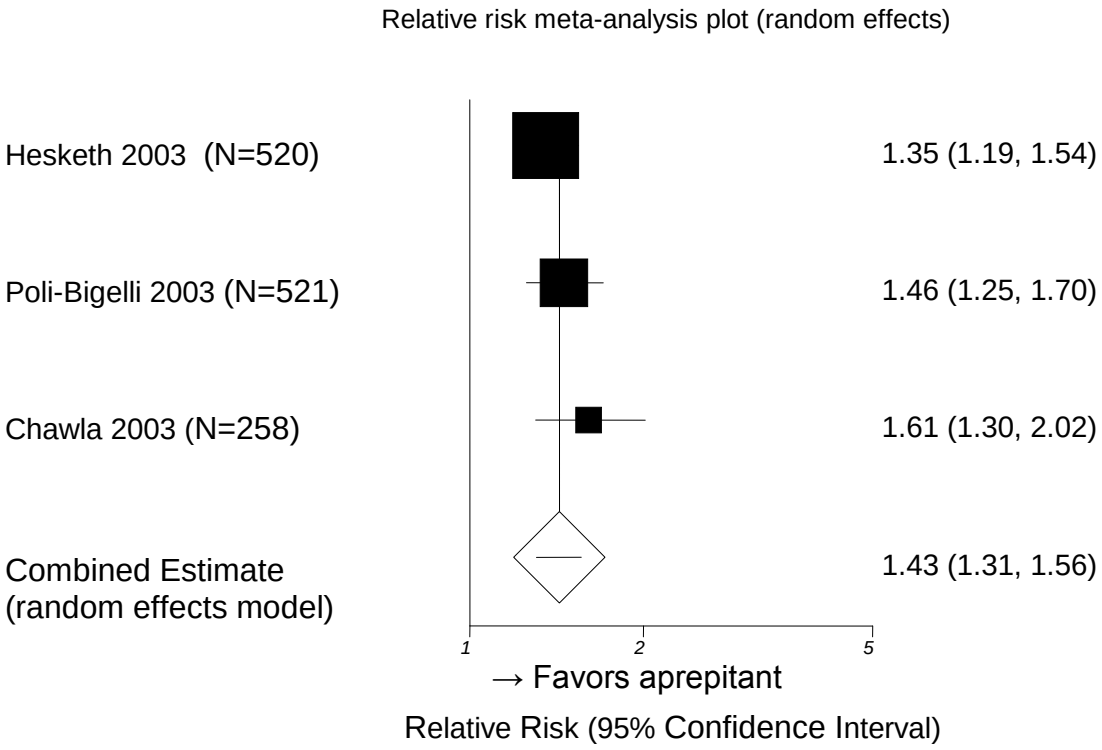
Three trials provided high-strength evidence that, compared with treatment with a mixed, two-drug regimen of intravenous ondansetron and oral dexamethasone on day 1 followed by monotherapy with oral dexamethasone on days 2 through 4 to 5, a mixed, three-drug regimen with oral aprepitant, intravenous ondansetron, and oral dexamethasone on day 1 followed by oral aprepitant and oral dexamethasone on days 2 through 3 to 5 significantly increases the proportion of patients undergoing highly emetogenic chemotherapy that reported total control (mean rates, 45% compared with 35%; RR, 1.30; 95% CI, 1.10 to 1.54) and complete response (mean rates, 68% compared with 47%, RR, 1.45; 95% CI, 1.32 to 1.60, Figure 2) during the overall study period (Appendix F).[20,22,19] The benefit of adding oral aprepitant may be particularly attributed to its continued administration during the delayed period (days 2 through 4 to 5), when therapy in the control group was limited to monotherapy with oral dexamethasone (delayed period total control: mean rates, 50% compared with 38%; RR, 1.36; 95% CI, 1.11 to 1.67; complete response [Figure 3]: mean rates, 72% compared with 50%; RR, 1.43; 95% CI, 1.31 to 1.56). Whereas the magnitude of benefit for a regimen of oral aprepitant on days 2 and 3 plus oral dexamethasone on days 2 through 4 compared with a regimen of oral ondansetron plus oral dexamethasone on days 2 through 4 for complete response was smaller, but still statistically significant in the overall study period (RR, 1.19; 95% CI, 1.05 to 1.35) and delayed period (RR, 1.17; 95% CI, 1.04 to 1.33).[23] Also, across all trials, the magnitude of benefit for an aprepitant-based regimen was smaller, but still statistically significant during the acute period for total control (mean rates, 67% compared with 60%; RR, 1.12; 95% CI, 1.03 to 1.21) and for complete response (mean rates, 84% compared with 72%; RR, 1.15; 95% CI, 1.10 to 1.21; Figure 4).

Figure 2. **Complete response during overall treatment period of mixed oral and injectable antiemetic regimens with aprepitant compared to without aprepitant**



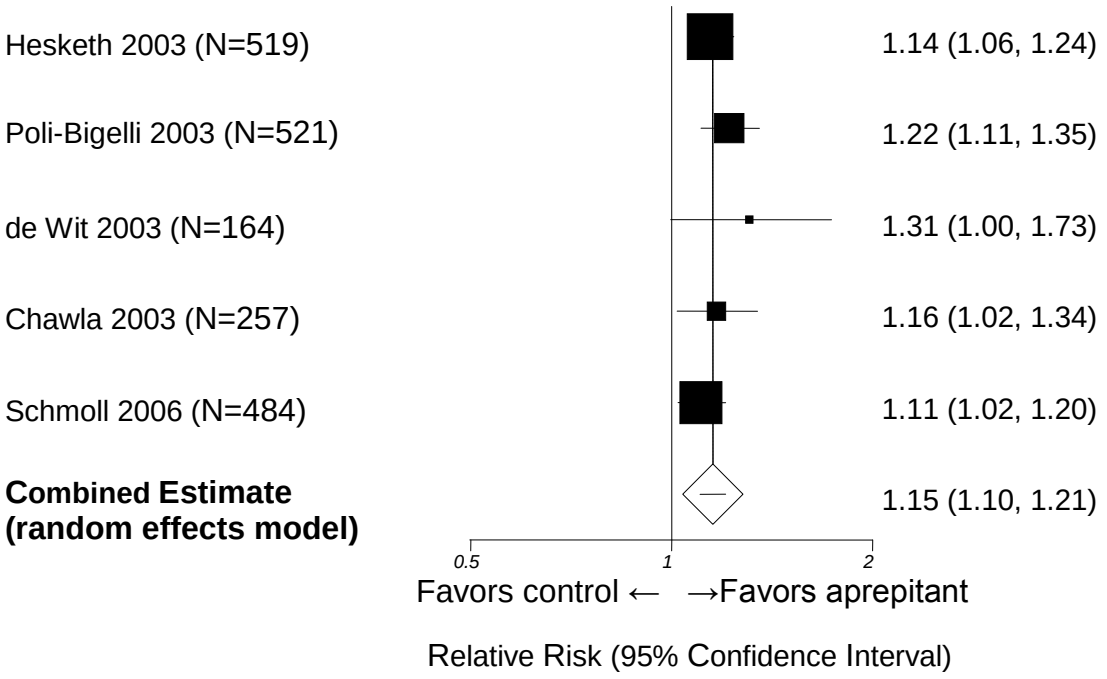
Evaluation of non-combinability of studies
Cochran Q = 1.335762 (*df*=2) *P*=0.5128
I^2 (inconsistency) = 0% (95% CI, 0 to 72.9)

Figure 3. Complete response during delayed treatment period of mixed oral and injectable antiemetic regimens of a 5-HT3 antagonist and a corticosteroid plus aprepitant compared to without aprepitant



Evaluation of non-combinability of studies
Cochran Q = 1.90926 (d*f*=2) *P*=0.385
I^2 (inconsistency) = 0% (95% CI, 0 to 72.9)

Figure 4. Complete response during acute treatment period of mixed oral and injectable antiemetic regimens of a 5-HT3 antagonist and a corticosteroid plus aprepitant compared to without aprepitant



Evaluation of non-combinability of studies
Cochran Q = 3.272039 (*df*=4) *P*=0.5134
I^2 (inconsistency) = 0% (95% CI, 0 to 64.1)

Quality-of-life assessment was conducted in two trials, again using the FLIE questionnaire.[20, 22] In both trials, greater proportions of patients in the aprepitant groups reported minimal or no impact of chemotherapy-induced nausea and vomiting on quality of life, as measured by the total FLIE score (mean rates, 74% compared with 64%; RR, 1.16; 95% CI, 1.07 to 1.26).

Evidence on the impact of antiemetic regimens on the patient's ability to tolerate subsequent chemotherapy sessions was limited to a pooled analysis of data from the multiple-cycles extensions of the two pivotal trials submitted to the FDA to obtain approval for aprepitant (study 052 and 054),[20, 22] which found that there was no significant difference between mixed oral and injectable regimens, with and without aprepitant, in rate of completion of all six cycles (26% in both groups).[25] However, because the reasons for not completing all six cycles were not limited to the impact of antiemetic regimens (e.g., ineligible, withdrawals of consent from study, completed chemotherapy, no response to chemotherapy, other, etc.), this evidence did not represent a direct link between these treatments and the specific outcome of interest.

Comparison of mixed oral and injectable regimens of a 5-HT3 antagonist plus a corticosteroid

We included five RCTs that compared mixed oral and injectable two-drug regimens.[26-30] Three trials were rated fair quality[26-28] and two trials were rated poor quality.[29, 30] Among the three fair-quality trials, all involved a comparison of a mixed regimen of an oral 5-HT3 antagonist plus intravenous dexamethasone to an all-injectable regimen of a 5-HT3 antagonist plus dexamethasone.[26-28] Further, one trial involved an additional comparison of two different mixed oral and injectable regimens, each comprised of an oral 5-HT3 antagonist plus intravenous dexamethasone.[28]

Table 5 provides details of the antiemetic regimens and patient characteristics. All three trials had small sample sizes (≤ 102 patients) and were conducted in single centers. The trials were heterogeneous with regard to chemotherapy emetic risk category, primary malignancy, and gender distribution. In two trials patients were receiving highly emetogenic chemotherapy.[27, 28] In the third trial, 43% of patients were receiving moderately emetogenic chemotherapy and 57% were receiving highly emetogenic chemotherapy.

Table 5. Antiemetic regimens and patient characteristics

Author Year (Sample size)	Granisetron regimen	Ondansetron regimen	Dexamethasone dosage	Primary malignancy	Female (%)
Fox-Geiman 2001 (N=102)	1 mg PO, Q12 hrs	(1) 32 mg IV qd (2) 8 mg PO, Q8 hrs	10 mg IV	100% bone marrow transplant	72%
Chiou 2000 (N=51)	1 mg PO, Q12 hrs	8 mg IV, Q8 hrs	10 mg IV	35% Non-Hodgkin's lymphoma	37%
Chua 2000 (N=94)	3 mg IV, qd	8 mg IV before chemo/8 mg PO at 4 and 8 hrs post-chemo	20 mg IV	80% nasopharynx	13%

Abbreviations: IV, intravenous; PO, palonosetron; qd, once daily; Q, every.

Overall, low- to moderate-strength of evidence (Appendix F) indicated that statistically significant differences were not found in complete acute response rates when mixed oral and injectable regimens were compared to all-injectable regimens (RR, 1.00; 95% CI, 0.88 to 1.13)[26-28] or when different mixed oral and injectable regimens were compared (RR, 0.97; 95% CI, 0.88 to 1.07).[28] In two trials, complete acute response rates ranged from 84% to 95%[26, 28] and in the third trial were not reported (P=0.262).[27]

Similarly, these trials provided low- to moderate-strength evidence (Appendix F) indicating that statistically significant differences were not found in complete and delayed complete response rates when mixed oral and injectable regimens were compared to all-injectable regimens (RR, 0.92; 95% CI, 0.59 to 1.45),[26, 28] or when different mixed oral and injectable regimens were compared (RR, 1.00; 95% CI, 0.60 to 1.66).[28] In patients undergoing highly emetogenic regimens prior to stem cell transplantation, rate of delayed complete response

ranged from 47% to 48% for mixed oral and injectable regimens and was 49% for the all-injectable regimen.[28] In patients with mixed malignancies in Taiwan, the rates of delayed complete response were relatively lower (16% for the mixed oral and injectable group and 19% for the all-injectable group).[26] These trials did not report total control, quality of life, or ability to tolerate sequential chemotherapy sessions.

D. How do regimens given immediately prior to and/or for 48 hours after initiation of chemotherapy compare to those regimens given for longer periods of time?

One RCT compared regimens given immediately prior to and for 48 hours after initiation of chemotherapy to those given for longer periods of time.[21] On day 1, all patients received oral aprepitant 400 mg, intravenous granisetron 10 μg/kg, and oral dexamethasone 20 mg. Then, on days 2 through 5, the patients in group 1 also received 300 mg of oral aprepitant whereas the patients in group 2 received placebo. Patients were primarily male undergoing highly emetogenic chemotherapy for lung, gastrointestinal, and head and neck malignancies. Although this trial found no significant difference in complete delayed response between the multi-day aprepitant group (52%) compared with the single-day group (43%; RR, 1.22; 95% CI, 0.82 to 1.84), because this trial evaluated an older formulation and dose of aprepitant that is unavailable in the United States, this evidence was insufficient for drawing conclusions for this question regarding the current FDA-approved product and dosage regimen.[21, 24]

E. Summary of evidence

The summary of evidence for this Key Question is presented in Table 6, below.

Table 6. Summary of the evidence for Key Question 1

Key Question	Outcome Strength of evidence	Conclusions
1.A. How do oral regimens compare to each other?		
Comparison of regimens with and without aprepitant in moderately emetogenic chemotherapy	Total Control Low	No significant advantage for all-oral regimens of aprepitant, a 5-HT3 antagonist and a corticosteroid for moderately emetogenic chemotherapy during overall (RR, 0.84; 95% CI, 0.48 to 1.47), acute (RR, 0.94; 95% CI, 0.68 to 1.30), or delayed periods (RR, 0.82; 95% CI, 0.57 to 1.17)
	Complete Response Moderate-High	High-strength evidence of modest, but significant, advantages for the aprepitant regimen during the overall (RR, 1.22; 95% CI, 1.12 to 1.33) and delayed period (RR, 1.15; 95% CI, 1.06 to 1.24). For the acute period, the strength of evidence for the advantage of the aprepitant regimen was only moderate (RR, 1.11; 95% CI, 1.06 to 1.16) due to the nonsignificant difference in the RCT of Chinese women (72.1% vs. 72.6%).
	Delay in subsequent chemotherapy	Significantly lower proportion of patients with a delay in subsequent chemotherapy in the aprepitant group (RR, 0.29; 95% CI, 0.12 to 0.71).

Key Question	Outcome Strength of evidence	Conclusions
	Moderate	
	Quality of life Not rated	Negative impact on quality of life was significantly lower in the aprepitant group in one of two RCTs, based on scores on the FLIE questionnaire.
Comparison of regimens of a 5-HT3 antagonist plus a corticosteroid	Total Control: Acute Low	No significant difference between regimens prior to moderately emetogenic chemotherapy (RR, 1.02; 95% CI, 0.58 to 1.76).
1.B. How do oral regimens compare to injectable regimens?		
	All Insufficient	No trials included.
1.C. How do mixed oral and injectable regimens compare?		
Comparison of regimens with and without aprepitant in highly emetogenic chemotherapy	Total Control High	Mixed oral and injectable regimens with aprepitant are superior to those without during the overall (RR, 1.30; 95% CI, 1.10 to 1.54), acute (RR, 1.12; 95% CI, 1.03 to 1.21), and delayed periods (RR, 1.36; 95% CI, 1.11 to 1.67).
	Complete Response High	Mixed oral and injectable regimens with aprepitant are superior to those without during the overall (RR, 1.45; 95% CI, 1.32 to1.60), acute (RR, 1.15; 95% CI, 1.10 to 1.21), and delayed periods (RR, 1.43; 95% CI, 1.31 to 1.56).
	Quality of life Not rated	Greater proportions in the aprepitant groups reported “minimal or no impact” of chemotherapy-induced nausea and vomiting on quality of life, based on total FLIE scores (RR, 1.16; 95% CI, 1.07 to 1.26).
Comparison of regimens of a 5-HT3 antagonist plus a corticosteroid	Complete Response Low	No significant differences between regimens during the overall (RR, 0.97; 95% CI, 0.88 to 1.07), acute (RR, 0.97; 95% CI, 0.88 to 1.07), or delayed treatment periods (RR, 1.00; 95% CI, 0.60 to 1.66) in patients undergoing moderate to highly emetic chemotherapy.
1.D. How do regimens given immediately prior to and/or for 48 hours after initiation of chemotherapy compare to those regimens given for longer periods of time?		
Comparison of regimens with and without aprepitant	Complete Response: Delayed Insufficient	Evidence from 1 RCT of an older, unavailable formulation and dose of aprepitant was insufficient for drawing conclusions about the current FDA-recommended dosage regimen for this question.

Abbreviations: FLIE, Functional Living Index-Emesis questionnaire; FDA, US Food and Drug Administration; RCT, randomized controlled trial.

Key Question 2. What are the harms of antiemetic regimens that consist of a 5-HT3 antagonist plus a corticosteroid, with or without aprepitant, given to prevent and/or treat nausea and/or vomiting caused by emetogenic anticancer chemotherapy and/or radiation?

Data on harms were obtained from the same groups of randomized controlled trials (RCTs) as included for evaluation of benefits. The details of their treatment regimen and patient population characteristics can be found in Key Question 1 (above).

A. How do all-oral regimens compare to each other?

Comparison of all-oral regimens with and without aprepitant

Data on harms was provided by three RCTs that compared oral regimens with and without aprepitant in patients undergoing moderately emetogenic chemotherapies.[13-15] Incidence of patients with one or more adverse event was only reported in one trial of 848 patients, which provided moderate strength evidence of no significant difference between all-oral regimens with or without aprepitant (63% compared with 67%; RR, 0.93; 95% CI, 0.85 to 1.03).[15] Differences in incidences of individual adverse events were not generally significant. The only exception came from the small, single-center trial of ethnic Chinese women in which neutropenia was found to occur statistically significantly more often in the two-drug group compared to the three-drug group (35% compared with 53%; P=0.05).[14]

Comparison of all-oral regimens of a 5-HT3 antagonist plus a corticosteroid

In one fair-quality RCT (N=65) that compared two oral regimens of a 5-HT3 antagonist plus a corticosteroid, there was no statistically significant difference (*P* values not reported) between a single-dose of oral granisetron 1 mg or oral ondansetron 16 mg, both in combination with oral dexamethasone 12 mg, in the proportion of patients with no adverse events (68% compared with 48%).[16] However, because the trial was small, and the absolute difference was 20%, there is a chance that a larger trial would identify a statistically significant difference. Significant differences were also not found with the most common adverse events of headache, dry mouth, diarrhea, and flushing.[16] Overall, this trial provided a low strength of evidence (Appendix F) that there is no significant difference between all-oral regimens in overall adverse events (RR, 1.40; 95% CI, 0.90 to 2.21).

B. How do all-oral regimens compare to all-injectable regimens?

We did not find any trials that compared an all-oral regimen to an all-injectable regimen, with or without aprepitant.

C. How do mixed oral and injectable regimens compare?

Comparison of mixed oral and injectable regimens, with and without aprepitant

Among the seven RCTs included for comparison of mixed oral and injectable regimens, with and without aprepitant,[17-23] all but one trial provided data on harms.[19] Four trials reported incidence of overall adverse events[17, 18, 20, 22] and provided high-strength evidence (Appendix F) that there is no statistically significant difference between mixed oral and injectable regimens, with or without aprepitant (pooled rates, 71% compared with 69%; RR, 1.03; 95% CI, 0.97 to 1.10). No statistically significant differences between groups with and without aprepitant were reported for any individual adverse events. The most commonly reported events were fatigue/asthenia (range, 9% to 26%) and constipation (range, 8% to 22%).

Comparison of mixed oral and injectable regimens of a 5-HT3 antagonist plus a corticosteroid

Only one[26] of three RCTs[26-28] involving mixed oral and injectable regimens reported rates of overall adverse events. This trial provided a low strength of evidence (Appendix F) that differences were not statistically significantly different between mixed oral and injectable regimens and all-injectable regimens (38% compared with 44%; RR, 0.85; 95% CI, 0.42 to 1.68; Appendix F).[26] Similarly, differences between groups were not found for any of the most frequently reported adverse events including headache, diarrhea, and constipation.

D. How do regimens given immediately prior to and/or for 48 hours after initiation of chemotherapy compare to those regimens given for longer periods of time?

The single RCT (N=108) that compared regimens given immediately prior to and for 48 hours after initiation of chemotherapy to those given for longer periods of time provided very sparse data on harms and did not include the incidence of overall adverse events.[21] Although this trial found no significant difference between the multi-day aprepitant group compared with the single-day aprepitant group for any specific adverse event, because this trial evaluated a formulation and dose of aprepitant that is unavailable in the United States, this evidence is insufficient for drawing conclusions about the current FDA-recommended dosage regimen for this question.

E. Summary of evidence

The summary of evidence for this Key Question is presented in Table 7, below.

Table 7. Summary of the evidence for Key Question 2

Key Question	Strength of evidence	Conclusions
2.A. How do oral regimens compare to each other? Outcome: Overall adverse events		
Comparison of regimens with and without aprepitant	Moderate	No significant differences (RR, 0.93; 95% CI, 0.85 to 1.03).
Comparison of regimens of a 5-HT3 antagonist plus a corticosteroid	Low	No significant differences (RR, 1.40; 95% CI, 0.90 to 2.21).
2.B. How do oral regimens compare to injectable regimens?		
	Insufficient	No trials included.
2.C. How do mixed oral and injectable regimens compare?		
Comparison of regimens with and without aprepitant	High	No significant differences (RR, 1.03; 95% CI, 0.97 to 1.10).
Comparison of regimens of a 5-HT3 antagonist plus a corticosteroid	Low	No significant differences (RR, 0.85; 95% CI, 0.42 to 1.68).
2.D. How do regimens given immediately prior to and/or for 48 hours after initiation of chemotherapy compare to those regimens given for longer periods of time?		
	Insufficient	Not reported.

Key Question 3. Are there subgroups of patients based on demographics (age, race, gender), socioeconomic status, other medications, or comorbidities for which one of these antiemetic regimens is more effective or associated with fewer adverse events in the context of emetogenic anticancer chemotherapy and/or radiation?

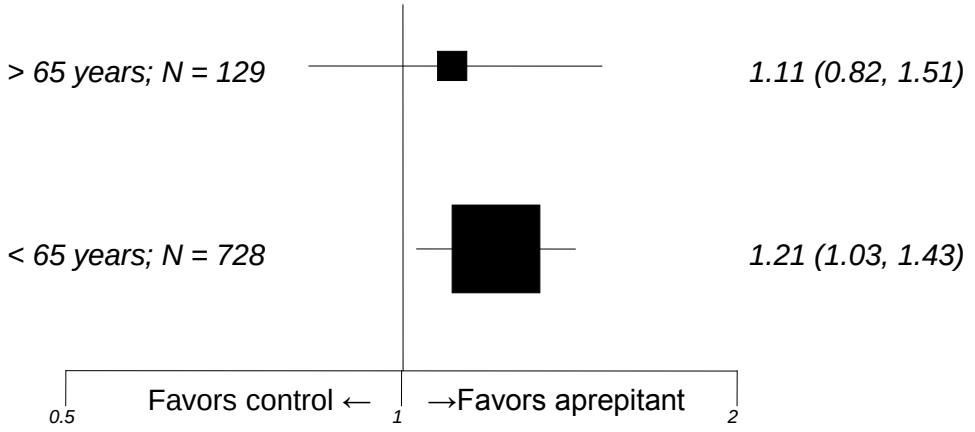
A. What is the applicability of the evidence to patients age 65 and older?

While older age has been shown to predict lower rates of emesis associated with chemotherapy,[31] relative to younger age, the evidence base evaluating comparisons of specific regimens to each other in this age group was somewhat limited. This was due largely to the fact that the majority of patients enrolled in these randomized controlled trials (RCTs) were younger than 65.

Among the RCTs comparing antiemetic regimens of drugs all given by the same route, the median or mean age of patients enrolled was 48,[16] 53,[13] and 61.[14] Of these, the most relevant evidence to patients over 65 years came from a trial comparing an oral three-drug regimen containing aprepitant to an oral two-drug regimen of 5-HT3 antagonist and corticosteroid, with an age range of 23 to 78 years (mean 53 years), where 15% were age 65 or over. For this trial both published and unpublished data were available.[13, 32] In the published article, it was stated that there was no interaction between treatment group and age (< 55 years, ≥ 55 years), with the oral three-drug regimen superior to the oral two-drug regimen, but analysis of patients over 65

was not reported.[13] Based on unpublished data submitted (Appendix G), multiple regression analysis was reported to show no effect of age on complete response rate between patients over 65 years and less than 65 years (*P*=0.788) or between patients aged 75 years and over and those less than 75 years (*P*=0.631). However, this analysis appeared to only address the question of whether complete response rate was affected by age. It did not take the specific antiemetic regimen into account (e.g. the effect on response of an interaction between treatment and age > 65), making a comparison across the two treatment regimens. For complete response (time period not specified) the rates in the group age 65 and over were reported to be 61% with the three-drug regimen compared to 55% with the two-drug regimen.[32] Our statistical analysis of these data indicated that the difference between regimens was not statistically significant for the age group 65 and over, but was significant for those under 65 years (Figure 5 below). The lack of a statistically significant finding may be due to inadequate power due to a small sample size (N=129 for age 65 and over compared with N=728 for younger than age 65) or to the fact that this was an unadjusted analysis.

Figure 5. Unadjusted relative risk for complete response by age: Oral three-drug regimen compared with oral two-drug regimen (Warr 2005; unpublished data)

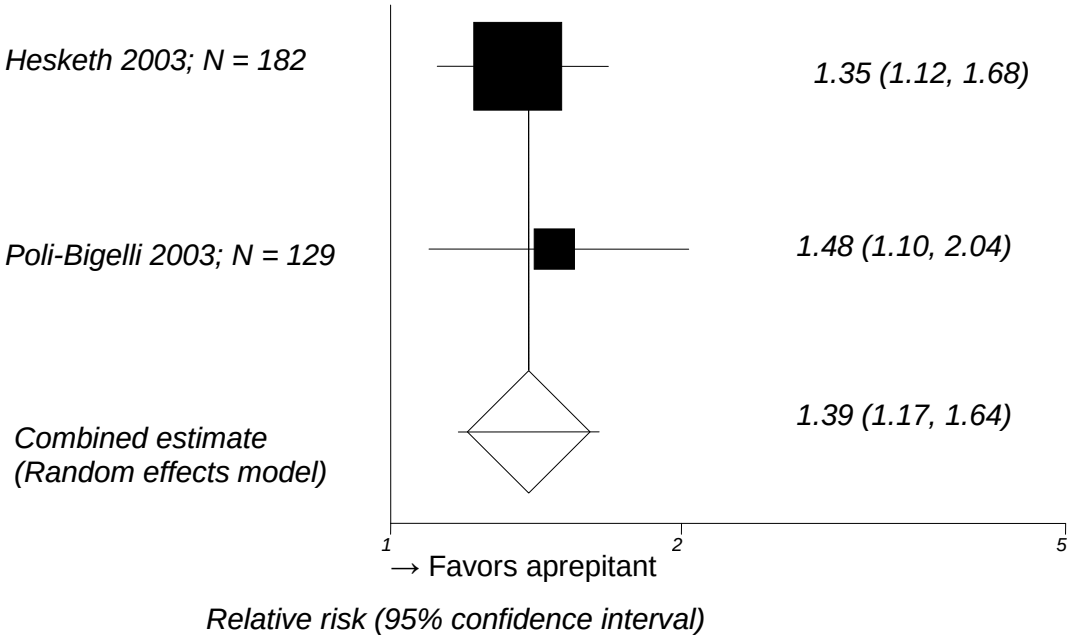


In nine other RTCs comparing mixed oral and intravenous regimens,[17-20, 22, 23, 26-29] the mean or median ages ranged from a low of 47 years[28] to a high of 62 years;[21] however, five of these trials included patients above 70 years.[18, 20, 22, 23, 26]

In a pooled analysis of patient-level data from two of these trials,[20, 22] data were analyzed according to age groups: < 60, 60 to 65, 65 to 70, and > 70 years.[33] These trials compared a three-drug regimen to a two-drug regimen, using an intravenous 5-HT3 antagonist and oral dexamethasone in both groups, but the three-drug group also had aprepitant on days 1 to 3, and received lower doses of dexamethasone than the two-drug group (see Evidence Table 1 for

details). In this prespecified subgroup analysis, 28% of patients were over 65 years. Analysis of complete response over the period of one to five days after start of chemotherapy indicated that the three-drug regimen was superior to the two-drug regimen in both older (76.1% compared with 54.1%; *P*<0.001) and younger (63.9% compared with 45.3%; *P*<0.001) patient groups (Figure 6 below is our analysis based on unpublished data submitted for these two trials). The difference between regimens was greatest for those younger than 60 years and older than 70 years, supporting the finding that older patients experience less emesis than younger patients overall.

Figure 6. Pooled unadjusted relative risk for complete response in patients age 65 and over: Mixed oral and intravenous three-drug regimen compared with two-drug regimen



Cochran Q = 0 (*df*=1) *P*>0.9999
I² (inconsistency) = too few studies to estimate

Unpublished data were submitted for a third trial that had a higher proportion of patients age 65 and over (32%).[23, 32] The regimens compared in this trial were ondansetron on days 1 to 4 and dexamethasone on days 1 to 4, compared with aprepitant on days 1 to 3, ondansetron on day 1, and dexamethasone on days 1 to 4, rather than a comparison of ondansetron on day 1 only, as in the trials above. Similar to our unadjusted analysis presented above of unpublished data submitted for a trial of an all-oral regimen, our analysis here did not find a significant difference in complete response among older patients (RR, 1.13; 95% CI, 0.94 to 1.38), while the analysis of data for younger patients indicated a statistically significant benefit for the three-drug regimen (RR, 1.22; 95% CI, 1.03 to 1.45).

Based on these RCTs, aprepitant-containing regimens were superior to regimens without aprepitant in rates of complete response over the entire treatment period in patients over 65 years where the comparison treatment administered the 5-HT3 antagonist on day 1 only. For comparisons of oral regimens, or mixed regimens where the two drug regimen included administration of a 5-HT3 antagonist through day 4, no benefit was found with a three-drug regimen. There was no evidence evaluating the comparative harms of these regimens in patients 65 and over, or evaluating other outcomes. The strength of this evidence was moderate, largely because of the risk of bias resulting from a pooled analysis including data from two of nine possible trials making comparisons of mixed oral and intravenous regimens, only one trial of regimens given by the same route, and no evidence on comparative harms. Further research may change our confidence in the estimate of effect and may change the estimate.

B. Is there evidence of disparate effects on age, gender, socioeconomic status, or ethnicity/race?

Age

Differences in outcome based on age have not been well studied, as discussed above.

Gender

Female gender has long been known to be associated with higher rates of chemotherapy-induced nausea and emesis.[31] The evaluation of gender in the trials in this report focused on the evidence of a difference in response between regimens based on gender. Most participants in the three RCTs comparing regimens given by a single route were women, with the two trials of aprepitant oral three-drug regimens compared to oral 5-HT3 antagonist two-drug regimens in women with breast cancer receiving cisplatin-based chemotherapy regimens.[13, 14] The third trial compared two oral 5-HT3 antagonist/corticosteroid regimens and enrolled 67% female participants. Analysis of effects based on gender was not undertaken.

Eleven other RCTs compared mixed oral and intravenous regimens. Two of these 11 trials undertook analyses of the effect of gender on response[20, 22] and were subsequently included in two pooled analysis of patient-level data.[33, 34] Both trials compared aprepitant-containing regimens to a 5-HT3 antagonist/corticosteroid regimen in patients receiving cisplatin-based chemotherapy and found the aprepitant regimen to be superior over a six-day period. While logistic regression indicated that women had lower response rates to the two-drug regimen compared with men in one trial (39% compared with 61%),[20] neither trial found the differences between men and women to be qualitatively significant using the Gail and Simon test, such that they felt combining these data in analyses was justified. Neither trial found differences in complete response based on gender for the aprepitant (three-drug) regimens. Because of these findings, an analysis of the results of these similar trials examining the effects of gender was undertaken.[33, 34] In these analyses, 42% (435/1043) of the patients were women and the rate of complete response across treatments was higher among men (61%) than women (53%). A difference between women and men was maintained when the data were evaluated by treatment group. In comparison to the two-drug regimen, the aprepitant-containing regimen resulted in a difference of 25% in complete response over five days in women (our calculation of unadjusted relative risk, 1.65; 95% CI, 1.37 to 2.00) while the difference among men was 16% (our

calculation of unadjusted relative risk, 1.30; 95% CI, 1.14 to 1.48). Similar differences were found with results in the acute and delayed phases. Female sex has been known to be a risk factor for chemotherapy induced nausea and vomiting, and in this analysis women benefited similarly but to a greater absolute amount than men from a three-drug aprepitant regimen.

The strength of this evidence was moderate largely because of the risk of bias resulting from a pooled analysis including data from two of eleven possible RCTs making comparisons of *mixed* oral and intravenous regimens, none of regimens given by the same route, and no evidence on comparative harms. Further research may change our confidence in the estimate of effect and may change the estimate.

Socioeconomic status

No evidence on socioeconomic status was provided by the trials.

Race

Of the three RCTs comparing antiemetic regimens of drugs all given by the same route, one reported that 80% of patients were white,[13] and a second, smaller, trial was conducted entirely with ethnic Chinese patients.[14] These studies were similar, and compared a 5-HT3 antagonist/corticosteroid regimen with the same regimen plus aprepitant. In the larger trial of mostly white patients, the analysis was adjusted for race. This trial also conducted a separate analysis of factors including race, and found no interaction between treatment (oral three-drug regimen or oral two-drug regimen) response and race. Given the high proportion of white patients and the lack of details on other races included, these findings should be considered preliminary. Although conducted in racially different populations, both trial results indicated that the aprepitant-containing regimen was superior in both acute and delayed outcomes. However, small differences were noted in adverse event rates and neither trial was designed to assess these outcomes properly. The third trial did not report the race of enrolled patients.[16]

Eleven other RCTs comparing mixed oral and intravenous regimens included a variety of races in their enrolled patient populations, including Asian, Black, Hispanic, white, and "other." Analysis of outcome by race was not undertaken in any trial.

C. Are certain groups more likely to receive one treatment over another, due to prescription trends in a geographic region, socioeconomic status, health insurance coverage, etc.?

Five fair-to-poor quality cohort studies of 3050 patients provided limited evidence to evaluate factors that influence the selection of specific antiemetic regimens.[35-39] Four of these studies found that among patients receiving primarily moderate to highly emetogenic single-day chemotherapy regimens, the choice of antiemetic regimen was not associated significantly with the patient's prior experience with chemotherapy induced nausea and vomiting.[36-39] These analyses did not, however, report results stratified by individual 5-HT3 antagonist drug and did not include aprepitant at all. Two studies also reported that there was also no association with choice of regimen and patient age, sex, or alcohol use.[35, 38] Only one of these studies reported specific 5-HT3 antagonist drugs: ondansetron, granisetron, and dolasetron (all given with dexamethasone).[35] This study also did not find association with baseline Eastern Cooperative

Oncology Group performance status. No evidence on prescription trends based on geographic region, socioeconomic status, or health insurance coverage was found.

The strength of this body of evidence was low, in that future, higher-quality studies with specific focus on these issues could change these findings (Appendix F). The currently available evidence has somewhat limited applicability. It primarily relates to patients receiving moderate to highly emetogenic chemotherapy given on a single day in inpatient or outpatient setting, and includes a variety of cancers with breast, colorectal, and lung cancer being the most common. It does not have applicability to the use of aprepitant or palonosetron.

D. Summary of evidence

The summary of evidence for this Key Question is presented in Table 8, below.

Table 8. Summary of the evidence for Key Question 3

Key Question	Strength of evidence	Conclusions
3.A. What is the applicability of the evidence to patients age 65 and older?		
How do oral regimens compare to each other?		
Comparison of regimens with and without aprepitant	Complete Response Overall: Low	No significant difference in patients 65 and over (RR, 1.11; 95% CI, 0.82 to 1.51); difference significant in younger patients (RR, 1.21; 95% CI, 1.03 to 1.43).
Comparison of regimens of a 5-HT3 antagonist plus a corticosteroid	Insufficient	Subgroup analyses not available.
How do mixed oral and injectable regimens compare?		
Comparison of regimens with and without aprepitant	Complete Response: Overall Treatment Period Moderate	Modest benefit with three-drug regimen (RR, 1.39; 95% CI, 1.17 to 1.64) compared with two-drug regimens administering a 5-HT3 antagonist on day 1 only. Compared with RR, 1.41; 95% CI, 1.23 to 1.62) in patients less than 65.
Comparison of regimens of a 5-HT3 antagonist plus a corticosteroid	Insufficient	Subgroup analyses not available.
Other outcomes, including harms have not been adequately evaluated in patients 65 and over		
3.B. Is there evidence of disparate effects on age, gender, socioeconomic status, or ethnicity/race?	Gender	
How do oral regimens compare to each other?		
Comparison of regimens with and without aprepitant	Complete Response High	Two of three trials included 99% to 100% women, the third enrolled 67% women. Results indicate modest a benefit for three-drug regimen (RR, 1.45; 95% CI, 1.32 to 1.60).
Comparison of regimens of a 5-HT3 antagonist plus a corticosteroid	Insufficient	Subgroup analyses not available.
How do mixed oral and injectable regimens compare?		

Key Question	Strength of evidence	Conclusions
Comparison of regimens with and without aprepitant	Complete Response: Overall Treatment Period Moderate	Three-drug regimen found superior to two-drug regimen, with larger effect in women than men (RR, 1.65; 95% CI, 1.37 to 2.00 in women compared with RR, 1.30; 95% CI, 1.14 to 1.48 in men).
Comparison of regimens of a 5-HT3 antagonist plus a corticosteroid	Insufficient	Subgroup analyses not available
Other outcomes, including harms have not been adequately evaluated in women.		
Other subgroups, including race, ethnicity, and socioeconomic status have not been adequately studied to make conclusions.		
3.C. Are certain groups more likely to receive one treatment over another, due to prescription trends in a geographic region, socioeconomic status, health insurance coverage, etc.?	Low	Choice of antiemetic regimen was not associated with the patient's prior experience with chemotherapy induced nausea and vomiting, age, sex, alcohol use, or baseline performance status.

Abbreviations: RCT, randomized controlled trial.

SUMMARY AND CONCLUSIONS

For the maximal patient outcome of total control (no emesis, no use of rescue medication, no or only mild nausea), the evidence was strongest in support of a significant increase with mixed oral and injectable three-drug regimens containing aprepitant compared to two-drug regimens without aprepitant during the overall study period, as well as during both the acute and delayed treatment periods in adults undergoing highly emetogenic chemotherapy. However, the benefit of a multi-day, three-drug, aprepitant-containing regimen was minimal during the acute period and only became larger in magnitude during the overall and delayed periods when the control group was administered the 5-HT3 antagonist on day 1 only. For all-oral regimens, comparisons of regimens with or without aprepitant or between two-drug regimens without aprepitant, there was low-strength evidence of no significant differences for the outcome of total control. No conclusions could be reached about total control for the comparison among different mixed two-drug regimens, without aprepitant, as evidence was unavailable for this outcome.

For complete response (no emesis, no use of rescue medication), there was predominantly high-strength evidence indicating a significant increase in benefit with three-drug regimens containing aprepitant compared to two-drug regimens without aprepitant during all study periods, regardless of whether the antiemetics were all given by an oral route or mixed oral and intravenous routes. Again, however, in the case where mixed routes were used in patients undergoing primarily highly emetogenic chemotherapy, the benefit of a multi-day, three-drug, aprepitant-containing regimen was minimal during the acute period and only became larger in magnitude during the overall and delayed periods when the control group was administered the 5-HT3 antagonist on day 1 only. There was only low-strength evidence of no significant differences in complete response between different mixed oral and intravenous route two-drug regimens, without aprepitant. No conclusions could be reached about complete response for the

comparison among different all-oral, two-drug regimens, without aprepitant, as evidence was unavailable for this outcome.

Overall, comparative evidence on the impact of antiemetic regimens on the patient's ability to tolerate subsequent chemotherapy sessions was low strength. Based on a single study of Chinese women undergoing moderately emetogenic chemotherapy, an all-oral, three-drug, aprepitant-containing regimen resulted in significantly fewer patients needing to delay subsequent chemotherapy sessions compared to an all-oral two-drug regimen not containing aprepitant. Applicability of these findings to a broader population was not clear. For mixed oral and intravenous regimens, no difference in the rate of completion of six cycles of chemotherapy was found between three-drug, aprepitant-containing regimens and two-drug regimens, based on a pooled analysis of data from extensions phases of two short-term randomized controlled trials. Further studies designed with this outcome as primary are needed to reliably answer this question.

There was no significant differences found between any regimens in incidence of overall adverse events for three-drug, aprepitant-containing regimens compared with two-drug regimens without aprepitant both when all-oral regimens were compared in patients undergoing moderately emetogenic chemotherapy (moderate-strength evidence) and when mixed oral and intravenous regimens were compared in patients undergoing highly emetogenic chemotherapy (high-strength evidence). There was only low-strength evidence of no significant differences in incidence of overall adverse events between different two-drug regimens without aprepitant, regardless of whether they were all given orally, or using a mixed oral and intravenous regimen.

The applicability of this evidence to patients age 65 and older is still somewhat limited, with only four studies reporting subgroup analyses. When compared to a two-drug regimen where the 5-HT3 antagonist was administered on day 1 only, a mixed oral and intravenous three-drug regimen containing aprepitant was superior in rates of complete response across the five-day period from start of chemotherapy. These findings were limited in that they only related to this specific comparison and to only one outcome measure, did not include evidence on comparative harms, and some of these data were unpublished. The evidence base had strong applicability to women, with approximately 60% of all enrolled patients across the studies being female. While women experienced higher rates of chemotherapy induced nausea and vomiting than men, it appeared that both oral and mixed intravenous/oral three-drug regimens were superior to two-drug regimens in women, with women achieving a slightly higher rate of complete response compared to men. However, there was inadequate evidence on any differences in harms to make conclusions.

Insufficient evidence was available for evaluating disparate effects on socioeconomic status or ethnicity/race. Although we attempted to identify studies in patients undergoing radiation, only one study was available, and it was rated poor quality.

As with other types of research, the limitations of this systematic review are important to recognize as well. These can be divided into two groups: those relating to generalizability of the results and those relating to methodology within the scope of this review. The generalizability of the results was affected by the scope of the key questions and inclusion criteria. The impact on generalizability determined by scope was separate to the applicability provided by the included studies themselves, as discussed above. In accordance with the specific programmatic interests of CMS, the scope of this systematic review was limited to studies of three-drug regimens including aprepitant, a 5-HT3 antagonist (e.g., dolasetron, granisetron, ondansetron, palonosetron), and a corticosteroid (e.g., dexamethasone, prednisone) or two-drug regimens including a 5-HT3

antagonist and a corticosteroid. Further, the primary focus was on comparing regimens where all drugs were given by the oral route to each other or to regimens where all drugs were given by the intravenous route, and to regimens given by mixed oral and intravenous routes. Consequently, evaluation of the evidence from the numerous studies that compared regimens where all drugs are given by intravenous routes was not represented here.

Methodological limitations of the review within the defined scope included the exclusion of studies published in languages other than English and lack of a specific search for unpublished studies.

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ABBREVIATIONS USED IN THE REPORT

Abbreviation	Term
5-HT3	5-hydroxytryptamine-3
AHRQ	Agency for Healthcare Research and Quality
bid	Twice daily
CI	Confidence interval
CMS	Centers for Medicare and Medicaid Services
DERP	Drug Effectiveness Review Project
FDA	US Food and Drug Administration
FLIE	Functional Living Index-Emesis questionnaire
IV	Intravenous
N	Number/population
NK1	P/neurokinin 1
NR	Not reported
Oregon EPC	Oregon Evidence-based Practice Center
PO	Palonosetron
qd	Once daily
RR	Relative risk
TAP	The Technology Assessment Program

Appendix A. US Food and Drug Administration recommendations for adult dosages

I. Dosages for prevention of emesis associated with chemotherapy[a,b]

Drug (brand name)	Form	Emetic risk	
		Moderate	**High**
Aprepitant (Emend®)	Capsule	125 mg once on day 1 then 80 mg once daily on days 2 to 3	125 mg once on day 1 then 80 mg once daily on days 2 to 3
Fosaprepitant (Emend®)	Injection	115 mg IV once on day 1 then 80 mg orally once daily on days 2 to 3	115 mg IV once on day 1 then 80 mg orally once daily on days 2 to 3
5-HT3 antagonists			
Dolasetron (Anzemet®)	Injection	1.8 mg/kg or 100 mg once	1.8 mg/kg or 100 mg once
	Tablet	100 mg once	Not established
Granisetron (Kytril®)	Injection	10 mcg/kg once	10 mcg/kg once
	Tablet, oral solution	2 mg once or 1 mg BID	2 mg once or 1 mg BID
Ondansetron (Zofran®)	Injection	32 mg once or 0.15 mg/kg TID	32 mg once
	Tablet, orally disintegrating tablet, oral solution	8 mg BID on Days 1 to 3	24 mg once
Palonosetron (Aloxi®)	Injection	0.25 mg once	0.25 mg once
	Tablet	0.5 mg once	Not established

Abbreviations: BID, twice daily; IV, intravenous; TID, three times daily.
[a] This table does not attempt to address any recommendations regarding the use of NK-1 and 5-HT3 antagonists in combination with other agents, such as steroids.
[b] Dosages are for day 1 administered once, prior to chemotherapy, unless otherwise noted.

II. Dosages for prevention of emesis following radiotherapy

Drug (brand name)	Form	Dosage[a]
Granisetron (Kytril®)	Injection	Not established
	Tablet, oral solution	2 mg once
Ondansetron (Zofran®)	Injection	Not established
	Tablet, orally disintegrating tablet, oral solution	8 mg three times daily

[a] Administered prior to radiotherapy, unless otherwise specified.

Appendix B. Glossary

This glossary defines terms as they are used in reports produced by the Drug Effectiveness Review Project. Some definitions may vary slightly from other published definitions.

Absolute risk: The probability or chance that a person will have a medical event. Absolute risk is expressed as a percentage. It is the ratio of the number of people who have a medical event divided by all of the people who could have the event because of their medical condition.

Add-on therapy: An additional treatment used in conjunction with the primary or initial treatment.

Adherence: Following the course of treatment proscribed by a study protocol.

Adverse drug reaction: An adverse effect specifically associated with a drug.

Adverse event: A harmful or undesirable outcome that occurs during or after the use of a drug or intervention but is not necessarily caused by it.

Adverse effect: An adverse event for which the causal relation between the intervention and the event is at least a reasonable possibility.

Active-control trial: A trial comparing a drug in a particular class or group with a drug outside of that class or group.

Allocation concealment: The process by which the person determining randomization is blinded to a study participant's group allocation.

Applicability: see *External Validity*

Before-after study: A type nonrandomized study where data are collected before and after patients receive an intervention. Before-after studies can have a single arm or can include a control group.

Bias: A systematic error or deviation in results or inferences from the truth. Several types of bias can appear in published trials, including selection bias, performance bias, detection bias, and reporting bias.

Bioequivalence: Drug products that contain the same compound in the same amount that meet current official standards, that, when administered to the same person in the same dosage regimen result in equivalent concentrations of drug in blood and tissue.

Black box warning: A type of warning that appears on the package insert for prescription drugs that may cause serious adverse effects. It is so named for the black border that usually surrounds the text of the warning. A black box warning means that medical studies indicate that the drug carries a significant risk of serious or even life-threatening adverse effects. The U.S. Food and Drug Administration (FDA) can require a pharmaceutical company to place a black box warning on the labeling of a prescription drug, or in literature describing it. It is the strongest warning that the FDA requires.

Blinding: A way of making sure that the people involved in a research study — participants, clinicians, or researchers —do not know which participants are assigned to each study group. Blinding usually is used in research studies that compare two or more types of treatment for an illness. Blinding is used to make sure that knowing the type of treatment does not affect a

participant's response to the treatment, a health care provider's behavior, or assessment of the treatment effects.

Case series: A study reporting observations on a series of patients receiving the same intervention with no control group.

Case study: A study reporting observations on a single patient.

Case-control study: A study that compares people with a specific disease or outcome of interest (cases) to people from the same population without that disease or outcome (controls).

Clinical diversity: Differences between studies in key characteristics of the participants, interventions or outcome measures.

Clinically significant: A result that is large enough to affect a patient's disease state in a manner that is noticeable to the patient and/or a caregiver.

Cohort study: An observational study in which a defined group of people (the cohort) is followed over time and compared with a group of people who were exposed or not exposed to a particular intervention or other factor of interest. A prospective cohort study assembles participants and follows them into the future. A retrospective cohort study identifies subjects from past records and follows them from the time of those records to the present.

Combination Therapy: The use of two or more therapies and especially drugs to treat a disease or condition.

Confidence interval: The range of values calculated from the data such that there is a level of confidence, or certainty, that it contains the true value. The 95% confidence interval is generally used in Drug Effectiveness Review Project reports. If the report was hypothetically repeated on a collection of 100 random samples of studies, the resulting 100 95% confidence intervals would include the true population value 95% of the time.

Confounder: A factor that is associated with both an intervention and an outcome of interest.

Controlled clinical trial: A clinical trial that includes a control group but no or inadequate methods of randomization.

Control group: In a research study, the group of people who do not receive the treatment being tested. The control group might receive a placebo, a different treatment for the disease, or no treatment at all.

Convenience sample: A group of individuals being studied because they are conveniently accessible in some way. Convenience samples may or may not be representative of a population that would normally be receiving an intervention.

Crossover trial: A type of clinical trial comparing two or more interventions in which the participants, upon completion of the course of one treatment, are switched to another.

Direct analysis: The practice of using data from head-to-head trials to draw conclusions about the comparative effectiveness of drugs within a class or group. Results of direct analysis are the preferred source of data in Drug Effectiveness Review Project reports.

Dosage form: The physical form of a dose of medication, such as a capsule, injection, or liquid. The route of administration is dependent on the dosage form of a given drug. Various dosage

forms may exist for the same compound, since different medical conditions may warrant different routes of administration.

Dose-response relationship: The relationship between the quantity of treatment given and its effect on outcome. In meta-analysis, dose-response relationships can be investigated using meta-regression.

Double-blind: The process of preventing those involved in a trial from knowing to which comparison group a particular participant belongs. While double-blind is a frequently used term in trials, its meaning can vary to include blinding of patients, caregivers, investigators, or other study staff.

Double-dummy: The use of two placebos in a trial that match the active interventions when they vary in appearance or method of administrations (for example, when an oral agent is compared with an injectable agent).

Effectiveness: The extent to which a specific intervention *used under ordinary circumstances* does what it is intended to do.

Effectiveness outcomes: Outcomes that are generally important to patients and caregivers, such as quality of life, responder rates, number and length of hospitalizations, and ability to work. Data on effectiveness outcomes usually comes from longer-term studies of a "real-world" population.

Effect size/estimate of effect: The amount of change in a condition or symptom because of a treatment (compared to not receiving the treatment). It is commonly expressed as a risk ratio (relative risk), odds ratio, or difference in risk.

Efficacy: The extent to which an intervention produces a beneficial result *under ideal conditions* in a selected and controlled population.

Equivalence level: The amount which an outcome from two treatments can differ but still be considered equivalent, as in an equivalence trial, or the amount which an outcome from treatment A can be worse than that of treatment B but still be considered noninferior, as in a noninferiority trial.

Equivalence trial: A trial designed to determine whether the response to two or more treatments differs by an amount that is clinically unimportant. This lack of clinical importance is usually demonstrated by showing that the true treatment difference is likely to lie between a lower and an upper equivalence level of clinically acceptable differences.

Exclusion criteria: The criteria, or standards, set out before a study or review. Exclusion criteria are used to determine whether a person should participate in a research study or whether an individual study should be excluded in a systematic review. Exclusion criteria may include age, previous treatments, and other medical conditions. Criteria help identify suitable participants.

External validity: The extent to which results provide a correct basis for generalizations to other circumstances. For instance, a meta-analysis of trials of elderly patients may not be generalizable to children. (Also called generalizability or applicability.)

Fixed-effect model: A model that calculates a pooled estimate using the assumption that all observed variation between studies is due to by chance. Studies are assumed to be measuring the same overall effect. An alternative model is the random-effects model.

Fixed-dose combination product: A formulation of two or more active ingredients combined in a single dosage form available in certain fixed doses.

Forest plot: A graphical representation of the individual results of each study included in a meta-analysis and the combined result of the meta-analysis. The plot allows viewers to see the heterogeneity among the results of the studies. The results of individual studies are shown as squares centered on each study's point estimate. A horizontal line runs through each square to show each study's confidence interval—usually, but not always, a 95% confidence interval. The overall estimate from the meta-analysis and its confidence interval are represented as a diamond. The center of the diamond is at the pooled point estimate, and its horizontal tips show the confidence interval.

Funnel plot: A graphical display of some measure of study precision plotted against effect size that can be used to investigate whether there is a link between study size and treatment effect.

Generalizability: See *External Validity.*

Half- life: The time it takes for the plasma concentration or the amount of drug in the body to be reduced by 50%.

Harms: See *Adverse Event*

Hazard ratio: The increased risk with which one group is likely to experience an outcome of interest. It is similar to a risk ratio. For example, if the hazard ratio for death for a treatment is 0.5, then treated patients are likely to die at half the rate of untreated patients.

Head-to-head trial: A trial that directly compares one drug in a particular class or group with another in the same class or group.

Health outcome: The result of a particular health care practice or intervention, including the ability to function and feelings of well-being. For individuals with chronic conditions – where cure is not always possible – results include health-related quality of life as well as mortality.

Heterogeneity: The variation in, or diversity of, participants, interventions, and measurement of outcomes across a set of studies.

I^2: A measure of statistical heterogeneity of the estimates of effect from studies. Values range from 0% to 100%. Large values of I^2 suggest heterogeneity. I^2 is the proportion of total variability across studies that is due to heterogeneity and not chance. It is calculated as (Q-(n-1))/Q, where n is the number of studies.

Incidence: The number of new occurrences of something in a population over a particular period of time, e.g. the number of cases of a disease in a country over one year.

Indication: A term describing a valid reason to use a certain test, medication, procedure, or surgery. In the United States, indications for medications are strictly regulated by the Food and Drug Administration, which includes them in the package insert under the phrase "Indications and Usage".

Indirect analysis: The practice of using data from trials comparing one drug in a particular class or group with another drug outside of that class or group or with placebo and attempting to draw conclusions about the comparative effectiveness of drugs within a class or group based on that data. For example, direct comparisons between drugs A and B and between drugs B and C can be used to make an indirect comparison between drugs A and C.

Intention to treat: The use of data from a randomized controlled trial in which data from all randomized patients are accounted for in the final results. Trials often incorrectly report results as being based on intention to treat despite the fact that some patients are excluded from the analysis.

Internal validity: The extent to which the design and conduct of a study are likely to have prevented bias. Generally, the higher the interval validity, the better the quality of the study publication.

Inter-rater reliability: The degree of stability exhibited when a measurement is repeated under identical conditions by different raters.

Intermediate outcome: An outcome not of direct practical importance but believed to reflect outcomes that are important. For example, blood pressure is not directly important to patients but it is often used as an outcome in clinical trials because it is a risk factor for stroke and myocardial infarction (hear attack).

Logistic regression: A form of regression analysis that models an individual's odds of disease or some other outcome as a function of a risk factor or intervention.

Masking: See *Blinding*

Mean difference: A method used to combine measures on continuous scales (such as weight) where the mean, standard deviation, and sample size are known for each group.

Meta-analysis: The use of statistical techniques in a systematic review to integrate the results of included studies. Although the terms are sometimes used interchangeably, meta-analysis is not synonymous with systematic review. However, systematic reviews often include meta-analyses.

Meta-regression: A technique used to explore the relationship between study characteristics (for example, baseline risk, concealment of allocation, timing of the intervention) and study results (the magnitude of effect observed in each study) in a systematic review.

Mixed treatment comparison meta analysis: A meta-analytic technique that simultaneously compares multiple treatments (typical 3 or more) using both direct and indirect evidence. The multiple treatments form a network of treatment comparisons. Also called multiple treatment comparisons, network analysis, or umbrella reviews.

Monotherapy: the use of a single drug to treat a particular disorder or disease.

Multivariate analysis: Measuring the impact of more than one variable at a time while analyzing a set of data.

N-of-1 trial: A randomized trial in an individual to determine the optimum treatment for that individual.

Noninferiority trial: A trial designed to determine whether the effect of a new treatment is not worse than a standard treatment by more than a prespecified amount. A one-sided version of an equivalence trial.

Nonrandomized study: Any study estimating the effectiveness (harm or benefit) of an intervention that does not use randomization to allocate patients to comparison groups. There are

many types of nonrandomized studies, including cohort studies, case-control studies, and before-after studies.

Null hypothesis: The statistical hypothesis that one variable (for example, treatment to which a participant was allocated) has no association with another variable or set of variables.

Number needed to harm: The number of people who would need to be treated over a specific period of time before one bad outcome of the treatment will occur. The number needed to harm (NNH) for a treatment can be known only if clinical trials of the treatment have been performed.

Number needed to treat: An estimate of how many persons need to receive a treatment before one person would experience a beneficial outcome.

Observational study: A type of nonrandomized study in which the investigators do not seek to intervene, instead simply observing the course of events.

Odds ratio: The ratio of the odds of an event in one group to the odds of an event in another group. An odds ratio of 1.0 indicates no difference between comparison groups. For undesirable outcomes an ood ratio that is <1.0 indicates that the intervention was effective in reducing the risk of that outcome.

Off-label use: When a drug or device is prescribed outside its specific FDA-approved indication, to treat a condition or disease for which it is not specifically licensed.

Outcome: The result of care and treatment and/ or rehabilitation. In other words, the change in health, functional ability, symptoms or situation of a person, which can be used to measure the effectiveness of care/ treatment/ rehabilitation. Researchers should decide what outcomes to measure before a study begins; outcomes are then assessed at the end of the study.

Outcome measure: Is the way in which an outcome is evaluated---the device (scale) used for measuring. With this definition YMRS is an outcome measure, and a patient's outcome after treatment might be a 12-point improvement on that scale.

One-tailed test (one-sided test): A hypothesis test in which the values that reject the null hypothesis are located entirely in one tail of the probability distribution. For example, testing whether one treatment is better than another (rather than testing whether one treatment is either better or worse than another).

Open-label trial: A clinical trial in which the investigator and participant are aware which intervention is being used for which participant (that is, not blinded). Random allocation may or may not be used in open-label trials.

Per protocol: The subset of participants from a randomized controlled trial who complied with the protocol sufficiently to ensure that their data would be likely to exhibit the effect of treatment. Per protocol analyses are sometimes misidentified in published trials as intention-to-treat analyses.

Pharmacokinetics: the characteristic interactions of a drug and the body in terms of its absorption, distribution, metabolism, and excretion.

Placebo: An inactive substance commonly called a "sugar pill." In a clinical trial, a placebo is designed to look like the drug being tested and is used as a control. It does not contain anything that could harm a person. It is not necessarily true that a placebo has no effect on the person taking it.

Placebo controlled trial: A study in which the effect of a drug is compared with the effect of a placebo (an inactive substance designed to resemble the drug). In placebo controlled clinical trials, participants receive either the drug being studied or a placebo. The results of the drug and placebo groups are then compared to see if the drug is more effective in treating the condition than the placebo is.

Point estimate: The results (e.g. mean, weighted difference, odds ratio, relative risk or risk difference) obtained in a sample (a study or a meta-analysis) which are used as the best estimate of what is true for the relevant population from which the sample is taken. A confidence interval is a measure of the uncertainty (due to the play of chance) associated with that estimate.

Pooling: The practice of combing data from several studies to draw conclusions about treatment effects.

Power: The probability that a trial will detect statistically significant differences among intervention effects. Studies with small sample sizes can frequently be underpowered to detect difference.

Precision: The likelihood of random errors in the results of a study, meta-analysis, or measurement. The greater the precision, the less the random error. Confidence intervals around the estimate of effect are one way of expressing precision, with a narrower confidence interval meaning more precision.

Prospective study: A study in which participants are identified according to current risk status or exposure and followed forward through time to observe outcome.

Prevalence: How often or how frequently a disease or condition occurs in a group of people. Prevalence is calculated by dividing the number of people who have the disease or condition by the total number of people in the group.

Probability: The likelihood (or chance) that an event will occur. In a clinical research study, it is the number of times a condition or event occurs in a study group divided by the number of people being studied.

Publication bias: A bias caused by only a subset of the relevant data being available. The publication of research can depend on the nature and direction of the study results. Studies in which an intervention is not found to be effective are sometimes not published. Because of this, systematic reviews that fail to include unpublished studies may overestimate the true effect of an intervention. In addition, a published report might present a biased set of results (for example, only outcomes or subgroups for which a statistically significant difference was found).

P value: The probability (ranging from zero to one) that the results observed in a study could have occurred by chance if the null hypothesis was true. A *P* value of ≤ 0.05 is often used as a threshold to indicate statistical significance.

Q-statistic: A measure of statistical heterogeneity of the estimates of effect from studies. Large values of Q suggest heterogeneity. It is calculated as the weighted sum of the squared difference of each estimate from the mean estimate.

Random-effects model: A statistical model in which both within-study sampling error (variance) and between-studies variation are included in the assessment of the uncertainty (confidence interval) of the results of a meta-analysis. When there is heterogeneity among the results of the

included studies beyond chance, random-effects models will give wider confidence intervals than fixed-effect models.

Randomization: The process by which study participants are allocated to treatment groups in a trial. Adequate (that is, unbiased) methods of randomization include computer generated schedules and random-numbers tables.

Randomized controlled trial: A trial in which two or more interventions are compared through random allocation of participants.

Regression analysis: A statistical modeling technique used to estimate or predict the influence of one or more independent variables on a dependent variable, for example, the effect of age, sex, or confounding disease on the effectiveness of an intervention.

Relative risk: The ratio of risks in two groups; same as a risk ratio.

Retrospective study: A study in which the outcomes have occurred prior to study entry.

Risk: A way of expressing the chance that something will happen. It is a measure of the association between exposure to something and what happens (the outcome). Risk is the same as probability, but it usually is used to describe the probability of an adverse event. It is the rate of events (such as breast cancer) in the total population of people who could have the event (such as women of a certain age).

Risk difference: The difference in size of risk between two groups.

Risk Factor: A characteristic of a person that affects that person's chance of having a disease. A risk factor may be an inherent trait, such as gender or genetic make-up, or a factor under the person's control, such as using tobacco. A risk factor does not usually cause the disease. It changes a person's chance (or risk) of getting the disease.

Risk ratio: The ratio of risks in two groups. In intervention studies, it is the ratio of the risk in the intervention group to the risk in the control group. A risk ratio of 1 indicates no difference between comparison groups. For undesirable outcomes, a risk ratio that is <1 indicates that the intervention was effective in reducing the risk of that outcome.

Run-in period: Run in period: A period before randomisation when participants are monitored but receive no treatment (or they sometimes all receive one of the study treatments, possibly in a blind fashion). The data from this stage of a trial are only occasionally of value but can serve a valuable role in screening out ineligible or non-compliant participants, in ensuring that participants are in a stable condition, and in providing baseline observations. A run-in period is sometimes called a washout period if treatments that participants were using before entering the trial are discontinued.

Safety: Substantive evidence of an absence of harm. This term (or the term ‘‘safe’’) should not be used when evidence on harms is simply absent or is insufficient.

Sample size: The number of people included in a study. In research reports, sample size is usually expressed as "n." In general, studies with larger sample sizes have a broader range of participants. This increases the chance that the study's findings apply to the general population. Larger sample sizes also increase the chance that rare events (such as adverse effects of drugs) will be detected.

Sensitivity analysis: An analysis used to determine how sensitive the results of a study or systematic review are to changes in how it was done. Sensitivity analyses are used to assess how robust the results are to uncertain decisions or assumptions about the data and the methods that were used.

Side effect: Any unintended effect of an intervention. Side effects are most commonly associated with pharmaceutical products, in which case they are related to the pharmacological properties of the drug at doses normally used for therapeutic purposes in humans.

Standard deviation (SD): A measure of the spread or dispersion of a set of observations, calculated as the average difference from the mean value in the sample.

Standard error (SE): A measure of the variation in the sample statistic over all possible samples of the same size. The standard error decreases as the sample size increases.

Standard treatment: The treatment or procedure that is most commonly used to treat a disease or condition. In clinical trials, new or experimental treatments sometimes are compared to standard treatments to measure whether the new treatment is better.

Statistically significant: A result that is unlikely to have happened by chance.

Study: A research process in which information is recorded for a group of people. The information is known as data. The data are used to answer questions about a health care problem.

Study population: The group of people participating in a clinical research study. The study population often includes people with a particular problem or disease. It may also include people who have no known diseases.

Subgroup analysis: An analysis in which an intervention is evaluated in a defined subset of the participants in a trial, such as all females or adults older than 65 years.

Superiority trial: A trial designed to test whether one intervention is superior to another.

Surrogate outcome: Outcome measures that are not of direct practical importance but are believed to reflect outcomes that are important; for example, blood pressure is not directly important to patients but it is often used as an outcome in clinical trials because it is a risk factor for stroke and heart attacks. Surrogate endpoints are often physiological or biochemical markers that can be relatively quickly and easily measured, and that are taken as being predictive of important clinical outcomes. They are often used when observation of clinical outcomes requires long follow-up.

Survival analysis: Analysis of data that correspond to the time from a well-defined time origin until the occurrence of some particular event or end-point; same as time-to-event analysis.

Systematic review: A review of a clearly formulated question that uses systematic and explicit methods to identify, select, and critically appraise relevant research and to collect and analyze data from the studies that are included in the review.

Tolerability: For therapeutic drugs, it refers a drug's lack of "nuisance side effects," side effects that are thought to have no long-term effect but that are unpleasant enough to the patient that adherence to the medication regimen is affected.

The extent to which a drug’s adverse effects impact the patient’s ability or willingness to continue taking the drug as prescribed. These adverse effects are often referred to as nuisance

side effects, because they are generally considered to not have long-term effects but can seriously impact compliance and adherence to a medication regimen.

Treatment regimen: The magnitude of effect of a treatment versus no treatment or placebo; similar to "effect size". Can be calculated in terms of relative risk (or risk ratio), odds ratio, or risk difference.

Two-tailed test (two-sided test): A hypothesis test in which the values that reject the null hypothesis are located in both tails of the probability distribution. For example, testing whether one treatment is different than another (rather than testing whether one treatment is either better than another).

Type I error: A conclusion that there is evidence that a treatment works, when it actually does not work (false-positive).

Type II error: A conclusion that there is no evidence that a treatment works, when it actually does work (false-negative).

Validity: The degree to which a result (of a measurement or study) is likely to be true and free of bias (systematic errors).

Variable: A measureable attribute that varies over time or between individuals. Variables can be

- *Discrete*: taking values from a finite set of possible values (e.g. race or ethnicity)
- *Ordinal*: taking values from a finite set of possible values where the values indicate rank (e.g. 5-point Likert scale)
- *Continuous:* taking values on a continuum (e.g. hemoglobin A1c values).

Washout period: [In a cross-over trial] The stage after the first treatment is withdrawn, but before the second treatment is started. The washout period aims to allow time for any active effects of the first treatment to wear off before the new one gets started.

Appendix C. Search strategies

Database: Ovid MEDLINE(R) <1996 to September Week 4 2009>
Search Strategy:
---
1 aprepitant.mp. (238)
2 dolasetron.mp. (210)
3 granisetron.mp. or Granisetron/ (771)
4 ondansetron.mp. or Ondansetron/ (1892)
5 palonosetron.mp. (113)
6 1 or 2 or 3 or 4 or 5 (2723)
7 limit 6 to (english language and humans) (1802)
8 (20081$ or 2009$).ed. (688349)
9 8 and 7 (147)
10 chemotherapy.mp. (128292)
11 Radiation/ (881)
12 11 or 10 (129166)
13 9 and 12 (43)
14 from 13 keep 1-43 (43)

Database: Ovid MEDLINE(R) <1996 to September Week 4 2009>
Search Strategy:
---
1 aprepitant.mp. (238)
2 dolasetron.mp. (210)
3 granisetron.mp. or Granisetron/ (771)
4 ondansetron.mp. or Ondansetron/ (1892)
5 palonosetron.mp. (113)
6 1 or 2 or 3 or 4 or 5 (2723)
7 limit 6 to (english language and humans) (1802)
8 exp Radiotherapy/ (54169)
9 exp Neoplasms/ (920446)
10 exp Antineoplastic Agents/ (323717)
11 8 or 10 or 9 (1104504)
12 11 and 7 (684)
13 (20081$ or 2009$).ed. (688349)
14 13 and 12 (54)
15 exp Nausea/pc, dt [Prevention & Control, Drug Therapy] (2827)
16 exp Vomiting/dt [Drug Therapy] (1093)
17 (nausea$ or emesis or emetic$ or antiemet$ or anti-emet$ or vomit$).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier] (33308)
18 16 or 17 or 15 (33342)
19 18 and 7 (1393)
20 19 and 13 (111)
21 20 not 14 (59)

22 from 14 keep 1-54 (54)

Database: Ovid MEDLINE(R) <1996 to September Week 4 2009>
Search Strategy:
---
1 aprepitant.mp. (238)
2 dolasetron.mp. (210)
3 granisetron.mp. or Granisetron/ (771)
4 ondansetron.mp. or Ondansetron/ (1892)
5 palonosetron.mp. (113)
6 1 or 2 or 3 or 4 or 5 (2723)
7 limit 6 to (english language and humans) (1802)
8 exp Radiotherapy/ (54169)
9 exp Neoplasms/ (920446)
10 exp Antineoplastic Agents/ (323717)
11 8 or 10 or 9 (1104504)
12 11 and 7 (684)
13 (20081$ or 2009$).ed. (688349)
14 13 and 12 (54)
15 exp Nausea/pc, dt [Prevention & Control, Drug Therapy] (2827)
16 exp Vomiting/dt [Drug Therapy] (1093)
17 (nausea$ or emesis or emetic$ or antiemet$ or anti-emet$ or vomit$).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier] (33308)
18 16 or 17 or 15 (33342)
19 18 and 7 (1393)
20 19 and 13 (111)
21 20 not 14 (59)
22 from 21 keep 1-59 (59)

Database: EBM Reviews - Cochrane Central Register of Controlled Trials <3rd Quarter 2009>
Search Strategy:
---
1 aprepitant.mp. (44)
2 dolasetron.mp. (141)
3 granisetron.mp. or Granisetron/ (526)
4 ondansetron.mp. or Ondansetron/ (1332)
5 palonosetron.mp. (25)
6 1 or 2 or 3 or 4 or 5 (1865)
7 chemotherapy.mp. (21556)
8 Radiation/ (22)
9 8 or 7 (21578)
10 6 and 9 (674)
11 limit 10 to yr="2008 - 2009" (11)

12 from 11 keep 1-11 (11)

Database: EBM Reviews - Cochrane Database of Systematic Reviews <3rd Quarter 2009>
Search Strategy:

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1 aprepitant.mp. (2)
2 dolasetron.mp. (6)
3 granisetron.mp. or Granisetron/ (11)
4 ondansetron.mp. or Ondansetron/ (22)
5 palonosetron.mp. (3)
6 1 or 2 or 3 or 4 or 5 (23)
7 chemotherapy.mp. [mp=title, short title, abstract, full text, keywords, caption text] (510)
8 radiation.mp. [mp=title, short title, abstract, full text, keywords, caption text] (269)
9 8 or 7 (630)
10 6 and 9 (9)
11 from 10 keep 1-9 (9)

Database: EBM Reviews - Database of Abstracts of Reviews of Effects <3rd Quarter 2009>
Search Strategy:

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1 aprepitant.mp. (0)
2 dolasetron.mp. (4)
3 granisetron.mp. or Granisetron/ (12)
4 ondansetron.mp. or Ondansetron/ (33)
5 palonosetron.mp. (0)
6 1 or 2 or 3 or 4 or 5 (34)
7 chemotherapy.mp. [mp=title, full text, keywords] (520)
8 radiation.mp. [mp=title, full text, keywords] (177)
9 8 or 7 (637)
10 6 and 9 (10)
11 from 10 keep 1-10 (10)

Database: Ovid MEDLINE(R) and Ovid OLDMEDLINE(R) <1948 to January Week 3 2010>
Search Strategy:

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1 (prescri$ adj5 pattern$).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier] (2307)
2 ondansetron.mp. or exp Ondansetron/ (2965)
3 1 and 2 (4)
4 (prescri$ adj7 pattern$).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier] (2472)
5 (prescri$ adj7 utiliz$).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier] (3529)
6 (prescri$ adj7 trend$).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier] (682)

7 (prescri$ adj7 us$).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier] (12253)
8 4 or 5 or 6 or 7 (16524)
9 aprepitant.mp. (246)
10 dolasetron.mp. (234)
11 granisetron.mp. or Granisetron/ (1162)
12 ondansetron.mp. or exp Ondansetron/ (2965)
13 palonosetron.mp. (119)
14 antiemetic.mp. or exp Antiemetics/ (116294)
15 9 or 10 or 11 or 12 or 13 or 14 (117071)
16 8 and 15 (161)
17 chemotherapy.mp. (218333)
18 exp Neoplasms/ or exp Antineoplastic Agents/ or chemo$.mp. or exp Antineoplastic Combined Chemotherapy Protocols/ (2598444)
19 radiation.mp. or exp Radiation/ (455654)
20 radiotherapy.mp. or exp Radiotherapy/ (159878)
21 cancer.mp. (703421)
22 17 or 18 or 19 or 20 or 21 (3001445)
23 16 and 22 (38)
24 from 23 keep 1-38 (38)

Database: Ovid MEDLINE(R) and Ovid OLDMEDLINE(R) <1948 to January Week 1 2010>
Search Strategy:
---
1 aprepitant.mp. (245)
2 dolasetron.mp. (234)
3 granisetron.mp. (1162)
4 ondansetron.mp. (2961)
5 palonosetron.mp. (117)
6 1 or 2 or 3 or 4 or 5 (4064)
7 exp Physician's Practice Patterns/ (28867)
8 exp Decision Making/ (86852)
9 exp Socioeconomic Factors/ (263621)
10 exp "Attitude of Health Personnel"/ (94635)
11 exp Drug Prescriptions/ (18574)
12 exp Drug Utilization/ (16012)
13 exp Health Services Accessibility/ (64229)
14 exp decision support techniques/ (42792)
15 6 and 7 (9)
16 6 and 8 (5)
17 6 and 9 (1)
18 6 and 10 (8)
19 6 and 11 (5)
20 6 and 12 (22)
21 6 and 13 (1)

22 6 and 14 (14)
23 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 (56)
24 exp Vomiting/dt [Drug Therapy] (2199)
25 Antiemetics/ad, ae, ct, tu, ec, sd (4798)
26 24 or 25 (5832)
27 7 and 26 (37)
28 8 and 26 (13)
29 9 and 26 (11)
30 10 and 26 (36)
31 11 and 26 (21)
32 12 and 26 (32)
33 13 and 26 (3)
34 14 and 26 (24)
35 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 (159)
36 exp Neoplasms/ (2099634)
37 exp Radiotherapy/ (110944)
38 rt.fs. (132454)
39 exp Antineoplastic Agents/ (663990)
40 36 or 37 or 38 or 39 (2507794)
41 35 and 40 (64)
42 23 or 41 (104)
43 limit 42 to english language (98)
44 from 43 keep 1-98 (98)

Database: Ovid MEDLINE(R) <1996 to January Week 1 2010>
Search Strategy:
---
1 aprepitant.mp. (245)
2 dolasetron.mp. (212)
3 granisetron.mp. or Granisetron/ (782)
4 ondansetron.mp. or exp Ondansetron/ (1915)
5 palonosetron.mp. (114)
6 1 or 2 or 3 or 4 or 5 (2762)
7 Drug Utilization.mp. or exp Drug Utilization/ (10618)
8 Drug Prescriptions/ or Physician's Practice Patterns/ (34094)
9 Health services needs.mp. or exp "Health Services Needs and Demand"/ (24224)
10 7 or 8 or 9 (64558)
11 6 and 10 (18)
12 from 11 keep 1-18 (18)

Database: EBM Reviews - Cochrane Central Register of Controlled Trials <4th Quarter 2009>
Search Strategy:
---
1 aprepitant.mp. (45)
2 dolasetron.mp. (142)
3 granisetron.mp. or exp Granisetron/ (532)

4 ondansetron.mp. or exp Ondansetron/ (1318)
5 palonosetron.mp. (26)
6 antiemetics.mp. or exp Antiemetics/ (12012)
7 1 or 2 or 3 or 4 or 5 or 6 (12736)
8 physician's practice patterns.mp. or exp Physician's Practice Patterns/ (633)
9 Prescribing.mp. (1038)
10 decision making.mp. or exp Decision Making/ (2296)
11 exp Socioeconomic Factors/ (3833)
12 attitude of health personnel.mp. or exp "Attitude of Health Personnel"/ (1112)
13 Drug Prescriptions.mp. or exp Prescriptions, Drug/ (279)
14 Drug Utilization.mp. or exp Drug Utilization/ (387)
15 Health Services Accessibility.mp. or exp Health Services Accessibility/ (390)
16 exp Decision Support Systems, Clinical/ or exp Decision Support Techniques/ (1533)
17 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 (10241)
18 7 and 17 (128)
19 neoplasms.mp. or exp Neoplasms/ (32300)
20 radiotherapy.mp. or exp Radiotherapy/ (8448)
21 rt.fs. (5493)
22 antineoplastic agents.mp. or exp Antineoplastic Agents/ (28005)
23 19 or 20 or 21 or 22 (49611)
24 18 and 23 (25)
25 from 24 keep 1-25 (25)

Database: EBM Reviews - Cochrane Central Register of Controlled Trials <1st Quarter 2010>
Search Strategy:
---
1 aprepitant.mp. (46)
2 dolasetron.mp. (145)
3 granisetron.mp. (538)
4 ondansetron.mp. (1382)
5 palonosetron.mp. (27)
6 1 or 2 or 3 or 4 or 5 (1927)
7 prescri$.mp. (6829)
8 ((decis$ adj3 (make or making or made)) or deciding or decide$).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword] (3165)
9 socioecon$.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword] (1892)
10 ((social$ or educat$) adj3 (class$ or status or standing or achiev$ or level$)).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword] (2864)
11 (poverty or indigen$).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword] (912)
12 ((care or therap$ or treat$) adj5 (access or ration or rationing or rationed or inacces$ or deny or denied or denial$ or denying)).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword] (729)
13 ((doctor$ or physician$ or specialist$ or oncologist$ or practice) adj5 (attitud$ or opinion$ or prefer$ or recommend$)).mp. (3485)

14 7 or 8 or 9 or 10 or 11 or 12 or 13 (18111)
15 6 and 14 (21)
16 (cancer$ or tumor$ or tumour$ or maligna$ or carcino$ or metasta$ or neoplas$ or radiother$ or chemother$ or radiation therap$).mp. (62839)
17 (anti-emetic$ or anti-nausea$ or antiemetic$).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword] (2906)
18 14 and 16 and 17 (21)
19 15 or 18 (35)
20 from 19 keep 1-35 (35)

Database: EBM Reviews - Cochrane Database of Systematic Reviews <4th Quarter 2009>
Search Strategy:
---
1 aprepitant.mp. (2)
2 dolasetron.mp. (6)
3 granisetron.mp. (11)
4 ondansetron.mp. (22)
5 palonosetron.mp. (3)
6 1 or 2 or 3 or 4 or 5 (23)
7 prescri$.mp. (1431)
8 ((decis$ adj3 (make or making or made)) or deciding or decide$).mp. [mp=title, abstract, full text, keywords, caption text] (1788)
9 socioecon$.mp. [mp=title, abstract, full text, keywords, caption text] (215)
10 ((social$ or educat$) adj3 (class$ or status or standing or achiev$ or level$)).mp. [mp=title, abstract, full text, keywords, caption text] (341)
11 (poverty or indigen$).mp. [mp=title, abstract, full text, keywords, caption text] (139)
12 ((care or therap$ or treat$) adj5 (access or ration or rationing or rationed or inacces$ or deny or denied or denial$ or denying)).mp. [mp=title, abstract, full text, keywords, caption text] (295)
13 ((doctor$ or physician$ or specialist$ or oncologist$ or practice) adj5 (attitud$ or opinion$ or prefer$ or recommend$)).mp. (593)
14 7 or 8 or 9 or 10 or 11 or 12 or 13 (3243)
15 6 and 14 (14)
16 (cancer$ or tumor$ or tumour$ or maligna$ or carcino$ or metasta$ or neoplas$ or radiother$ or chemother$ or radiation therap$).mp. (1894)
17 (anti-emetic$ or anti-nausea$ or antiemetic$).mp. [mp=title, abstract, full text, keywords, caption text] (65)
18 14 and 16 and 17 (26)
19 15 or 18 (34)
20 from 19 keep 1-34 (34)

Database: EBM Reviews - Cochrane Database of Systematic Reviews <4th Quarter 2009>
Search Strategy:
---
1 aprepitant.mp. (2)

2 dolasetron.mp. (6)
3 granisetron.mp. or exp Granisetron/ (11)
4 ondansetron.mp. or exp Ondansetron/ (22)
5 palonosetron.mp. (3)
6 antiemetics.mp. or exp Antiemetics/ (36)
7 1 or 2 or 3 or 4 or 5 or 6 (49)
8 physician's practice patterns.mp. or exp Physician's Practice Patterns/ (23)
9 Prescribing.mp. (306)
10 decision making.mp. or exp Decision Making/ (360)
11 attitude of health personnel.mp. or exp "Attitude of Health Personnel"/ (6)
12 Drug Prescriptions.mp. or exp Prescriptions, Drug/ (5)
13 Drug Utilization.mp. or exp Drug Utilization/ (5)
14 Health Services Accessibility.mp. or exp Health Services Accessibility/ (8)
15 socioeconomic.mp. [mp=title, short title, abstract, full text, keywords, caption text] (212)
16 decision support.mp. [mp=title, short title, abstract, full text, keywords, caption text] (36)
17 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 (831)
18 7 and 17 (3)
19 from 18 keep 1-3 (3)

Database: EBM Reviews - Database of Abstracts of Reviews of Effects <4th Quarter 2009>
Search Strategy:
---
1 aprepitant.mp. (0)
2 dolasetron.mp. (6)
3 granisetron.mp. (14)
4 ondansetron.mp. (36)
5 palonosetron.mp. (0)
6 1 or 2 or 3 or 4 or 5 (37)
7 prescri$.mp. (339)
8 ((decis$ adj3 (make or making or made)) or deciding or decide$).mp. [mp=title, full text, keywords] (353)
9 socioecon$.mp. [mp=title, full text, keywords] (96)
10 ((social$ or educat$) adj3 (class$ or status or standing or achiev$ or level$)).mp. [mp=title, full text, keywords] (129)
11 (poverty or indigen$).mp. [mp=title, full text, keywords] (20)
12 ((care or therap$ or treat$) adj5 (access or ration or rationing or rationed or inacces$ or deny or denied or denial$ or denying)).mp. [mp=title, full text, keywords] (60)
13 ((doctor$ or physician$ or specialist$ or oncologist$ or practice) adj5 (attitud$ or opinion$ or prefer$ or recommend$)).mp. (526)
14 7 or 8 or 9 or 10 or 11 or 12 or 13 (1359)
15 6 and 14 (6)
16 (cancer$ or tumor$ or tumour$ or maligna$ or carcino$ or metasta$ or neoplas$ or radiother$ or chemother$ or radiation therap$).mp. (1950)
17 (anti-emetic$ or anti-nausea$ or antiemetic$).mp. [mp=title, full text, keywords] (73)
18 14 and 16 and 17 (4)
19 15 or 18 (8)

20 from 19 keep 1-8 (8)

Database: EBM Reviews - Database of Abstracts of Reviews of Effects <4th Quarter 2009>
Search Strategy:
---
1 aprepitant.mp. (0)
2 dolasetron.mp. (6)
3 granisetron.mp. or exp Granisetron/ (14)
4 ondansetron.mp. or exp Ondansetron/ (36)
5 palonosetron.mp. (0)
6 antiemetics.mp. or exp Antiemetics/ (59)
7 1 or 2 or 3 or 4 or 5 or 6 (67)
8 physician's practice patterns.mp. or exp Physician's Practice Patterns/ (53)
9 Prescribing.mp. (96)
10 decision making.mp. or exp Decision Making/ (160)
11 attitude of health personnel.mp. or exp "Attitude of Health Personnel"/ (20)
12 Drug Prescriptions.mp. or exp Prescriptions, Drug/ (18)
13 Drug Utilization.mp. or exp Drug Utilization/ (19)
14 Health Services Accessibility.mp. or exp Health Services Accessibility/ (32)
15 socioeconomic.mp. [mp=title, full text, keywords] (94)
16 decision support.mp. [mp=title, full text, keywords] (57)
17 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 (474)
18 7 and 17 (1)
19 from 18 keep 1 (1)

Appendix D. Methods to assess quality of studies

Study quality was objectively assessed using predetermined criteria for internal validity, which were based on a combination of the US Preventive Services Task Force and the National Health Service Centre for Reviews and Dissemination[1, 2] criteria.

All included studies, regardless of design, were assessed for quality and assigned a rating of "good," "fair," or "poor". Studies that have a fatal flaw were rated poor quality. A fatal flaw was the failure to meet combinations of criteria that may be related to indicate the presence of bias. An example would be inadequate procedures for allocation concealment combined with important differences between groups in prognostic factors at baseline and following randomization. Studies that meet all criteria were rated good quality; the remainder were rated fair quality. As the fair-quality category was broad, studies with this rating varied in their strengths and weaknesses: The results of some fair-quality studies were *likely* to be valid, while others were only *possibly* valid. A poor-quality trial was not valid; the results were at least as likely to reflect flaws in the study design as a true difference between the compared drugs.

Systematic Reviews

1. Does the systematic review report a clear review question and clearly state inclusion and exclusion criteria for primary studies?

A good-quality review focuses on a well-defined question or set of questions, which ideally refer to the inclusion/exclusion criteria by which decisions are made about whether to include or exclude primary studies. These criteria would relate to the four components of study design, indications (patient populations), interventions (drugs), and outcomes of interest. A good-quality review also includes details about the process of decision-making, that is, how many reviewers were involved, whether the studies were examined independently, and how disagreements between reviewers were resolved.

2. Is there evidence of a substantial effort to find all relevant research?

If details of electronic database searches and other identification strategies are given, the answer to this question usually is yes. Ideally, search terms, date restrictions, and language restrictions are presented. In addition, descriptions of hand-searches, attempts to identify unpublished material, and any contact with authors, industry, or research institutes should be provided. The appropriateness of the database(s) searched by the authors should also be considered. For example, if only MEDLINE is searched for a systematic review about health education, then it is unlikely that all relevant studies will be located.

3. Is the validity of included studies adequately assessed?

If the review systematically assesses the quality of primary studies, it should include an explanation of the basis for determining quality (for example, method of randomization, whether outcome assessment was blinded, whether analysis was on an intention-to-treat basis) and the process by which assessment is carried out (that is, how many reviewers are involved, whether the assessment is independent, and how discrepancies between reviewers are resolved). Authors may have used either a published checklist or scale or one that they designed specifically for their review.

4. Is sufficient detail of the individual studies presented?

The review should show that the included studies are suitable to answer the question posed and that a judgment on the appropriateness of the authors' conclusions can be made. It is usually considered sufficient if a paper includes a table giving information on the design and results of individual studies or includes a narrative description of the studies. If relevant, the tables or text should include information on study design, sample size for each study group, patient characteristics, interventions, settings, outcome measures, follow-up, drop-out rate (withdrawals), effectiveness results, and adverse events.

5. Are the primary studies summarized appropriately?

The authors should attempt to synthesize the results from individual studies. In all cases, there should be a narrative summary of results, which may or may not be accompanied by a quantitative summary (meta-analysis).

For reviews that use a meta-analysis, heterogeneity between studies should be assessed using statistical techniques. If heterogeneity is present, the possible reasons (including chance) should be investigated. In addition, the individual evaluations should be weighted in some way (for example, according to sample size or according to inverse of the variance) so that studies that are thought to provide the most reliable data have greater impact on the summary statistic.

Controlled Trials

Assessment of Internal Validity

1. Was the assignment to the treatment groups really random?	
• Yes	Use of the term "randomized" alone is not sufficient for a judgment of "Yes". Explicit description of method for sequence generation must be provided. Adequate approaches include: Computer-generated random numbers, random numbers tables
• No	Randomization was either not attempted or was based on an inferior approach (e.g., alternation, case record number, birth date, or day of week)
• Unclear	Insufficient detail provided to make a judgment of yes or no.
2. Was the treatment allocation concealed?	
• Yes	Adequate approaches to concealment of randomization: Centralized or pharmacy-controlled randomization, serially-numbered identical containers, on-site computer based system with a randomization sequence that is not readable until allocation *Note: If a trial did not use adequate allocation concealment methods, the highest rating it can receive is "Fair".*
• No	Inferior approaches to concealment of randomization: Use of alternation, case record number, birth date, or day of week, open random numbers lists, serially numbered envelopes (even sealed opaque envelopes can be subject to manipulation)
• Unclear	No details about allocation methods. A statement that "allocation was concealed" is not sufficient; details must be provided.

3. Were groups similar at baseline in terms of prognostic factors?	
• Yes	Parallel design: No clinically important differences Crossover design: Comparison of baseline characteristics must be made based on order of randomization. *Note: Determine beforehand which prognostic factors are important to consider. A statistically significant difference does not automatically constitute a clinically important difference.*
• No	Parallel design: Clinically important differences Crossover design: Only reported baseline characteristics of the overall group.
• Unclear	Statement of "no differences at baseline", but data not reported; or data not reported by group, or no mention at all of baseline characteristics
4. Were eligibility criteria specified?	
• Yes	Eligibility criteria were specified a priori.
• No	Criteria not reported or description of enrolled patients only.
5. Were outcome assessors blinded to treatment allocation? **6. Was the care provider blinded?** **7. Was the patient blinded?**	
• Yes	Explicit statement(s) that outcome assessors/care provider/patient were blinded. Double-dummy studies and use of identically-appearing treatments are also considered sufficient blinding methods for patients and care providers.
• No	No blinding used, open-label
• Unclear, described as double-blind	Study described as double-blind but no details provided.
• Not reported	No information about blinding
8. Did the article include an intention-to-treat analysis or provide the data needed to calculate it (that is, number assigned to each group, number of subjects who finished in each group, and their results)?	
• Yes	All patients that were randomized were included in the analysis. Specify if imputation methods (e.g., last-observation carried forward) were used. OR Exclusion of 5% of patients or less is acceptable, given that the reasons for exclusion are not related to outcome (e.g., did not take study medication) and that the exclusions would not be expected to have an important impact on the effect size
• No	Exclusion of greater than 5% of patients from analysis OR less than 5%, with reasons that may affect the outcome (e.g., adverse events, lack of efficacy) or reasons that may be due to bias (e.g., investigator decision)
• Unclear	Numbers analyzed are not reported
9. Did the study maintain comparable groups?	
• Yes	No attrition. OR, the groups analyzed remained similar in terms of their

	baseline prognostic factors.
• No	Groups analyzed had clinically important differences in important baseline prognostic factors
• Unclear	There was attrition, but insufficient information to determine if groups analyzed had clinically important differences in important baseline prognostic factors
10. Were levels of crossovers (≤ 5%), adherence (≤ 20%), and contamination (≤ 5%) acceptable?	
• Yes	Levels of crossovers, adherence and contamination were below specified cut-offs.
• No	Levels or crossovers, adherence, and contamination were above specified cut-offs.
• Unclear	Insufficient information provided to determine the level of crossovers, adherence and contamination.
11. Was the rate of overall attrition and the difference between groups in attrition within acceptable levels?	
Overall attrition: There is no empirical evidence to support establishment of a specific level of attrition that is universally considered "important". The level of attrition considered important will vary by review and should be determined a priori by the review teams. Attrition refers to discontinuation for ANY reason, including lost to follow-up, lack of efficacy, adverse events, investigator decision, protocol violation, consent withdrawal, etc.	
• Yes	The overall attrition rate was below the level that was established by the review team.
• No	The overall attrition rate was above the level that was established by the review team.
• Unclear	Insufficient information provided to determine the level of attrition
Differential attrition	
• Yes	The absolute difference between groups in rate of attrition was below 10%.
• No	The difference between groups in the overall attrition rate or in the rate of attrition for a specific reason (e.g., adverse events, protocol violations, etc.) was 10% or more.
• Unclear	Insufficient information provided to determine the level of attrition

Note: For any "no" response, provide an explanation; e,g., describe inadequate allocation concealment methods

Nonrandomized studies

Assessment of Internal Validity

1. Was the selection of patients for inclusion unbiased? (Was any group of patients systematically excluded?)

2. Was there important differential loss to follow-up or overall high loss to follow-up? (Numbers should be given for each group.)

3. Were the events investigated specified and defined?

4. Was there a clear description of the techniques used to identify the events?

5. Was there unbiased and accurate ascertainment of events (that is, by independent ascertainers using a validated ascertainment technique)?

6. Were potential confounding variables and risk factors identified and examined using acceptable statistical techniques?

7. Was the duration of follow-up reasonable for investigated events?

References

1. Center for Reviews and Dissemination, University of York, 2001. Undertaking systematic reviews of research on effectiveness: CRD's guidance for those carrying out or commissioning reviews. *CRD ReportNumber 4(2nd edition)*..

2. Harris RP, Helfand M, Woolf SH. Current methods of the US Preventive Services Task Force: a review of the process. . *American Journal of Preventive Medicine.* 2001;20(3 Suppl):21-35.

Appendix E. Excluded studies

Exclusion codes: 1=foreign language, 2=outcome not included, 3=intervention not included e.g. all iv versus all iv; monotherapy; dosage form or the route of the corticosteroid was variable, unclear, or both; regimen included combination of 5-HT3 with another non corticosteroid drug, 4=population not included, 5=publication type not included, 6=study design not included.

Excluded studies	Exclusion code
Head-to-head trials	
Adamo V, Aiello R, Altavilla G, et al. Ondansetron (OND) vs granisetron (GRA) in the control of chemotherapy-induced acute emesis. European Journal of Cancer. 1995;31Ÿ(Suppl 5):S256 Abs. 1225.	5
Aapro M, Bertoli L, Lordick F, Bogdanova N, Macciocchi A. Palonosetron (PALO) is effective in preventing acute and delayed chemotherapy-induced-nausea and vomiting (CINV) in patients receiving highly emetogenic chemotherapy (HEC). [abstract]. Support Care Cancer. 2003;11(Suppl):391.	6
Aapro MS, Grunberg SM, Manikhas GM, et al. A phase III, double-blind, randomized trial of palonosetron compared with ondansetron in preventing chemotherapy-induced nausea and vomiting following highly emetogenic chemotherapy. Ann Oncol. 2006;17(9):1441-1449.	6
Abali H, Celik I. Tropisetron, ondansetron, and granisetron for control of chemotherapy-induced emesis in Turkish cancer patients: a comparison of efficacy, side-effect profile, and cost. Cancer Invest. 2007;25(3):135-139.	6
Abang AM, Takemoto MH, Pham T, et al. Efficacy and safety of oral granisetron versus i.v. granisetron in patients undergoing peripheral blood progenitor cell and bone marrow transplantation. Anticancer Drugs. 2000;11(2):137-142.	3
Anonymous. Ondansetron versus granisetron, both combined with dexamethasone, in the prevention of cisplatin-induced emesis. Italian Group of Antiemetic Research. Ann Oncol. 1995;6(8):805-810.	6
Audhuy B, Cappelaeare P, Claverie N. Double-blind, comparative trial of the anti-emetic efficacy of two IV doses of dolasetron mesilate (DM) and granisetron (G) after infusion of high-dose cisplatin chemotherapy (CT). Eur-J-Cancer. 1995;31ƒ(Suppl 5):S253 Abs.1213.	5
Audhuy B, Cappelaere P, Claverie N. Double-blind comparison of the antiemetic efficacy of two single IV doses of dolasetron and one IV dose of granisetron after cisplatin (80 mg/m2) chemotherapy. Supportive Care in Cancer. 1995;3(338):21.	5
Audhuy B, Cappelaere P, Martin M, et al. A double-blind, randomised comparison of the anti-emetic efficacy of two intravenous doses of dolasetron mesilate and granisetron in patients receiving high dose cisplatin chemotherapy. Eur J Cancer. 1996;32A(5):807-813.	6
Barrajon E, De Las Penas R. Randomised double blind crossover study comparing ondansetron, granisetron and tropisetron. A cost-benefit analysis. Support Care Cancer. 2000;8(4):323-333.	6
Beck T, Bryson J, Crawford K, McQuade B. Oral ondansetron (OND) for the prevention of nausea and vomiting (n&v) associated with cisplatin (CDDP) chemotherapy (CT). Ann-Oncol. 1998;9(Suppl 4):142.	5
Birmingham SD, Mecklenburg BW, Lujan E, Dacanay RG, Boyle PK, Green R. Dolasetron versus ondansetron as single-agent prophylaxis for patients at increased risk for postoperative nausea and vomiting: a prospective, double-blind, randomized trial. Military Medicine. 2006;171(9):913-916.	6
Bonneterre J, Hecquet B, Fenaux I, et al. Granisetron (IV) compared with ondansetron (IV plus oral) in the prevention of nausea and vomiting induced by moderately-emetogenic chemotherapy. A cross-over study. Bulletin du Cancer. 1995;82(12):1038-1043.	1
Bubalo J, Seelig F, Karbowicz S, Maziarz RT. Randomized open-label trial of dolasetron for the control of nausea and vomiting associated with high-dose chemotherapy with	6

Excluded studies	Exclusion code
hematopoietic stem cell transplantation. Biology of blood and marrow transplantation : journal of the American Society for Blood and Marrow Transplantation. 2001;7(8):439-445.	
Bubalo J, Seelig F, Karbowicz S, Maziarz RT. Randomized open-label trial of dolasetron for the control of nausea and vomiting associated with high-dose chemotherapy with hematopoietic stem cell transplantation. Biology of Blood and Marrow Transplantation. 2001;7(8):439-445.	3
Buyukavci M, Olgun H, Ceviz N. The effects of ondansetron and granisetron on electrocardiography in children receiving chemotherapy for acute leukemia. American Journal of Clinical Oncology. Apr 2005;28(2):201-204.	2
Candiotti KA, Nhuch F, Kamat A, et al. Granisetron versus ondansetron treatment for breakthrough postoperative nausea and vomiting after prophylactic ondansetron failure: a pilot study. Anesthesia & Analgesia. 2007;104(6):1370-1373.	6
Cho JY, Park JO, Rha SY, Yoo NC, Kim JH, Roh JK. A comparative study of granisetron i.v. versus ondansetron i.v./oral in the prevention of nausea and vomiting associated with moderately emetogenic chemotherapy. Ann-Oncol. 1996;7(Suppl 5):142.	5
Cocquyt V, Van Belle S, Reinhardt RR, et al. Comparison of L-758,298, a prodrug for the selective neurokinin-1 antagonist, L-754,030, with ondansetron for the prevention of cisplatin-induced emesis. Eur J Cancer. 2001;37(7):835-842.	6
Corapcioglu F, Sarper N. A prospective randomized trial of the antiemetic efficacy and cost-effectiveness of intravenous and orally disintegrating tablet of ondansetron in children with cancer. Pediatr Hematol Oncol. Mar 2005;22(2):103-114.	6
de Wit R, de Boer AC, vd Linden GH, Stoter G, Sparreboom A, Verweij J. Effective cross-over to granisetron after failure to ondansetron, a randomized double blind study in patients failing ondansetron plus dexamethasone during the first 24 hours following highly emetogenic chemotherapy. Br J Cancer. 2001;85(8):1099-1101.	6
Del Favero A, Bergerat J, Chemaissani A, Dressler H. Single oral doses of dolasetron versus multiple doses of ondansetron in preventing emesis after moderately emetogenic chemotherapy. Supportive Care in Cancer. 1995A;3(337):19.	5
Del Favero A, Roila F, Tonato M, et al. Ondansetron versus granisetron, both combined with dexamethasone, in the prevention of cisplatin-induced emesis. Ann Oncol. 1995;6(8):805-810.	6
Diemunsch P, Gan TJ, Philip BK, et al. Single-dose aprepitant vs ondansetron for the prevention of postoperative nausea and vomiting: a randomized, double-blind phase III trial in patients undergoing open abdominal surgery. British Journal of Anaesthesia. 2007;99(2):202-211.	6
Eisenberg P, Figueroa-Vadillo J, Zamora R, et al. Improved Prevention of Moderately Emetogenic Chemotherapy-Induced Nausea and Vomiting with Palonosetron, a Pharmacologically Novel 5-HT3 Receptor Antagonist: Results of a Phase III, Single-Dose Trial Versus Dolasetron. Cancer. 2003;98(11):2473-2482.	6
Fabi A, Ciccarese M, Metro G, et al. Oral ondansetron is highly active as rescue antiemetic treatment for moderately emetogenic chemotherapy: results of a randomized phase II study. Support Care Cancer. Dec 2008;16(12):1375-1380.	3
Fauser AA, Bergerat Cocquyt V, Chemaissani A, Del Favero A, Dressler HT. Double-blind, comparison trial of four single oral doses of dolasetron mesilate (DM) and multiple doses of ondansetron (OND) for emesis prevention after moderately emetogenic chemotherapy (CT). Eur-J-Cancer. 1995;31ƒ(Suppl 5):S254 Abs. 1217.	5
Fauser AA, Duclos B, Chemaissani A, et al. Therapeutic equivalence of single oral doses of dolasetron mesilate and multiple doses of ondansetron for the prevention of emesis after moderately emetogenic chemotherapy. European Journal of Cancer Part A. 1996;32(9):1523-1529.	3
Forni C, Ferrari S, Loro L, et al. Granisetron, tropisetron, and ondansetron in the prevention of acute emesis induced by a combination of cisplatin-Adriamycin and by high-dose ifosfamide delivered in multiple-day continuous infusions. Support Care Cancer.	6

Excluded studies	Exclusion code
2000;8(2):131-133.	
Fumoleau P, Giovannini M, Rolland F, Votan B, Paillarse JM. Ondansetron suppository: An effective treatment for the prevention of emetic disorders induced by cisplatin-based chemotheraphy. Oral Oncology. 1997;33(5):354-358.	6
Gan TJ, Apfel CC, Kovac A, et al. A randomized, double-blind comparison of the NK1 antagonist, aprepitant, versus ondansetron for the prevention of postoperative nausea and vomiting. Anesthesia & Analgesia. 2007;104(5):1082-1089.	6
Gebbia V, Cannata G, Testa A, et al. Ondansetron versus granisetron in the prevention of chemotherapy-induced nausea and vomiting: Results of a prospective randomized trial. Cancer. 1994;74(7):1945-1952.	3
Gralla R, Lichinitser M, Van der Vegt S, et al. Palonosetron improves prevention of chemotherapy-induced nausea and vomiting following moderately emetogenic chemotherapy: Results of a double-blind randomized phase III trial comparing single doses of palonosetron with ondansetron. Ann Oncol. 2003;14(10):1570-1577.	6
Gralla RJ, Navari RM, Hesketh PJ, et al. Single-dose oral granisetron has equivalent antiemetic efficacy to intravenous ondansetron for highly emetogenic cisplatin-based chemotherapy. J Clin Oncol. 1998;16(4):1568-1573.	3
Hesketh P, Navari R, Grote T, et al. Double-blind, randomized comparison of the antiemetic efficacy of intravenous dolasetron mesylate and intravenous ondansetron in the prevention of acute cisplatin-induced emesis in patients with cancer. J Clin Oncol. 1996;14(8):2242-2249.	6
Jaing T-H, Tsay P-K, Hung I-J, Yang C-P, Hu W-Y. Single-dose oral granisetron versus multidose intravenous ondansetron for moderately emetogenic cyclophosphamide-based chemotherapy in pediatric outpatients with acute lymphoblastic lukemia. Pediatr Hematol Oncol. 2004;21(3):227-235.	6
Jantunen IT, Muhonen TT, Kataja VV, Flander MK, Teerenhovi L. 5-HT3 receptor antagonists in the prophylaxis of acute vomiting induced by moderately emetogenic chemotherapy--a randomised study. Eur J Cancer. 1993;29A(12):1669-1672.	6
Kalaycio M, Mendez Z, Pohlman B, et al. Continuous-infusion granisetron compared to ondansetron for the prevention of nausea and vomiting after high-dose chemotherapy. J Cancer Res Clin Oncol. 1998;124(5):265-269.	6
Lacerda JF, Martins C, Carmo JA, et al. Randomized trial of ondansetron, granisetron, and tropisetron in the prevention of acute nausea and vomiting. Transplantation Proceedings. 2000;32(8):2680-2681.	5
Leonardi V, Iannitto E, Meli M, Palmeri S. Ondansetron (OND) vs granisetron (GRA) in the control of chemotherapy induced acute emesis: A multicentric randomized trial. Oncol Rep. 1996;3(5):919-923.	6
Lofters WS, Pater JL, Zee B, et al. Phase III double-blind comparison of dolasetron mesylate and ondansetron and an evaluation of the additive role of dexamethasone in the prevention of acute and delayed nausea and vomiting due to moderately emetogenic chemotherapy. J Clin Oncol. 1997;15(8):2966-2973.	6
Lofters WS, Zee B. Dolasetron (DOL) vs ondansetron (OND) with and without dexamethasone (DEX) in the prevention of nausea (N) and vomiting (V) in patients (pts) receiving moderately emetogenic chemotherapy (MEC). Eur-J-Cancer. 1995A;31?(Suppl 5):S252 Abs. 1205.	5
Lofters WS, Zee B. Dolasetron (DOL) vs ondansetron (OND) with and without dexamethasone (DEX) in the prevention of nausea (N) and vomiting (V) in patients (PTS) receiving moderately emetogenic chemotherapy (MEC). The Symptom Control Commitee of the National Cancer Institute of Canada Clinical Trials Group and Nordic Merrel Dow Research Canada. Supportive Care in Cancer. 1995;3(338).	5
Mabro M, Kerbrat P. Comparative trial of oral granisetron and intravenous ondansetron in patients receiving chemotherapy for breast cancer. Bulletin du Cancer. 1999;86(3):295-301.	1

Excluded studies	Exclusion code
Mantovani G, Maccio A, Bianchi A, et al. Comparison of granisetron vs ondansetron vs tropisetron in the prophylaxis of acute nausea and vomiting induced by highly emetogenic chemotherapy (high-dose cisplatin) for treatment of primary head and neck cancer: an open cross-over randomized controlled trial. Eur-J-Cancer. 1995;31?(Suppl 5):S252 Abs. 1206.	5
Mantovani G, Maccio A, Bianchi A, et al. Comparison of granisetron, ondansetron, and tropisetron in the prophylaxis of acute nausea and vomiting induced by cisplatin for the treatment of head and neck cancer: A randomized controlled trial. Cancer. 1996;77(5):941-948.	6
Martoni A, Angelelli B, Guaraldi M, Strocchi E, Pannuti F. An open randomised cross-over study on granisetron versus ondansetron in the prevention of acute emesis induced by moderate dose cisplatin-containing regimens. Eur J Cancer. 1996;32A(1):82-85.	3
Massidda B, Ionta MT. Prevention of delayed emesis by a single intravenous bolus dose of 5-HT3-receptor-antagonist in moderately emetogenic chemotherapy. J Chemother. 1996;8(3):237-242.	6
Muller D, Armbruster W, Unkel W, Apfel CC, Bornfeld N, Peters J. Blockade nozizeptiver ocularer Afferenzen durch Retrobulbaranasthesie vermindert nicht Ubelkeit und Erbrechen nach Propofol- Remifentanil-Anasthesie. [Blocking nociceptive afferents by retrobulbar bupivacaine does not decrease nausea and vomiting after propofol-remifentanil anaesthesia]. Anasthesiol-Intensivmed-Notfallmed-Schmerzther. 2003;Anasthesiologie,-Intensivmedizin,-Notfallmedizin,-Schmerztherapie-AINS. 38(11):689-694.	1
Navari R, Gandara D, Hesketh P, et al. Comparative clinical trial of granisetron and ondansetron in the prophylaxis of cisplatin-induced emesis. J Clin Oncol. 1995;13(5):1242-1248.	6
Noble A, Bremer K, Goedhals L, Cupissol D, Dilly SG. A double-blind, randomised, crossover comparison of granisetron and ondansetron in 5-day fractionated chemotherapy: assessment of efficacy, safety and patient preference. The Granisetron Study Group. Eur J Cancer. 1994;30A(8):1083-1088.	6
Oge A, Alkis N, Oge O, Kartum A. Comparison of granisetron, ondansetron and tropisetron for control of vomiting and nausea induced by cisplatin. J Chemother. 2000;12(1):105-108.	6
Orchard PJ, Rogosheske J, Burns L, et al. A prospective randomized trial of the anti-emetic efficacy of ondansetron and granisetron during bone marrow transplantation. Biol Blood Marrow Transplant. 1999;5(6):386-393.	6
Park JO, Rha SY, Yoo NC, et al. A comparative study of intravenous granisetron versus intravenous and oral ondansetron in the prevention of nausea and vomiting associated with moderately emetogenic chemotherapy. Am J Clin Oncol. 1997;20(6):569-572.	3
Pater JL, Lofters WS, Zee B, et al. The role of the 5-HT3 antagonists ondansetron and dolasetron in the control of delayed onset nausea and vomiting in patients receiving moderately emetogenic chemotherapy. Ann Oncol. 1997;8(2):181-185.	6
Pectasides D, Dafni U, Aravantinos G, et al. A randomized trial to compare the efficacy and safety of antiemetic treatment with ondansetron and ondansetron zydis in patients with breast cancer treated with high-dose epirubicin. Anticancer Res. 2007;27(6C):4411-4418.	3
Perez EA, Hesketh P, Sandbach J, et al. Comparison of single-dose oral granisetron versus intravenous ondansetron in the prevention of nausea and vomiting induced by moderately emetogenic chemotherapy: A multicenter, double-blind, randomized parallel study. J Clin Oncol. 1998;16(2):754-760.	3
Perez EA, Lembersky B, Kaywin P, Kalman L, Yocom K, Friedman C. Comparable safety and antiemetic efficacy of a brief (30-second bolus) intravenous granisetron infusion and a standard (15-minute) intravenous ondansetron infusion in breast cancer patients receiving moderately emetogenic chemotherapy. Cancer J Sci Am. 1998;4(1):52-58.	6
Poon RTP, Chow LWC. Comparison of antiemetic efficacy of granisetron and ondansetron in Oriental patients: A randomized crossover study. Br J Cancer. 1998;77(10):1683-1685.	6
Raynov J, Raynova P, Kancheva T, Georgiev G. Antiemetic control in cancer patients	3

Excluded studies	Exclusion code
treated with highly emetogenic chemotherapy. Journal of B.U.ON. 2000;5(3):287-291.	
Ruff P, Paska W, Goedhals L, et al. Ondansetron compared with granisetron in the prophylaxis of cisplatin-induced acute emesis: a multicentre double-blind, randomised, parallel-group study. The Ondansetron and Granisetron Emesis Study Group. [erratum appears in Oncology 1994 May-Jun;51(3):243]. Oncology. 1994;51(1):113-118.	6
Saito M, Aogi K, Sekine I, et al. Palonosetron plus dexamethasone versus granisetron plus dexamethasone for prevention of nausea and vomiting during chemotherapy: a double-blind, double-dummy, randomised, comparative phase III trial. Lancet Oncology. Feb 2009;10(2):115-124.	6
Scoponi CA, Torresi U, Di Giuseppe M, Giustozzi M. Are 5-HT3 antagonists a standard antiemetic treatment also in slightly and moderately emetogenic regimens? Oncologia. 1998;21(9):40-44.	1
Sepulveda-Vildosola AC, Betanzos-Cabrera Y, Lastiri GG, et al. Palonosetron hydrochloride is an effective and safe option to prevent chemotherapy-induced nausea and vomiting in children. Archives of Medical Research. Aug 2008;39(6):601-606.	6
Slaby J, Trneny M, Prochazka B, Klener P. Antiemetic efficacy of three serotonin antagonists during high-dose chemotherapy and autologous stem cell transplantation in malignant lymphoma. Neoplasma. 2000;47(5):319-322.	6
Spector JI, Lester EP, Chevlen EM, et al. A comparison of oral ondansetron and intravenous granisetron for the prevention of nausea and emesis associated with cisplatin-based chemotherapy. Oncologist. 1998;3(6):432-438.	3
Spina M, Valentini M, Fedele P, et al. Randomized comparison of granisetron vs ondansetron in patients (pts) with HIV-related non-Hodgkin's lymphoma (HIV-NHL) receiving moderately emetogenic chemotherapy (CT) regimens [abstract]. Proceedings of the American Society of Clinical Oncology. 1995;14(532).	5
Spitzer TR, Friedman CJ, Bushnell W, Frankel SR, Raschko J. Double-blind, randomized, parallel-group study on the efficacy and safety of oral granisetron and oral ondansetron in the prophylaxis of nausea and vomiting in patients receiving hyperfractionated total body irradiation. Bone Marrow Transplantation. 2000;26(2):203-210.	6
Stewart A, McQuade B, Cronje JDE, et al. Ondansetron compared with granisetron in the prophylaxis of cyclophosphamide-induced emesis in out-patients: A multicentre, double-blind, double-dummy, randomised, parallel-group study. Oncology. 1995;52(3):202-210.	3
Stewart L, Crawford SM, Taylor PA. The comparative effectiveness of ondansetron and granisetron in a once daily dosage in the prevention of nausea and vomiting caused by cisplatin: A double-blind clinical trial. Pharmaceutical Journal. 2000;265(7104):59-62.	6
Sukhani R, Pappas AL, Lurie J, Hotaling AJ, Park A, Fluder E. Ondansetron and dolasetron provide equivalent postoperative vomiting control after ambulatory tonsillectomy in dexamethasone-pretreated children. Anesthesia and Analgesia. 2002;95(5):1230-1235.	6
Tsavaris N, Kosmas C, Samarkos M, et al. Randomized comparative study of antiemetic activity of metoclopramide (M) vs ondansetron (Od) vs tropisetron vs granisetron (G) in patients receiving moderately emetogenic chemotherapy. Supportive Care in Cancer. 1996;4(252):114.	5
Van Belle S, Lichinitser MR, Navari RM, et al. Prevention of cisplatin-induced acute and delayed emesis by the selective neurokinin-1 antagonists, L-758,298 and MK-869: A randomized controlled trial. Cancer. 2002;94(11):3032-3041.	6
Walsh T, Morris AK, Holle LM, et al. Granisetron vs ondansetron for prevention of nausea and vomiting in hematopoietic stem cell transplant patients: Results of a prospective, double-blind, randomized trial. Bone Marrow Transplant. 2004;34(11):963-968.	6
White L, Daly SA, McKenna CJ, et al. A comparison of oral ondansetron syrup or intravenous ondansetron loading dose regimens given in combination with dexamethasone for the prevention of nausea and emesis in pediatric and adolescent patients receiving moderately/highly emetogenic chemotherapy. Pediatr Hematol Oncol. 2000;17(6):445-455.	6
White PF, Tang J, Hamza MA, et al. The use of oral granisetron versus intravenous	6

Excluded studies	Exclusion code
ondansetron for antiemetic prophylaxis in patients undergoing laparoscopic surgery: the effect on emetic symptoms and quality of recovery. Anesthesia & Analgesia. May 2006;102(5):1387-1393.	
Yalcin S, Tekuzman G, Baltali E, Ozisik Y, Barista I. Serotonin receptor antagonists in prophylaxis of acute and delayed emesis induced by moderately emetogenic, single-day chemotherapy: A randomized study. American Journal of Clinical Oncology: Cancer Clinical Trials. 1999;22(1):94-96.	6
Yonemura M, Katsumata N, Hashimoto H, et al. Randomized controlled study comparing two doses of intravenous granisetron (1 and 3 mg) for acute chemotherapy-induced nausea and vomiting in cancer patients: a non-inferiority trial. Jpn J Clin Oncol. Jul 2009;39(7):443-448.	6
Yu Z, Liu W, Wang L, et al. The efficacy and safety of palonosetron compared with granisetron in preventing highly emetogenic chemotherapy-induced vomiting in the Chinese cancer patients: a phase II, multicenter, randomized, double-blind, parallel, comparative clinical trial. Support Care Cancer. Jan 2009;17(1):99-102.	6
Zeidman A, Dayan DB, Zion TB, Kaufman O, Cohen AM, Mittelman M. Granisetron and ondansetron for chemotherapy-related nausea and vomiting. Haematologia (Budap). 1998;29(1):25-31.	3
Active-control trials	
On the relationship between nausea and vomiting in patients undergoing chemotherapy. Italian Group for Antiemetic Research. Support Care Cancer. May 1994;2(3):171-176."	2
Aapro MS, Thuerlimann B, Sessa C, de Pree C, Bernhard J, Maibach R. A randomized double-blind trial to compare the clinical efficacy of granisetron with metoclopramide, both combined with dexamethasone in the prophylaxis of chemotherapy-induced delayed emesis. Annals of Oncology. 2003;14(2):291-297.	2
Advani SH, Gopal R, Dhar AK, Lal HM, Cooverji ND. Comparative evaluation of the clinical efficacy and safety of ondansetron and metoclopramide in the prophylaxis of emesis induced by cancer chemotherapy regimens including cisplatin. Journal of the Association of Physicians of India. 1996;44(2):127-130.	2
Ahn MJ, Lee JS, Lee KH, Suh C, Choi SS, Kim SH. A randomized double-blind trial of ondansetron alone versus in combination with dexamethasone versus in combination with dexamethasone and lorazepam in the prevention of emesis due to cisplatin-based chemotherapy. American Journal of Clinical Oncology. 1994;17(2):150-156.	2
Aksoylar S, Akman SA, Ozgenc F, Kansoy S. Comparison of tropisetron and granisetron in the control of nausea and vomiting in children receiving combined cancer chemotherapy. Pediatric Hematology and Oncology. 2001;18(6):397-406.	2
Alfieri AB, Cubeddu LX. Comparative efficacy of a single oral dose of ondansetron and of buspirone against cisplatin-induced emesis in cancer patients. British Journal of Cancer. 1995;72(4):1013-1015.	2
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Anonymous. Delayed emesis induced by moderately emetogenic chemotherapy: do we need to treat all patients? The Italian Group for Antiemetic Research. Annals of Oncology. 1997;8(6):561-567.	2
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Spitzer TR, Bryson JC, Cirenza E, et al. Randomized double-blind, placebo-controlled evaluation of oral ondansetron in the prevention of nausea and vomiting associated with fractionated total- body irradiation. Journal of Clinical Oncology. 1994;12(11):2432-2438.	6
Suminaga M, Furue H, Ohta K, Taguchi T, Niitani H, Ogawa N. Clinical evaluation of granisetron for nausea and vomiting induced by anticancer drugs - Multi centered placebo controlled double-blind comparative study. Japanese Journal of Cancer and Chemotherapy. 1993;20(9):1211-1219.	2
Tiley C, Powles R, Catalano J, et al. Results of a double blind placebo controlled study of ondansetron as an antiemetic during total body irradiation in patients undergoing bone marrow transplantation. Leukemia and Lymphoma. 1992;7(4):317-321.	6
Triem JG, Piper SN, Maleck WH, Schenck A, Schmidt CC, Boldt J. Prevention of postoperative nausea and vomiting (PONV) with single oral dose of dolasetron, compared	1

Excluded studies	Exclusion code
to single dose of intravenous droperidol and a combination of both substances in patients undergoing hysterectomy. Objective. Anasthesiologie, Intensivmedizin, Notfallmedizin, Schmerztherapie. 1999;34(6):340-344.	
Uchida K, Akaza H, Hattori K, et al. Antiemetic efficacy of granisetron: a randomized crossover study in patients receiving cisplatin-containing intraarterial chemotherapy. Japanese Journal of Clinical Oncology. 1999;29(2):87-91.	2
Watcha MF, Bras PJ, Cieslak GD, Pennant JH. The dose-response relationship of ondansetron in preventing postoperative emesis in pediatric patients undergoing ambulatory surgery. Anesthesiology. 1995;82(1):47-52.	2
Yuksek MS, Alici HA, Erdem AF, Cesur M. Comparison of prophylactic anti-emetic effects of ondansetron and dexamethasone in women undergoing day-case gynaecological laparoscopic surgery. Journal of International Medical Research. 2003;31(6):481-488.	2

Appendix F. Strength of evidence

Table 1. Key Question 1a: Comparative benefits for all-oral regimens with and without aprepitant

Domains pertaining to strength of evidence					Magnitude of effect	Strength of evidence
Number of Studies; # of Subjects	**Risk of Bias (Design/ Quality)**	**Consistency**	**Directness**	**Precision**	**Relative Risk (95% Confidence Interval)**	**Low, Moderate, High**
Total Control: Overall						
1; 124	Moderate (RCT, fair)	N/A	Direct	Imprecise	0.84 (0.48, 1.47)	Low
Total Control: Acute						
1; 124	Moderate (RCT, fair)	N/A	Direct	Imprecise	0.94 (0.68, 1.30)	Low
Total Control: Delayed						
1; 124	Moderate (RCT, fair)	N/A	Direct	Imprecise	0.82 (0.57, 1.17)	Low
Complete Response: Overall						
3; 1769	Moderate (RCT, fair)	Consistent	Direct	Precise	1.22 (1.12, 1.33)[a]	High
Complete Response: Acute						
3; 1767	Moderate (RCT, fair)	Inconsistent	Direct	Precise	1.11 (1.06, 1.16)[a]	Moderate
Complete Response: Delayed						
3; 1769	Moderate (RCTs, fair)	Consistent	Direct	Precise	1.15 (1.06, 1.24) [a]	High
Delay in Subsequent Chemotherapy						
1, 124	Moderate (RCT; fair)	N/A	Direct	Precise	0.29 (0.12, 0.71)	Moderate

[a]Does not included data from Yeo 2009, due to overlap of 44 patients from Warr 2005. In Yeo 2009, the differences between aprepitant-based and standard antiemetic regimens in acute and delayed complete response rates were not statistically significant.

Table 2. Key Question 1a: Comparative benefits for all-oral, two-drug regimens of a 5-HT3 antagonist and dexamethasone

Domains pertaining to strength of evidence					Magnitude of effect	Strength of evidence
Number of Studies; # of Subjects	**Risk of Bias (Design/ Quality)**	**Consistency**	**Directness**	**Precision**	**Relative Risk (95% CI)**	**Low, Moderate, High**
Total Control: Acute						
1; 61	Moderate (RCT; Fair Quality)	N/A	Direct	Imprecise	1.02 (0.58, 1.76)	Low
Total Control: Delayed						
Not reported						
Complete Response: Acute						
Not reported						
Complete Response: Delayed						
Not reported						
Ability to tolerate sequential chemotherapy sessions						
Not reported						

Table 3. Key Question 1c: Comparative benefits of mixed oral and injectable regimens, with and without aprepitant

Domains pertaining to strength of evidence					Magnitude of effect	Strength of evidence
Number of Studies; # of Subjects	**Risk of Bias (Design/ Quality)**	**Consistency**	**Directness**	**Precision**	**Relative Risk (95% Confidence Interval)**	**Low, Moderate, High**
Total Control: Overall						
3; 1300	Moderate (RCTs, all fair)	Consistent	Direct	Precise	1.30 (1.10, 1.54)	High
Total Control: Acute						
3; 1301	Moderate (RCTs, all fair)	Consistent	Direct	Precise	1.12 (1.03, 1.21)	High
Total Control: Delayed						
3; 1301	Moderate (RCTs, all fair)	Consistent	Direct	Precise	1.36 (1.11, 1.67)	High
Complete Response: Overall						
3; 1300	Moderate (RCTs; all fair)	Consistent	Direct	Precise	1.45 (1.32, 1.60)[a]	High
Complete Response: Acute						
5; 2175	Moderate (RCTs; all fair)	Consistent	Direct	Precise	1.15 (1.10, 1.21)	High
Complete Response: Delayed						
3; 1299	Moderate (RCTs; all fair)	Consistent	Direct	Precise	1.43 (1.31, 1.56)[a]	High
Ability to tolerate sequential chemotherapy sessions						
Not reported						

[a]Data were pooled from 3 trials with similar control-group regimens on days 2 through 4-5 (i.e., monotherapy with oral dexamethasone 8 mg bid or qd). Meta-analyses did not include data from another trial (Schmoll 2006), in which the control group regimen consisted of oral ondansetron 8 mg plus dexamethasone 8 mg, both BID, on days 2 through 4. In Schmoll 2006, the magnitudes of effect were smaller, but still significant, in the overall study period (RR 1.19, 95% CI 1.05 to 1.35) and delayed period (RR, 1.17; 95% CI, 1.04 to 1.33).

Table 4. Key Question 1c: Comparative benefits of mixed oral and injectable regimens containing a 5-HT3 antagonist plus dexamethasone

Domains pertaining to strength of evidence					Magnitude of effect	Strength of evidence
Number of Studies; # of Subjects	**Risk of Bias (Design/ Quality)**	**Consistency**	**Directness**	**Precision**	**Relative Risk (95% CI)**	**Low, Moderate, High**
Total Control: Acute						
Not reported						
Total Control: Delayed						
Not reported						
Complete Response: Overall						
1; 102	Moderate (RCT; Fair quality	N/A	Indirect	Imprecise	0.97 (0.88, 1.07)	Low
Complete Response: Acute						
1; 102	Moderate (RCT; Fair quality	N/A	Indirect	Imprecise	0.97 (0.88, 1.07)	Low
Complete Response: Delayed						
1; 102	Moderate (RCT; Fair quality	N/A	Indirect	Imprecise	1.00 (0.60, 1.66)	Low
Ability to tolerate sequential chemotherapy sessions						
Not reported						

Table 5. Key Question 2a: Comparative harms for all-oral regimens with and without aprepitant

Domains pertaining to strength of evidence					Magnitude of effect	Strength of evidence
Number of Studies; # of Subjects	Risk of Bias (Design/ Quality)	Consistency	Directness	Precision	Relative Risk (95% Confidence Interval)	Low, Moderate, High
Overall Adverse Events						
1, 848	Moderate (RCT; fair)	N/A	Direct	Precise	0.93 (0.85, 1.03)	Moderate

Table 6. Key Question 2a: Comparative harms for all-oral, two-drug regimens of a 5-HT3 antagonist and dexamethasone

Domains pertaining to strength of evidence					Magnitude of effect	Strength of evidence
Number of Studies; # of Subjects	Risk of Bias (Design/ Quality)	Consistency	Directness	Precision	Relative Risk (95% CI)	Low, Moderate, High
Overall Adverse Events						
1; 61	Moderate (RCT; Fair Quality)	N/A	Direct	Imprecise	1.40 (0.9, 2.21)	Low

Table 7. Key Question 2c: Comparative harms of mixed oral and injectable regimens, with and without aprepitant

Domains pertaining to strength of evidence					Magnitude of effect	Strength of evidence
Number of Studies; # of Subjects	Risk of Bias (Design/ Quality)	Consistency	Directness	Precision	Relative Risk (95% Confidence Interval)	Low, Moderate, High
Overall Adverse Events						
4; 1640	Moderate (RCTs, all fair)	Consistent	Direct	Precise	1.03 (0.97, 1.10)	High

Table 8. Key Question 2c: Comparative benefits of mixed oral and injectable regimens containing a 5-HT3 antagonist plus dexamethasone

Domains pertaining to strength of evidence					Magnitude of effect	Strength of evidence
Number of Studies; # of Subjects	Risk of Bias (Design/ Quality)	Consistency	Directness	Precision	Relative Risk (95% CI)	Low, Moderate, High
Overall Adverse Events						
1; 51	Moderate (RCT, fair)	N/A	Direct	Imprecise	0.85 (0.42, 1.68)	Low

Table 9. Key Question 3a: Comparison of mixed oral and injectable regimens, with and without aprepitant in patients age 65 and over

Outcome	Number of studies; Number of subjects	Risk of Bias (Design/ Quality)	Consistency	Directness	Precision	Relative risk (95% CI)	Strength of evidence
Complete Response: Total	3; 467	High (1 pooled analysis of 2 RCTs, unpublished data for 3 RCTs)	Consistent	Direct	Precise	1.28 (1.09, 1.49)	Moderate
Overall Adverse Events	Not Reported						

Table 10. Key Question 3c: Factors associated with prescription of antiemetic regimen

Domains pertaining to strength of evidence					Magnitude of effect	Strength of evidence
Number of Studies; # of Subjects	**Risk of Bias (Design/ Quality)**	**Consistency**	**Directness**	**Precision**	**Proportion of induced TOL**	**Low, Moderate, High**
5 3050	Medium to low Cohort 3 Fair quality, 2 poor quality	Consistent	Direct	Unable to assess	NA	Low
Applicability						
Primarily relates to patients receiving moderate to highly emetogenic chemotherapy given on a single day in inpatient or outpatient setting, and including a variety of cancers with breast, colorectal, and lung cancer being the most common. Does not relate to aprepitant or palonosetron.						

Appendix G. Data submitted by Merck Inc. through public comment process

The text states that *P* values were not provided for some quality of life outcomes. We apologize for the omission, and present them below. Please add these *P* values to the discussion of quality of life for these studies. In the study by Hesketh et al (Reference 33) the numbers of patients reporting no significant impact of chemotherapy-induced nausea and vomiting on quality of life was 188 out of 254 (74.0%) in the aprepitant-treated group, compared to 162/252 (64.3%) in the standard care group. The difference between groups was statistically significant ($P<0.05$). In the study by Poli-Bigelli et al (Reference 35) the numbers of patients reporting no significant impact of chemotherapy-induced nausea and vomiting on quality of life was 189 out of 253 (74.7%) in the aprepitant-treated group, compared to 162/255 (63.5%) in the standard care group. The difference between groups was statistically significant ($P<0.01$).

The question of whether the results of this review can be applied patients over the age of 65 is of special interest to the agency contracting for this technology assessment. For this reason it is important that all available evidence be considered when addressing the issue. The EPC has not considered evidence that had previously been made available to it during the DERP review process. Further, it has not considered the results of a good quality review assessing subgroup data in two previously published trials. This review, by Hesketh et al. (Supportive Care in Cancer; published first online September 2009) assesses subgroup analyses conducted as part of two trials discussed in the current AHRQ review. The trials are Hesketh et al., 2003 (Reference 33) and Poli-Bigelli et al., 2003 (Reference 35).

- The review found that younger age is associated with a greater risk of chemotherapy-induced nausea and vomiting, but that aprepitant reduces risk of this outcome to the same extent among patients younger than age 65 and among those older than age 65. That is, aprepitant reduced the risk of chemotherapy-induced nausea and vomiting regardless of the presence or absence of risk factors for this outcome. We urge the EPC to examine this review and incorporate its findings into the final version of its document.
- Examination of data from the same two studies (Hesketh et al., 2003 and Poli-Bigelli et al., 2003) led the US FDA to conclude that "No overall differences in safety or effectiveness were observed between these subjects [Those over the ages of 65 or 75] and younger subjects." This observation has been incorporated into the FDA-approved product label.
- The subgroup analyses supporting this wording in the product label were conducted a priori as part of the planned protocols of the two studies. The results of these analyses were not published for reasons of space, but were shared with the EPC as part of their DERP review. We present them once again here and urgently request that the EPC incorporate them into their review.
- 13 were age 75 or over, 9 (69.2%) of these had a complete response to antiemetic therapy
- 247 were under age 75, 127 (51.4%) of these had a complete response to antiemetic therapy

"Complete response" was defined as no emesis and no need for rescue therapy. Multiple regression analysis conducted as part of the a priori study protocol found no effect of age on response rate (*P* value not recorded).

In the study published by Hesketh et al., (2003; Reference 33), patients ranged in age from 18 to 84. Patients were randomized to an aprepitant regimen including aprepitant, ondansetron and dexamethasone, or a control regimen including ondansetron and dexamethasone. There were 520 patients with evaluable data in the intent to treat population. Of these, there were 182 patients aged 65 or over, and 30 aged 75 or over.

- In the Aprepitant group, there were 260 patients, of whom:
  - 98 were age 65 or over, 79 (80.6%) of these had a complete response to antiemetic therapy.
  - 162 were under age 65, 110 (67.9%) of these had a complete response to antiemetic therapy.
  - 17 were age 75 or over, 16 (94.1%) of these had a complete response to antiemetic therapy.
  - 243 were under age 75, 173 (71.2%) of these had a complete response to antiemetic therapy.

- In the Control group, there were 260 patients, of whom:
  - 84 were age 65 or over, 50 (59.5%) of these had a complete response to antiemetic therapy.
  - 176 were under age 65, 86 (48.9%) of these had a complete response to antiemetic therapy

In the study published by ***Poli-Bigelli et al***., (2003; Reference 35), patients ranged in age from 18 to 82. Patients were randomized to an aprepitant regimen including aprepitant, ondansetron and dexamethasone, or a control regimen including ondansetron and dexamethasone. There were 523 patients with evaluable data in the intent to treat population. Of these, there were 129 patients aged 65 or over, and 21 aged 75 or over.

- In the Aprepitant group, there were 260 patients, of whom:
  - 65 were age 65 or over, 45 (69.2%) of these had a complete response to antiemetic therapy.
  - 195 were under age 65, 118 (60.5%) of these had a complete response to antiemetic therapy.
  - 11 were age 75 or over, 9 (81.8%) of these had a complete response to antiemetic therapy.
  - 249 were under age 75, 154 (61.8%) of these had a complete response to antiemetic therapy.
- In the Control group, there were 263 patients, of whom:
  - 64 were age 65 or over, 30 (46.9%) of these had a complete response to antiemetic therapy.
  - 199 were under age 65, 84 (42.2%) of these had a complete response to antiemetic therapy.
  - 10 were age 75 or over, 5 (50.0%) of these had a complete response to antiemetic therapy.
  - 253 were under age 75, 109 (43.1%) of these had a complete response to antiemetic therapy.

"Complete response" was defined as no emesis and no need for rescue therapy. Multiple regression analysis conducted as part of the a priori study protocol found no effect of age on response rate (p value not recorded).

In addition to the two studies on which the FDA and Hesketh (2009) based their conclusions, at least two other clinical trials meeting EPC inclusion criteria included a priori analyses of the effect of age on complete response, the results of which were not published. We present them here, and request that the EPC include them in their final analysis.

- In the study by Warr et al., 2005 (Reference 27), patients were randomized to an aprepitant regimen including aprepitant, ondansetron and dexamethasone, or a control regimen including ondansetron and dexamethasone. Patient ages ranged from 23 to 78 years. There were 857 patients with evaluable data in the intent to treat population. Of these, there were 129 patients aged 65 or over, and 19 aged 75 or over.
  - In the Aprepitant group, there were 433 patients, of whom:
    - 69 were age 65 or over, 42 (60.9%) of these had a complete response to antiemetic therapy.
    - 364 were under age 65, 178 (48.9%) of these had a complete response to antiemetic therapy.
    - 12 were age 75 or over, 9 (75.0%) of these had a complete response to antiemetic therapy.
    - 421 were under age 75, 211 (50.1%) of these had a complete response to antiemetic therapy.
  - In the Control group, there were 424 patients, of whom:
    - 60 were age 65 or over 33 (55.0%) of these had a complete response to antiemetic therapy.
    - 364 were under age 65, 147 (40.4%) of these had a complete response to antiemetic therapy.
    - 7 were age 75 or over, 4 (57.1%) of these had a complete response to antiemetic therapy
    - 417 were under age 75, 176 (42.2%) of these had a complete response to antiemetic therapy.
    - "Complete response" was defined as no emesis and no need for rescue therapy. Multiple regression analysis conducted as part of the a priori study protocol found no effect of age on response rate between patients aged 65 and over and patients who were less than 65 years old (p=0.788) or between patients aged 75 and over and patients who were less than 75 years old (p=0.631).
  - In the study published by Schmoll et al., (2006; Reference 36), patients were randomized to an aprepitant regimen including aprepitant, ondansetron and dexamethasone, or a control regimen including ondansetron and dexamethasone. Patients raged in age from 20 to 82. There were 484 patients with evaluable data in the intent to treat population. Of these, there were 156 patients aged 65 or over, and 15 aged 75 or over.

- In the Aprepitant group, there were 243 patients, of whom:
  - 80 were age 65 or over 63 (78.8%) of these had a complete response to antiemetic therapy.
  - 163 were under age 65, 112 (68.7%) of these had a complete response to antiemetic therapy.
  - 9 were age 75 or over 7 (77.8%) of these had a complete response to antiemetic therapy.
  - 234 were under age 75, 168 (71.8%) of these had a complete response to antiemetic therapy.
- In the Control group, there were 241 patients, of whom:
  - 76 were age 65 or over, 53 (69.7%) of these had a complete response to antiemetic therapy.
  - 165 were under age 65, 93 (56.4%) of these had a complete response to antiemetic therapy.
  - 6 were age 75 or over, 3 (50.0%) of these had a complete response to antiemetic therapy.
  - 235 were under age 75, 143 (60.9%) of these had a complete response to antiemetic therapy.

"Complete response" was defined as no emesis and no need for rescue therapy. Multiple regression analysis conducted as part of the a priori study protocol found no effect of age on response rate between patients aged 65 and over and patients who were less than 65 years old (P=0.919) or between patients aged 75 and over and patients who were less than 75 years old (P=0.612).

Abbreviations used in evidence tables

Abbreviation	Term
BEAM	Carmustine, etoposide, cytosine, arabinoside, melphalan
BU/CY	Busulfan
ICE	Ifosfamide, carboplatin, VP-16
MMT	Malignant Mesenchymal Tumor
ACSO	American Society of Clinical Oncology
AEs	Adverse Events
Apr	Aprepitant
BCNU/VP/CY	Carmustine
bid	Twice daily
BMT	Bone marrow transplant
CA	Cancer
Chemo	Chemotherapy
CHOP	Cyclophosphamide, hydroxydaunomycin, Oncovin, and prednisone
CINV	Chemotherapy-Induced Nausea and Vomiting
CMV	Cisplatin, methotrexate, vinblastine
CP	Complete protection
CR	Complete Response
CT	Controlled trial
CY	Cyclophosphamide
DB	Double-blind
Dex	Dexamethasone
ECOG	Eastern Cooperative Oncology Group
EP	Etoposide and cisplatin
FAC	5-fluorouracil, doxorubicin and cyclophosphamide
FEC	Fluorouracil, epirubicin, cyclophosphamide
FEP	Fluorouracil (bolus), epirubicin, cisplatin
FLIE	Functional Living Index-Emesis questionnaire

Abbreviation	Term
FU	Follow-up
GRADEX	Granisetron+dexamethasone
Hrs	Hours
IV	Intravenous
Mg	Milligrams
mm	Millimeter
MR	Major Response
MTZ	Mitoxantrone
N/A	Not applicable
N/V	Nausea/vomiting
NCI	National Cancer Institute
NR	Not reported
NS	Not specified
Ond	Ondansetron
ONDEX	Ondansetron+dexamethasone
PO	Palonosetron
Pts	patients
QD	Daily
RCT	Randomized controlled trial
TANC	Paclitaxel and carboplatin
TBI	Total body irradiation based
TC	Total control
TMI	Total marrow irradiation
TRODEX	Tropisetron+dexamethasone
ULN	Upper limit of normal
VAS	Visual analog score
VP	Etoposide
wk	Week
yr	Year

Evidence Table 1. Chemotherapy: Placebo-controlled trials

Author Year Country Emetogenic potential	Study Design Setting	Interventions (drug Regiment, duration)	Eligibility criteria	Age Gender Ethnicity	Other population characteristics	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/analyzed	Allowed other medications/ interventions
Campos 2001 International High	Multicenter DB parallel	Arm A (N= 90) Day 1: Placebo po x2 Granis 10µg/kg IV Dex 20 mg po Days2-5: Placebo po Arm B (N= 86) Day 1: Placebo po Granis 10µg/kg IV Dex 20 mg po MK-869 400 mg po Days 2-5: MK-869 300 mg po Arm C (N= 89) Day 1: MK-869 400 mg po x2 Placebo IV Dex 20 mg po Days 2-5: MK-869 300 mh po Arm D (N= 86) Day 1: Placebo po Placebo IV Dex 20 mg po MK-869 400 mg po Days 2-5: MK-869 mg po	Male and female cisplatin-naïve patients ≥ 16 years scheduled to receive their first course of cisplatin-based chemotherapy at a dose ≥ 70 mg/m2 were enrolled. Female patient of reproductive potential demonstrated a negative assay for serum β-human chorionic gonadotropin at prestudy visit. Primary criteria for exclusion included: Karnofsky score <60; allergy or intolerance to metoclopramide, dexamethasone, or granisetron; use of another antiemetic agent with 72 hrs of study day 1 ; an episode of vomiting or retching within 24 hrs before the start of cisplatin infusion on study day 1; treatment for or history of a seizure within past 2 years; severe concurrent illness other than neoplasia; GI obstruction or an active peptic ulcer; radiation therapy to the abdomen or pelvis within 1 week before or after study day 1; or one of the following lab values: Hemoglobin < 8.5 g/dL, WBC < 3,500/µL, platelets < 100,000 µ/L, AST > 2 x ULN (upper limit of normal), bilirubin > 2x ULN, alkaline phosphatase >2x ULN, albumin < 3 g/dL, serum creatinine > 2.0mg/dL	Age Mean: 54 yrs Gender Male: 57.4% Ethnicity NR although several centers were in Latin America	Alcohol Intake: 0-4 drinks/wk: 84.7% 5-10 drinks/wk:: 5.5% ≥11 drinks/wk: 9.7% Type of Cancer: Lung: 42% Gastrointestinal: 3% Head and Neck:19% Genitourinary: 31% Other: 5%	NR/353/351	4 (acute); 5 (delayed) /0/347-acute analysis;346-delayed analysis	Additional highly emetogenic chemotherapy: 24% Rescue therapy of metoclopramide 20-30 mg po qid OR metoclopramide 1-2 mg IV qid for day was permitted prn Rescue therapy of Dex 8 mg po bid for days 2-5 was permitted prn The investigator could also prescribe metoclopramide in addition to dexamethasone as rescue therapy for days 2-5 prn

Author Year Country Emetogenic potential	Definition of Outcomes	Method of outcome assessment and timing of assessment	Results	Method of adverse effects assessment	Adverse effects reported	Total withdrawals; withdrawals due to adverse events	Comments
Campos 2001 International High	Primary outcome: no vomiting/retching during days 2-5 Secondary outcomes: No vomiting/retching during day 1 No nausea days 1-5 Global satisfaction with antiemetic days 2-6	Vomiting/retching, nausea, and assumed global satisfaction: patient diary Nausea: 100-mm horizontal visual analog scale Global satisfaction: 100-mm horizontal visual analog scale	Acute emesis prevention (Day 1): CR: Group A (Granis+Dex) vs Group B (Granis+Dex+MK-869)=57% vs 80% (p<0.01) CR: Group A (Granis+Dex) vs Group C (Dex+MK-869)=57% vs 46% (NS) CR: Group A (Granis+Dex) vs Group D (Dex+MK-869)=57% vs 43% (NS) Acute emesis prevention+no use of rescue medication (Day 1): TC: Group A (Granis+Dex) vs Group B (Granis+Dex+MK-869)=51% vs 75% (p<0.01) TC: Group A (Granis+Dex) vs Group C (Dex+MK-869)=51% vs 44% (NS) TC: Group A (Granis+Dex) vs Group D (Dex+MK-869)=51% vs 41% (NS) Delayed emesis prevention (Day 2-5): CR: Group A (Granis+Dex+placebo) vs Group B (Granis+Dex+MK-869+MK-869)=29% vs 63% (P<0.01) CR: Group A (Granis+Dex+placebo) vs Group C (Dex+MK-869+MK-869)=29% vs 51% (p<0.01) CR: Group A (Granis+Dex+placebo) vs Group D (Dex+MK-869+MK-869)=29% vs 57% (P<0.01) Delayed emesis prevention+no use of rescue medication (Day 2-5): TC: Group A (Granis+Dex+placebo) vs Group B (Granis+Dex+MK-869+MK-869)=22% vs 41% (p<0.05) TC: Group A (Granis+Dex) vs Group C (Dex+MK-869)=22% vs 39% (p<0.05) TC: Group A (Granis+Dex+placebo) vs Group D (Dex+MK-869+MK-869)=22% vs 39% (p<0.05) Delayed emesis prevention+at least one emetic episode during acute period: Group A (Granis+Dex+placebo) vs Group C (Dex+MK-869+MK-869)=13% vs 30% (NS) Group A (Granis+Dex+placebo) vs Group D (Dex+MK-869+MK-869)=13% vs 35% (p<0.01) Nausea VAS -0-100 with 100 being "nausea as bad as it could be": Acute (0-24h): Group A (Granis+Dex) vs Group B (Granis+Dex+MK-869)=7.5 vs 1 (p<0.05) Group A (Granis+Dex) vs Group C (Dex+MK-869)=7.5 vs 8.5(NS) Group A (Granis+Dex) vs Group D (Dex+MK-869)=7.5 vs 9.5 (NS) Delayed Nausea:(Days 2-5) Group A (Granis+Dex+placebo) vs Group B (Granis+Dex+MK-869+MK-869)=7 vs 2 (p<0.05) Group A (Granis+Dex+placebo) vs Group C (Dex+MK-869+MK-869)=7 vs 3 (p<0.05) Group A (Granis+Dex+placebo) vs Group D (Dex+MK-869+MK-869)=7 vs 3 (NS) Nausea (Day 2 only): Group A (Granis+Dex+placebo) vs Group D (Dex+MK-869+MK-869)=12 vs 3 (p<0.05) other comparisons NS Global satisfaction with antiemetic treatment: no significant differences between the four groups	Patient diary; Patients were evaluated on study day 6-8 and again on day 17-29 for laboratory safety (routine hematology, serum chemistry, and urinalysis), ECGs, and physical examinations.	Constipation: 16% vs 16% vs 14% vs 13% Diarrhea: 17% vs 16% vs 40% vs 36% (Groups C and D reported higher percentages but p-value not given) Abdominal Pain: 21% vs 15% vs 13% vs 13% Dizziness: 22% vs 15% vs 21% vs 18% Headache: 33% vs 27% vs 24% vs 23% Hiccups: 16% vs 21% vs 21% vs 26% Asthenia/fatigue: 31% vs 22% vs 22% vs 22% Anorexia: 21% vs 15% vs 18% vs 17% Decrease in total WBC: 0% vs 0% vs 5% vs 0% Decrease in neutrophils: 3% vs 1% vs 5% vs 0% Elevated AST: 0% vs 3% vs 1% vs 0% Elevated ALT: 5% vs 6% vs 1% vs 9%	A vs B vs C vs D: 0 (0%) vs 2 (2.3%) vs 0 (0%) acute 1 (1.1%) delayed vs 2 (2.3%) Due to AEs: 0 (0%) vs 1 (1.2%) vs 0 (0%) vs 2 (2.3%)	

Author Year Country Emetogenic potential	Study Design Setting	Interventions (drug Regiment, duration)	Eligibility criteria	Age Gender Ethnicity	Other population characteristics	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/analyzed	Allowed other medications/ interventions
Chawla 2003 International High	Multicenter DB parallel	Arm A (N = 134) Day 1: Apr 40 mg po Days 2-5: Apr 25 mg po Arm B (N= 120) Day 1: Apr 125 mg po Days 2-5: Apr 80 mg po Arm C (N= 127) Day 1: placebo Days 2-5: placebo Arm D (N= 34) (discontinued and not analyzed) Day 1: Apr 375 mg po Days 2-5: Apr 250 mg po Apr (or placebo) given one hour prior to cisplatin infusion; Ond and Dex given 30 min prior to cisplatin infusion on day 1. Days 2-5: pts took Apr or placebo between 8 AM and 10 AM Corticosteroids given concomitantly; see "Allowed other medications"	Cisplatin-naïve pts age ≥18 yrs who had histologically confirmed solid tumors, had a Karnofsky score ≥ 60, and were scheduled to receive a chemo regimen that included cisplatin ≥70 mg/m2. Female pts of childbearing potential were required to have a negative beta-human chorionic gonadotropin test result.	Age Mean: 56.0 yrs Gender % Male: 56.4% Ethnicity % White: 58.3% % Black: 6.3% % Other: 35.4%	Mean cisplatin dose: 81.2 mg/m2 Primary cancer diagnosis: respiratory: 43.6% urogenital: 27.0% other: 28.9% Alcohol intake - % of pts (drinks/wk): 0 drinks: 74.5% 1-10 drinks: 19.4% >10 drinks: 5.8% % receiving concurrent emetogenic chemo (Hesketh level ≥3): 18.1%	663/NR/583	18/NR/377 for primary efficacy analysis	Arm A Day 1: Ond 32 mg IV + Dex 20 mg po Day 2-5: Dex 8 mg po Arm B Day 1: Ond 32 mg IV + Dex 20 mg po Day 2-5: Dex 8 mg po Arm C Day 1: Ond 32 mg IV + Dex 20 mg po Day 2-5: Dex 8 mg po Arm D Day 1: Ond 32 mg IV + Dex 20 mg po Day 2-5: Dex 8 mg po

Author Year Country Emetogenic potential	Definition of outcomes	Method of outcome assessment and timing of assessment	Results	Method of adverse effects assessment	Adverse effects reported	Total withdrawals; withdrawals due to adverse events	Comments
Chawla 2003 International High	Primary response: Complete response (**CR**): no emetic episodes and no rescue therapy for Days 1-5 Total control (**TC**): no emetic episodes, no use of rescue therapy, and maximum nausea VAS< 5mm Complete protection (CP): no emesis, no rescue therapy, and no significant nausea (VAS<25 mm) No emesis No rescue therapy No nausea (maximum VAS <5 mm) No significant nausea (max. VAS <25 mm) Total number of emetic episodes (0, 1, 2, ≥3)	Pt diary for emetic episodes and use of rescue 100 mm Nausea visual analog scale (VAS): 0mm = no nausea 100mm = nausea as bad as it could be Pts marked this nausea VAS every morning (8 AM-10AM) for the nausea they experienced the previous day. Pts had a post-study visit between Day 1 and 3 days after last dose of study medication; and another visit between days 19-29 post cisplatin for FU and lab tests.	*Comparisons are for groups A vs B vs C* Complete response Day 1 (Acute): 5.6% vs 83.2% vs 71.4% (p=NR for A vs C; p=0.014 for B vs C) Days 2-5 (delayed): 63.9% vs 72.7% vs 45.2% (p=0.002 for A vs C; p<0.001 for B vs C) Overall (Days 1-5): 58.8% vs 71.0% vs 43.7% (p<0.05 for A vs C; p<0.01 for B vs C) Total Control Day 1: 63.0% vs 67.9% vs. 58.7% (p=NR for both comparisons) days 2-5: 51.3% vs 51.5% vs 32.5% (p<0.01 for A vs C and B vs C) Overall (Days 1-5): 44.5% vs 47.3% vs 31.0% (p<0.05 for A vs C; p<0.01 for B vs C) Complete Protection Day 1: 72.3% vs 79.4% VS 66.7% (P<0.05 for A vs C; p=NR for B vs C) Days 2-5: 58.0% vs 67.4% vs 41.3% (p<0.01 for A vs C and B vs C) Overall (Days 1-5): 44.5 % vs 47.3% vs 31.0% (p<0.05 for A vs C; p<0.01 for B vs C) No Emesis Day 1: 80.7% vs 87.0% vs 73.0% (p=NR for A vs C;p<0.01 for B vs C) days 2-5: 69.7% vs 77.3% vs 50.0% (p<0.01 for A vs C and B vs C) Overall (days 1-5) 6.3% vs 65.5% vs 48.4% (p<0.01 for A vs C and B vs C) No Rescue Day 1: 87.4% vs 93.9% vs 93.7% (p=NR for both comparisons) Days 2-5:75.6% vs 85.6% vs 63.5% (p<0.05 for A vs C; p<0.01 for B vs C) Overall (Days 1-5):3.1% vs 83.2% vs 63.5% (p=NS for A vs C; p<0.01 for B vs C) No nausea Day 1:7 0.6% vs 71.8% vs 66.7% (p=NR for both comparisons) Days 2-5: 52.9% vs 58.3% vs 36.5% (p<0.01 for A vs C and B vs C) Overall (Days 1-5): 48.7% vs 52.7% vs 34.1% (p=0.05 for A vs C; p<0.01 for B vs C) No significant Nausea Day 1: 86.6% vs 90.8% vs 87.3% (p=NR for both comparisons) Days 2-5: 68.9% vs 83.3% vs 62.7% (p=NR for A vs C; p<0.01 for B vs C) Overall (Days 1-5): 68.9% vs 81.7% vs 58.7% (p=NR for A vs C; p<0.01 for B vs C)	Tolerability was monitored by physical exams, including vital signs and weight measurements, lab studies, and electrocardiograms.	*Comparisons are for groups A vs B vs C vs D* ≥ 1 adverse event (AEs): 71% vs 76% vs 72% vs 85% Drug-related AEs: 27% vs 27% vs 26% vs 15% Serious AEs: 17% vs 22% vs 12% vs 21% Discontinued due to AEs: 1% vs 2% vs 1% vs 9% ≥ 1 laboratory AE: 22% vs 23% vs 22% vs 27% Drug-related laboratory AE: 6% vs 8% vs 9% vs 0% Most common AEs (≥10% in at least 1 treatment group): Asthenia/fatigue: 13% vs 20% vs 17% vs 21% Constipation: 12% vs 14% vs 13% vs 15% Diarrhea: 11% vs 11% vs 12% vs 12% Nausea: 12% vs 13% vs 11% vs 21% Neutropenia: 2% vs 3% vs 6% vs 12% Anorexia: 6% vs 12% vs 11% vs 0% Headache: 8% vs 8% vs 10% vs 9% Hiccup: *16% vs 12% vs 9% vs 9%* Febrile neutropenia: *9% vs 6% vs 4% vs 6%* *"No pt died or discontinued due to lab AEs"*	18/583= 3.1%; 13 withdrew due to AEs	The Apr 375/250 mg regimen (n=34) was replaced by the Apr 40/25mg regimen due to pharmacokinetic data and data showing an interaction between Apr and dexamethasone. No statistical comparisons were made for this group, and the results reported were for the complete response: Acute: 91%; Delayed: 73%; Overall: 70%

Author Year Country Emetogenic potential	Study Design Setting	Interventions (drug Regiment, duration)	Eligibility criteria	Age Gender Ethnicity	Other population characteristics	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/analyzed	Allowed other medications/ interventions
de Wit 2003 International High	Multicenter DB parallel	Arm A (N= 34) Day 1: Apr 375 mg Days 2-5: Apr 250 mg Arm B (N= 80) Day 1: Apr 125 mg Days 2-5: Apr 80 mg Arm C (N= 81) Days 1-5: placebo *corticosteroids given concomitantly (see "Allowed other medications")*	Cisplatin naïve patients ≥ 18 years, who had histologically confirmed solid malignancies, a Karnofsky score of ≥ 60, and who were scheduled to receive a chemo regiment with at least on cycle including cisplatin ≥70 mg/m2. If pts satisfactorily completed the preceding cycle and related study procedures including efficacy assessments and FU visits, and if their continued participation was considered appropriate by the investigator, pts could remain in the study for up to 5 additional cycles of chemo (if the minimum dose of cisplatin was >= 70 mg/m2 in any cycle)	Age Mean: 57.7 yrs Range: 20-82 yrs Gender % Male: 63.9% Ethnicity % White: 73.8% % Black: 4.4% % Other: 21.8%	Mean cisplatin dose: 80.3 mg/m2 % cisplatin ≥ 100 mg/m2: 5.9% Primary cancer diagnosis: respiratory: 45.0% urogenital: 19.8% other: 35.1% Alcohol intake - % of pts (drinks/wk): 0 drinks: 64.3% 1-10 drinks: 26.7% >10 drinks: 8.4% % receiving concurrent emetogenic chemo (Hesketh level ≥3): 17.3%	NR/NR/202	(#s changed from cycle to cycle)	Day 1: Ond 32 mg IV + Dex 20 mg po; Days 2-5: Dex 8 mg po Corticosteroid therapy equivalent to ≤10mg of prednisone was allowed provided it was not initiated within 72hrs of day 1 of cycle 1
Herrington 2008 Texas High	Single-Center DB RCT Parallel	Arm A (N= 29) Day 1 - Palonosetron 0.25 mg IV & dexamethasone 12 mg; Aprepitant 125 mg orally Day 2 & 3 - Aprepitant 80 mg orally Arm B (N=30) Day 1 - Palonosetron 0.25 mg IV & dexamethasone 12 mg; Aprepitant 125 mg orally Day 2 & 3 - Placebo Arm C (N=16) Day 1 - Palonosetron 0.25 mg IV & dexamethasone 18 mg; Placebo Day 2 & 3 - Placebo	Patients ≥ 18 years, histologically or cytologically confirmed malignant disease and an Eastern Cooperative Oncology Group performance status of 0-2. Chemotherapy naïve or chemotherapy non-naïve with the last chemotherapy separated by at least 3 weeks; however, study criteria demanded that they not have greater than grade 1 nausea.	Age Mean: 58 yrs Gender 26.6% male Ethnicity NR	Mean weight (kg): 87.5 Cancer diagnosis Breast: 54.6% Lung: 13.3% Head and neck: 18.6% Other: 13.5%	NR/82/75	NR/NR/75	All treatment arms received dexamethasone 8 mg orally on days 2-4 Rescue medication was allowed

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de Wit 2003 International High	Complete response: no emesis and no rescue therapy Partial response: 0-2 emetic episodes and no rescue therapy Failed response: >2 emetic episodes and/or use of rescue therapy	Patient diaries, efficacy assessments before each cisplatin infusion, patient records of episodes of emesis, usage of rescue medicine.	Cycle 1 data: (Group B vs. C(Complete response: 63.8% vs. 48.8%, p<0.05 Partial response: 11.2% vs. 13.1%, p=NR Failures: 25.0% vs. 38.1%, p=NR Cycle 2 data: (Group B vs. C) Complete response: 80% vs 71%, p=NR Partial response: 10.9% vs15.8%, p=NR Failures: 8.7% vs 13.1%, p=NR	Tolerability was monitored by physical examinations including vital signs, weight measurement, lab studies, ECGs, and adverse events reported.	*Comparisons are for groups A vs B vs C* **For AEs in cycles 2-6** ≥ 1 adverse event (AEs): 74 vs 76 vs 73 Drug-related AEs: 26 vs 34 vs 25 Serious AEs: 9 vs 26 vs 15 Discontinued due to AEs: 13 vs 10 vs 10 ≥1 laboratory AE: 22 vs 26 vs 27 Drug-related laboratory AE: 0 vs 7 vs 5 Most common AEs (≥10% in at least 1 treatment group): Abdominal pain: 9 vs 10 vs 10 Fatigue: 26 vs 18 vs 17 Dehydration: 0 vs 13 vs 10 Dizziness: 9 vs 13 vs 10 Influenza-like disease: 13 vs 2 vs 2 Constipation: 22 vs 10 vs 13 Diarrhea: 9 vs 23 vs 13 Dysgeusia: 17 vs 5 vs 7 Nausea: 17 vs 18 vs 13 Anemia: 13 vs 7 vs 13 Febrile neutropenia: 0 vs 11 vs 2 Headache: 4 vs 11 vs 15 Hiccups: 9 vs 15 vs 8 Dyspnea: 13 vs 2 vs 5	128 ; 27	Group A was discontinued early due to pharmacokinetic data suggesting the dose was too high; between treatment comparisons were made between Groups B and C only. 6 pts died between Cycles 2 and 6: 3 were in Group B (1 pt=cancer progression and respiratory insufficiency, 1 pt =cancer progression, 1 pt =hemoptysis) and 3 were in Group C (2 pts = cardiac arrest, 1 pt = metastasis)
Herrington 2008 Texas High	Proportion of patients with emesis in the acute (Day 1) and delayed (Days 2-5) phases after chemotherapy	Patient diary for emetic episodes, breakthrough nausea medications, and nausea severity during the 120-hour observation period	*Comparisons are for A vs B vs C* Proportion of patients without emesis Day 1: 96.4% vs 100% vs 93.8% Day 2-5: 92.9% vs 92.6% vs 50% Severity of Nausea Using Mean VAS Day 1: 12.6% vs 8.7% vs 15.6% Day 2: 15.2% vs 11% vs 28.4% Day 3: 15% vs 12.3% vs 30.3% Day 4: 10.5% vs 16.6% vs 19.6% Day 5: 12% vs 18.3% vs 20.6% Percentage with no rescue medication (Day 1) Day 1: 81.5% vs85.2% vs 75% Day 2-5: 55.6% vs 70.4% vs 43.8% Percentage with complete response (no emesis and no rescue medication: Day 1) Day 1: 66.7% vs 70.4% vs 56.2% Day 2-5: 63% vs 59.3% vs 31.2%	Patient report	NR	NR; NR	

Author Year Country Emetogenic potential	Study Design Setting	Interventions (drug Regiment, duration)	Eligibility criteria	Age Gender Ethnicity	Other population characteristics	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/analyzed	Allowed other medications/ interventions
Hesketh 2003 International High	Multicenter DB parallel	Arm A (N= 264) Day 1: Apr 125 mg po Days 2-3: Apr 80 mg po Day 4: placebo Arm B (N=266) Day 1: placebo Days 2-4: placebo 1 hour before cisplatin on Day 1, pts received Apr or placebo *Corticosteroids given concomitantly; see "Allowed other medications"*	Cisplatin-naïve pts age ≥18 yrs who had histologically confirmed solid tumors, had a Karnofsky score ≥ 60, and were scheduled to receive a chemo regimen that included cisplatin ≥70 mg/m2. Female pts of childbearing potential were required to have a negative beta human chorionic gonadotropin test result.	Age Mean: 58.5 yrs Range: 18-84 yrs Gender % Male: 62.5% Ethnicity % White: 3.0% % Black: 90.6% % Other: 6.4%	Mean cisplatin dose: 80.5 mg/m2 Primary cancer diagnosis: Respiratory: 42% Urogenital: 23% Other: 35% Alcohol intake - % of pts (drinks/wk): 0 drinks: 58% 1-10 drinks: 23.5% >10 drinks: 16% % receiving concurrent emetogenic chemo (Hesketh level ≥3): 15.5% % within US: 22% History of motion sickness: 6% History of morning sickness: 5.3% History of chemo: 14.5% History of CINV: 6%	562/536/530	NR/NR /521	Arm A Day 1: Ond 32 mg IV + Dex 12 mg po Day 2-4: Dex 8 mg po once/day Arm B Day 1: Ond 32 mg IV + Dex 20 mg po Day 2-4: Dex 8 mg po twice/day given 30 min before cisplatin on Day 1

Author Year Country Emetogenic potential	Definition of outcomes	Method of outcome assessment and timing of assessment	Results	Method of adverse effects assessment	Adverse effects reported	Total withdrawals; withdrawals due to adverse events	Comments
Hesketh 2003 International High	Primary response Complete response (CR): no emetic episodes and no rescue therapy for Days 1-5 Total control (TC): no emesis, no rescue therapy, and no nausea (nausea VAS< 5mm) Complete protection (CP): no emesis, no rescue therapy, no significant nausea (VAS <25mm) No emesis No rescue therapy No nausea (maximum VAS <5 mm) No significant nausea (max. VAS<25 mm) Impact of CINV on daily life, as measured by an FLIE total score of >108	Pt diary for # of emetic episodes and use of rescue therapy. 100 mm Nausea visual analog scale (VAS)	*Comparisons are for A vs B* Complete response Day 1: 89.2% vs 78.1%; p<0.001 Day 2-5: 72.1% vs 72.6% (P=0.95) Day 1-5 (overall): 72.7% vs 52.3%, p<0.001 Total Control Day 1: 70.7% vs 64.2%, p=NR Day 2-5: 49.0% vs 42.7%, p=NR Day 1-5 (overall): 45.5% vs 40.0%, p=NR Complete Protection Day 1: 84.8% vs 74.6%, p<0.01 Day 2-5: 66.4% vs 51.5%, p<0.01 Day 1-5 (overall):63.4% vs 49.2%, p<0.01 No emesis Day 1: 90.0% vs 79.3%, p<0.01 Day 2-5: 80.8% vs 58.8%, p<0.01 Day 1-5 (overall): 77.7% vs 55.0%, p<0.01 No rescue Day 1: 94.2% vs 88.8%, p<0.05 Day 2-5: 81.2% vs 73.5%, p<0.05 Day 1-5 (overall): 80.8% vs 70.8%, p<0.01 No nausea Day 1: 72.3% vs 69.1%, p=NR Day 2-5: 51.0% vs 47.7%, p=NR Day 1-5 (overall): 47.5% vs 44.2%, p=NR No significant nausea Day 1: 90.6% vs 86.5%, p=NR Day 2-5: 75.3% vs 68.5%, p=NR Day 1-5 (overall): 73.2% vs 66.0%, p=NR FLIE: minimal or no impact of CINV on daily life: 74.0% vs 64.3% (p="significant" but not specified)	AE reported up to 14 days after treatment	***Comparisons made between Groups A (n=261) and B (n=264)*** ≥ 1 clinical adverse event (AE): 65.1% vs 61.4% Drug-related clinical AEs: 14.6% vs 11.0% Serious clinical AEs: 16.1% vs 17.0% ≥ 1 laboratory AE: 14.0% vs 13.5% Drug-related laboratory AE: 2.3% vs 1.2% Most common AEs (≥10% in at least 1 treatment group): Asthenia/fatigue: 17.2% vs 9.5% Constipation: 8.0% vs 12.1% Hiccups: 13.8% vs 6.8% Nausea (considered to be an AE if occurred after Day 5 or if determined at any time by the investigator to be serious, be drug-related, or to result in discontinuation): 10.7% vs 8.7% Dehydration: 1.9% vs 1.1% Febrile neutropenia: 2.3% vs 1.9% Neutropenia: 2.7% vs 0% Thrombocytopenia: 1.5% vs 0% Deaths (none considered drug-related): A: 2.7% vs B: 3.4% 3 serious AEs considered drug related: 1 in Group A = 1 pt with perforating duodenal ulcer, considered related to Dex 2 in group B = 1 pt with chills and leg pain; 1 pt with hyponatremia	NR; 13	

Author Year Country Emetogenic potential	Study Design Setting	Interventions (drug Regiment, duration)	Eligibility criteria	Age Gender Ethnicity	Other population characteristics	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/analyzed	Allowed other medications/ interventions
Navari 1999 USA High	Multicenter DB parallel	Arm A (N=54) Day 1: Apr 400 mg po Days 2-5: Apr 300 mg po Arm B (N=54) Day 1: Apr 400 mg po Days 2-5: placebo Arm C (N=51) Days 1-5: placebo Pts received Gran + Dex 30 min before cisplatin on Day 1 *corticosteroids given concomitantly (see "Allowed other medications")*	Cisplatin-naïve patients ≥18 years who were scheduled to receive a first course of cisplatin at a dose of ≥70 mg/m2. Women of child-bearing age had to have a negative test for the beta subunit of human chorionic gonadotropin in serum.	Age Mean: 61.7 yrs Range: NR Gender % Male: 62.9% Ethnicity NR	Mean cisplatin dose: 79.3 mg/m2 Type of cancer: lung: 68.5 % gastrointestinal: 9.4% head and neck: 10.1% genitourinary: 7.5% other: 4.4% % receiving additional emetogenic chemo: 4% Alcohol intake - % of pts (drinks/wk): 0-4 drinks: 82.4% 5-10 drinks: 7.5% ≥11 drinks: 7.5%	NR/NR/159	3/NR/155	Day 1: Gran 10 mcg/kg + Dex 20 mg po; Days 2-5: not allowed except as rescue

Author Year Country Emetogenic potential	Definition of outcomes	Method of outcome assessment and timing of assessment	Results	Method of adverse effects assessment	Adverse effects reported	Total withdrawals; withdrawals due to adverse events	Comments
Navari 1999 USA High	Primary measure: proportion of pts without emesis in the delayed emesis phase Numbers of episodes of vomiting Pts' nausea assessment (100 mm horizontal visual analogue scale [VAS]: 0mm= "no nausea" and 100mm="nausea as bad as it could be") Pts global satisfaction with antiemetic treatment (100 mm VAS): 0mm="not at all satisfied" and 100mm="completely satisfied"	Episodes of vomiting or retching as recorded in patient diaries, nausea was assesed using 100-mm horizontal visual-analogue scale headed "How much nausea have you had over the past 24 hours?" and global satisfaction evaluated with scaled headed "how satisfied are you with your anti-emetic treatment over the past 24 hours?"	*All comparisons: Group A vs. B vs. C* No vomiting Day 1: 93% vs 94% vs 67% (p<0.001 for Groups A&B combined vs C) Days 2-5: 82% vs 78% vs 33% (p<0.001 for Groups A&B combined vs C) No emesis and no rescue therapy Day 1: 2% vs 43% vs 16% (p<0.001 for A vs C; p=0.003 for B vs C) Days 2-5: 2% vs 43% vs 16% (p<0.001 for A vs C; p=0.003 for B vs C) Median Nausea VAS Scores Day 1: 0mm vs 0mm vs 1mm Days 2-5: 1mm vs 3mm vs 10mm Overall (Days 1-5): 1mm vs 2mm vs 5mm No or minimal Nausea Days 2-5: 51% vs 48% vs 24% (p=0.007 for A vs C; p=0.01 for B vs C) Overall (Days 1-5): 49% vs 48% vs 25% (p=0.02 for A vs C; p=0.03 for B vs C) Pts with 0-2 emetic episodes (for Days 2-5) 98% vs 93% vs 59% (p<0.001 for Groups A& B combined vs C) Global satisfaction median rating (overall, Days 1-5) 100 vs 98 vs 82 (p=0.001 for A vs C; p=0.03 for B vs C)	Patients kept diary cards and recorded episodes of vomiting or retching and nausea. AEs were recorded up to the post-study visit and patients underwent lab safety studies, electrocardiography and physical exams	*Comparisons are made between Groups A vs B vs C; and p=NS for all comparisons* *(Numbers reported are % of pts with the AE)* Clinical events: Constipation: 19 % vs 13% vs 18% Diarrhea: 17% vs 7% vs 10% Dehydration: 6% vs 6% vs 14% Headache: 22% vs 17% vs 20% Hiccups: 15% vs 17% vs 14% Asthenia: 26% vs 26% vs 25% Hematologic changes: Decrease in total white cell count: 2% vs 2% vs 2% Decrease in neutrophils: 0% vs 2% vs 2% Serum aminotransferase elevations (transient increase >2.5X ULN range in pts who had normal or below normal baseline values (NCI toxicity grade II, III, or IV): Aspartate aminotransferase: 0% vs 0% vs 8% Alanine aminotransferase: 9% vs 0% vs 14%	3; 0	

Author Year Country Emetogenic potential	Study Design Setting	Interventions (drug Regiment, duration)	Eligibility criteria	Age Gender Ethnicity	Other population characteristics	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/analyzed	Allowed other medications/ interventions
Poli-Bigelli 2003 Latin America High	Multicenter DB parallel	Arm A (N=283) Day 1: Apr 125 mg po Days 2 & 3: Apr 80 mg po Day 4: no Apr given Arm B (N=286) Day 1: placebo Days 2-4: placebo *corticosteroids given concomitantly*	Cisplatin-naïve pts >18 yrs who had histologically confirmed solid tumors, a Karnofsky score ≥60, and who were scheduled to receive a chemo regimen that included cisplatin ≥70 mg/m2 were eligible. Female pts of childbearing potential were required to have a negative beta-human chorionic gonadotropin test result.	Age Mean: 53.5 yrs Range: 18-82 yrs Gender % Male: 51.5% Ethnicity Black: 5.4% White: 29.5% Other: 65.0%	Mean cisplatin dose: 81 mg/m2 % pts with a cisplatin dose ≥70-100 mg/m2: 82% Type of cancer: respiratory: 38.6% urogenital: 38.5% eyes/ears/nose/throat: 8.4% other: 16.5% % receiving additional emetogenic chemo: 17% Alcohol intake - % of pts (drinks/wk): 0 drinks: 85.5% 1-10 drinks: 13 % ≥11 drinks: 1.5% % pts with a history of morning sickness: 8.4% % pts with a history of motion sickness: 4% % pts with a history of chemotherapy: 8.6% % pts with a history of CINV: 5.5%	624/NR/569	89/2/480	Arm A Day 1: Ond 32 mg IV Days 2-4: Dex 8 mg po Arm B Day 1: Ond 32 mg IV Days 2-4: Dex 8 mg po

Author Year Country Emetogenic potential	Definition of outcomes	Method of outcome assessment and timing of assessment	Results	Method of adverse effects assessment	Adverse effects reported	Total withdrawals; withdrawals due to adverse events	Comments
Poli-Bigelli 2003 Latin America High	Primary measure Complete response (**CR**): no emetic episodes and no use of rescue therapy Complete protection (**CP**): no emesis, no rescue therapy, and nausea VAS <25mm Total control (**TC**): no emesis, no rescue therapy, nausea VAS <5mm No Emesis No use of rescue medication Impact of CINV on daily life (as measured by an FLIE score >108) No significant nausea (VAS <25mm) No nausea (VAS <5mm)	Acute results: Day 1 results only Delayed results: Days 2-5 Overall: Days 1-5	*Comparisons are for group A vs. Group B* Complete Response: Day 1 (acute results): 82.8% vs 68.4% (p<0.001) Day 2-5 (delayed results): 7.7% vs 46.8% (p<0.001) Days 1-5 (overall): 62.7% vs 43.3% (p<0.001) Complete Protection Day 1 (acute results): 80.0% vs 64.6% (p<0.01) Day 2-5 (delayed results): 60.9% vs 44.1% (p<0.01) Days 1-5 (overall): 55.6% vs 40.7% (p<0.01) Total Control Day 1 (acute results): 64% vs 57% (p=NS) Day 2-5 (delayed results): 50% vs 34% (p<0.01) Days 1-5 (overall): 44% vs 32 % (p<0.01) No emesis Day 1 (acute results): 84% vs 69% (p<0.01) Days 2-5 (delayed results): 72% vs 48% (p<0.01) Days 1-5 (overall): 66% vs 44% (p<0.01) No rescue Day 1 (acute results): 96% vs 90% (p<0.01) Days 2-5 (delayed results): 83% vs 74% (p<0.05) Days 1-5 (overall): 82% vs 73% (p<0.01) FLIE: minimal or no impact on daily life*: 74.7% vs 63.5% (p=<0.05)*		*Comparisons made between Aprepitant (n=282) and Placebo (n=285)* ≥ 1 clinical adverse event (AE): 72.7% vs 72.6% Drug-related clinical AEs: 19.5% vs 14.4% Serious clinical AEs: 11.0% vs 9.8% Discontinued due to a clinical AE: 7.1% vs 5.3% ≥ 1 laboratory AE: 29.6% vs 25.2% Drug-related laboratory AE: 5.7% vs 3.9% Most common clinical AEs (≥10% in at least 1 treatment group): Anorexia: 15.2% vs 14.0% Asthenia/fatigue: 18.4% vs 14.0% Constipation: 12.4% vs 12.3% Diarrhea: 12.1% vs 10.5% Headache: 9.9% vs 11.6% Nausea (nausea & vomiting considered AEs if they occurred >Day 5 or if determined at any time to be serious, drug-related, or to result in discontinuation): 14.5% vs 14.4% Vomiting: 8.9% vs 12.6% Dehydration: 1.8% vs 0.7% Febrile neutropenia: 0.4% vs 0.7% Neutropenia: 1.8% vs 2.1% Septic shock: 1.1% vs 0.7% Dyspnea: 1.1% vs 0.7% Respiratory insufficiency: 1.8% vs 0.4% Deaths (not considered to be drug-related): 4.6% vs 3.9% 3 serious AEs were thought to be drug related: 1 AE of worsening diabetes mellitus and 1 event of hyperglycemia in Group B; 1 event of disorientation in Group A	Nr; Aprepitant 7.1, Standard therapy 5.3	

Author Year Country Emetogenic potential	Study Design Setting	Interventions (drug Regiment, duration)	Eligibility criteria	Age Gender Ethnicity	Other population characteristics	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/analyzed	Allowed other medications/ interventions
Rapoport 2010 International Moderate	RCT, DB, Parallel	Arm A (N=430) Day 1: Arp 125 mg po; Ondan 8 mg po x2; Dex 12 mg po Day 2: Arp 80 mg po Placebo po bid Day 3: Arp 80 mg po Placebo po bid Arm B (N=418) Day 1: Placebo po Ondan 8mg po x2 Dex 20 mg po Day 2: Placebo po Ondan 8m x2 Day 3: Placebo po Ondan 8 mg po	Inclusion: male and female patients ≥18 years, naïve to MEC or HEC, with histologically confirmed malignancies, Karnofsky scores ≥60, predicted life expectancy ≥4 months, and scheduled to be treated with a single dose of one or more of the following MEC agents: any IV dose of oxaliplatin, carboplatin, epirubicin, idarubicin, ifosfamide, irinotecan, daunorubicin, doxorubicin, cyclophosphamide IV (<1,500 mg/m2), or cytarabine IV (>1 g/m2).	Age Mean: 56.5 yrs Gender Female 77% Ethnicity White 69%	Type of Cancer Breast: 52% Colorectal: 20% Lung: 13% Ovarian: 4.6%	949/883/848	30/9/832	If a patient was scheduled to receive a taxane as part of chemo regimen, they were premedicated with non-study dexamethasone and were not given study drug dexamethasone; patients receiving Paclitaxel were given dexamethasone 20mg po 12hr and again 6hr prior to paclitaxel; patients receiving Docetaxel were given Dexamethasone 8 mg po bid, 1 day prior to docetaxel, the day of docetaxel, and the day after docetaxel

Author Year Country Emetogenic potential	Definition of outcomes	Method of outcome assessment and timing of assessment	Results	Method of adverse effects assessment	Adverse effects reported	Total withdrawals; withdrawals due to adverse events	Comments
Rapoport 2010 International Moderate	Primary outcome: no vomiting during the 5 days following initiation of chemotherapy Secondary outcome complete response: no vomiting and no use of rescue medication during the 5 days following initiation of chemotherapy	Nausea, vomiting, and rescue medication use: diary Nausea: 100-mm horizontal visual analog scale	All chemotherapies *Aprepitant group vs control group* Complete response: 0-120h after initiation of chemotherapy: 68.7% vs 56.3% (p <0.001) 0-24h after initiation of chemotherapy: 89.2% vs 80.3% (p <0.001) >24-120h after initiation of chemotherapy: 70.8% vs 60.9% (p <0.01) No Vomiting: 0-120h after initiation of chemotherapy: 76.2% vs 62.1% (p <0.001) 0-24h after initiation of chemotherapy: 92.0% vs 83.7% (p <0.001) >24-120h after initiation of chemotherapy: 77.9% vs 66.8% (p <0.001) Anthracycline/cyclophosphamide-based chemotherapy *Aprepitant group vs control group* Complete response 0-120h after initiation of chemotherapy: 62.8% vs 47.1% (p <0.05) 0-24h after initiation of chemotherapy: 84.3% vs 72.5% (p <0.05) >24-120h after initiation of chemotherapy: 64.8% vs 52.9% (p <0.05) No vomiting 0-120h after initiation of chemotherapy: 68.3% vs 52.9% (p <0.05) 0-24h after initiation of chemotherapy: 86.9% vs 76.0% (p <0.05) >24-120h after initiation of chemotherapy: 70.4% vs 59.8% (p <0.05) Non anthracycline/cyclophosphamide-based chemotherapy *Aprepitant group vs control group* Complete response 0-120h after initiation of chemotherapy: 73.9% vs 65.5% (NS) 0-24h after initiation of chemotherapy: 93.4% vs 88.1% (NS) >24-120h after initiation of chemotherapy: 76.1% vs 69.0% (NS) No vomiting 0-120h after initiation of chemotherapy: 83.2% vs 71.3% (p <0.05) 0-24h after initiation of chemotherapy: 96.5% vs 91.6% (p <0.05) >24-120h after initiation of chemotherapy: 84.5% vs 73.9% (p <0.05)	NR	Aprepitant vs Placebo Overall incidence of AEs: 62.8% vs 67.2% AE's thought to be drug-related: 7.2% vs 9.3% Serious AEs: 2.8% vs 4.8% Constipation: 8.6% vs 13.4% Fatigue: 10.9% vs 9.8% Headache: 10.0% vs 12.2% Diarrhea: 9.8% vs 11.2% Anorexia: 8.1% vs 8.9% Alopecia: 6.5% vs 7.7% Asthenia 6.3% vs 5.5% Nausea day 6 of later: 4.4% vs 2.6% Vomiting day 6 of later: 2.1% vs 1.4% Neutropenia: 2.6% vs 2.8% Febrile neutropenia: 1.2% vs 0.7%	Apr vs Control: 18 (4.2%) vs 12 (2.9%) Due to AEs: 5 (1.2%) vs 3 (0.7%)	

Author Year Country Emetogenic potential	Study Design Setting	Interventions (drug Regiment, duration)	Eligibility criteria	Age Gender Ethnicity	Other population characteristics	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/analyzed	Allowed other medications/ interventions
Schmoll 2006 International High	RCT, DB, Parallel	Aprepitant group (N=244) Aprepitant 125mg on day 1; aprepitant 80mg days 2 -3 Control group (N=245) ondansetron 32mg IV on day 1; oral placebo days 2-3	Inclusion: Cisplatin naïve patients ≥ 18 years, confirmed solid malignancies, scheduled chemotherapy regimen with at least on cycle including cisplatin ≥70 mg/m^2, Karnofsky score of ≥ 60, life expectancy of ≥ 3 months Exclusion: 5-HT3 antagonists with 48 hours, radiation therapy to abdomen/pelvis from 1 week before day 1 to day 6; active infection; symptomatic primary or metastatic CNS malignancy; any uncontrolled disease other than malignancy; vomiting and/or dry heaves/retching 24 hours before cisplatin; abnormal laboratory values	Age Mean: 59 yrs Gender 63% male Ethnicity Asian: 17.5% Black: 3% Hispanic: 12.5% White: 61% Other: 6%	History of motion sickness: 5.5% History of vomiting associated with pregnancy (females only): 26.5% History of CINV: 5% Type of Cancer Respiratory: 45% Urogenital: 19% Gastrointestinal: 12% Eyes/ears/nose/throat: 10% Other: 14%	516/NR/489	29/3/484	All received dexamethasone days 1-4

Author Year Country Emetogenic potential	Definition of outcomes	Method of outcome assessment and timing of assessment	Results	Method of adverse effects assessment	Adverse effects reported	Total withdrawals; withdrawals due to adverse events	Comments
Schmoll 2006 International High	Complete response: no vomiting and no use of rescue medication	Vomiting: patient-rated using validated 100-mm horizontal visual analog scale Rescue medication use: patient diary	*Aprepitant group vs control group* Complete response 0-12h after surgery: 72% vs 60.6% (p=0.003) 0-24h after surgery: 87.7% vs 79.3% (p=0.005) >24-120h after surgery: 74.1% vs 63.1% (p=0.004) No vomiting 0-120h after surgery: 76.5% vs 62.2% (p<0.001) 0-24h after surgery: 88.9% vs 80.5% (p=0.004) >24-120h after surgery: 79% vs 64.3% (p<0.001) No significant nausea 0-120h after surgery: 73.1% vs 69.7% (NS) 0-24h after surgery: 92.1% vs 89.5% (NS) >24-120h after surgery: 75.9% vs 72.1% (NS) No use of rescue therapy 0-120h after surgery: 82.3% vs 79.7% (NS) 0-24h after surgery: 94.2% vs 92.9% (NS) >24-120h after surgery: 83.5% vs 81.7% (NS)	Tolerability assessments included physical examination, vital signs, 12-lead electrocardiogram and lab tests, including hematology, chemistry, urinalysis, and pregnancy tests.	*Aprepitant group vs Control group* Overall incidence of AEs: 79% vs 81.6% Drug-related AEs: 23.5% vs 24.2% Serious AEs: 13.6% vs 15.2% Serious drug-related AEs: 0.8 vs 0.4 ≥ laboratory AEs: 21.1% vs 21.3% Most common clinical AEs Anorexia: 14% vs 14.8% Asthenia: 13.6% vs 15.2% Constipation: 15.6% vs 22.1% Diarrhea: 12.8% vs 9.4% Dyspepsia: 13.6% vs 11.1% Fatigue: 9.1% vs 6.1% Hiccups: 9.9% vs 9.8% Nausea: 15.6% vs 9.8% Vomiting: 9.1% vs 9.8%	NR; 4 from Control, 0 from Aprepitant	

Author Year Country Emetogenic potential	Study Design Setting	Interventions (drug Regiment, duration)	Eligibility criteria	Age Gender Ethnicity	Other population characteristics	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/analyzed	Allowed other medications/ interventions
Warr 2005 International (95 centers) Moderate	Multicenter DB parallel	Arm A (N=438) Day 1: Apr 125 mg po 1 hr before chemo+ Ond 8 mg po 30-60 min before chemo + dex 12 mg po 30 min before chemo Ond 8 mg po 8 hrs after first dose Day 2-3: Apr 80 mg po Arm B (N=428) Day 1: placebo po+Ond 8 mg po 30-60 min before chemo + dex 20 mg po 30 min before chemo Ond 8 mg po 8 hrs after first dose Day 2-3: placebo po+ Ond 8 mg po bid	Patients ≥18 years with breast cancer being treated with moderately emetogenic chemo (hesketh level ≥ 3) and scheduled to receive their first course of moderately emetogenic chemotherapy. Patients had to have a predicted life expectancy of ≥4 months and a Karnofsky score of ≥60 to be eligible.	Age Mean: 52.6 yrs Gender Female: 99.8% Ethnicity White: 78.6%	Motion sickness: 18.9% History of vomiting during pregnancy: 30.5%	910 / unclear / 866	122 / NR / 857	Arm A Day 1:Ond 8 mg po 30-60 min before chemo +dex 12 mg po 30 min before chemo Ond 8 mg po 8 hrs after first dose Day 2-3: placebo po bid Arm B Day 1: Ond 8 mg po 30-60 min before chemo + dex 20 mg po 30 min before chemo Ond 8 mg po 8 hrs after first dose Day 2-3: Ond 8 mg po bid Antiemetic treatments were not allowed within 48 hour before treatment, except for single daily doses of lorazepam.

Author Year Country Emetogenic potential	Definition of outcomes	Method of outcome assessment and timing of assessment	Results	Method of adverse effects assessment	Adverse effects reported	Total withdrawals; withdrawals due to adverse events	Comments
Warr 2005 International (95 centers) Moderate	Complete response: no vomiting and no rescue therapy throughout the acute and delayed phases (120 hrs)	Patient diary for emetic episodes, use of rescue medication, and daily nausea ratings (on a VAS where 0="n from Day 1 to day 6. FLIE questionnaire (9 items on vomiting and 9 items on nausea) administered on day 1 and day 6; "minimal or no impact of CINV on daily life" is defined for this study as average score of >6 on the 7-point scale for each item.	*Aprepitant vs placebo* Complete response 0-24 h (acute phase): 76% vs 69%, p=0.34 24-120h (delayed phase): 55% vs 49%, p=0.64 0-120 hours (overall): 51% vs 42%, p=0.015 No vomiting 76% vs 59%, p<0.001 No significant difference between groups in use of rescue therapy FLIE Minimal or no impact on daily living overall: 63.5% vs 55.6%, p=0.019 Minimal impact or no impact of vomiting on daily living: 85.7% vs 71.8%, p<0.001 Minimal impact or no impact of nausea on daily living: 53.5% vs 50.5%, p=NS	Safety and tolerability assessed by clinical and statistical review of AEs, vital signs, and laboratory values.	Aprepitant vs placebo AE's thought to be drug-related: 21.5% vs 19.6% Serious AEs: 3.4% vs 4.2% Febrile neutropenia: 2.1% vs 2.1% Constipation: 12.3% vs 18.0% Dyspepsia: 8.4% vs 4.9%	Total withdrawals: NR Total withdrawals due to AEs: 1.4% (12/866 patients) By drug: apr 1.6% vs placebo 2.1%	

Author Year Country Emetogenic potential	Study Design Setting	Interventions (drug Regiment, duration)	Eligibility criteria	Age Gender Ethnicity	Other population characteristics	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/analyzed	Allowed other medications/ interventions
Yeo **2009** Single Center (China) Moderate	DB, RCT, Parallel	Arm A (N=62) Day 1: Aprepitant 125mg, ondansetron 8mg, dexamethasone 12mg, before chemotherapy and ondansetron 8mg 8 hours later on day 1 Day 2-3: aprepitant 80 qd Arm B (N= 62) Day 1: Ondansetron 8mg and dexamethasone 20mg before chemotherapy and ondansetron 8mg 8hours later on day 1; Days 2-3: ondansetron 8mg BID	Patients ≥ 18 years, ethnic Chinese females, diagnosed with breast cancer and scheduled to receive their first course of adjuvant chemotherapy. Predicted life expectancy of ≥ 4 months, Karnofsky score ≥ 60, negative for pregnancy.	Age Median A: 46.5 yrs B: 48.5 yrs Gender 100% female Ethnicity 100% Chinese	A vs B History of motion sickness: 22.6% vs 19.4% History of vomiting during pregnancy: 35.5% vs 27.4% Stage of Disease I: 29% vs 14.5% II: 45.2% vs 54.8% IIIa: 21% vs 16.1% IIIb: 4.8% vs 14.5%	NR/NR/127	3/NR/124	Rescue medication was allowed

Author Year Country Emetogenic potential	Definition of outcomes	Method of outcome assessment and timing of assessment	Results	Method of adverse effects assessment	Adverse effects reported	Total withdrawals; withdrawals due to adverse events	Comments
Yeo **2009** Single Center (China) Moderate	Complete Response: No vomiting and no use of rescue therapy Complete Protection : No vomiting with no rescue therapy and nausea VAS <25mm Total Control: No vomiting with no rescue therapy and nausea VAS <5mm	Patient Diary VAS Every hour	*Comparisons are for groups A vs B* Complete response 0-120h: 46.8% vs 41.9% (P=0.58) 0-24h: 72.1% vs 72.6% (P=0.95) 24-120h: 64.4% vs 57.8% (P=0.51) Complete protection 0-120h: 38.7% vs 41.9% (P=0.71) 0-24h: 67.2% vs 72.6% (P=0.51) 24-120h: 56.1% vs 57.8% (P=0.87) Total control 0-120h: 25.8% vs 30.6% (P=0.55) 0-24h: 54.1% vs 56.5% (P=0.79) 24-120h: 45.5% vs 54.3% (P=0.47) No vomiting 0-120h: 54.8% vs 50% (P=0.58) 0-24h: 72.1% vs 74.2% (P=0.79) 24-120h: 75.6% vs 67.4% (P=0.39) No rescue therapy 0-120h: 82.3% vs 67.7% (P=0.06) 0-24: 98.4% vs 95.2% (P=0.31) 24-120h: 83.6% vs 71.2% (P=0.10) No significant nausea 0-120h: 30.6% vs 35.5% (P=0.71) 0-24h: 88.5% vs 83.9% (P=0.45) 24-120h: 74.1% vs 75% (P=0.91) No nausea 0-120h: 30.6% vs 35.5% (P=0.57) 0-24h: 62.3% vs 59.7% (P=0.76) 24-120h: 47.3% vs 59.5% (P=0.29)	Patient report	Incidence of AEs that occurred in > 3% of patients A vs B Alopecia: 85.5% vs 79% Insomnia: 6.5% vs 8.1% Dizziness: 6.5% vs 3.2% Fatigue: 25.8% vs 21% Anorexia: 16.1% vs 21% Constipation: 11.3% vs 22.6% Diarrhea: 16.3% vs 9.7% Oral mucositis: 29% vs 38.7% Heartburn: 4.8% vs 4.8% Nausea: 11.3% vs 11.3% Vomiting: 3.2% vs 4.8% Febrile neutropenia: 4.8% vs 8.1% Fever: 4.8% vs 4.8% Neutropenia: 35.5% vs 53.2% Rigors/chills: 3.2% vs 3.2% Cough: 6.5% vs 9.6% Dermatology/skin other: 3.2% vs 9.6% Headache: 3.2% vs 4.8% Pain-throat/pharynx/larynx: 9.6% vs 9.6%	3 were not assessable, all 124 completed	

Evidence Table 2. Quality assessments of the chemotherapy placebo-controlled trials

Author Year	Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors masked?	Care provider masked?
Campos 2001	Yes	NR	Yes	Yes	NR	Yes
Chawla 2002	Yes	NR	Yes	Yes	NR	Yes
de Wit 2003	Unclear	NR	Yes	Yes	Yes	Yes
Herrington 2008	Unclear	Unclear	Yes	Yes	Yes	Yes
Hesketh 2003	Yes	Unclear; "allocation numbers were created by an assistant statistician otherwise uninvolved with the study"	Yes	Yes	Yes	Yes
Navari 1999	Yes	NR	Yes	Yes	NR	Yes
Poli-Bigelli 2003	Yes	Unclear; "centrally generated"	Several statistically insignificant differences	Yes	Yes	Yes
Rapoport 2010	Yes	Unclear; "To ensure in-house blinding, the randomized allocation schedule was generated by an assistant statistician who was otherwise uninvolved with the study."	Yes	Yes	Yes	Yes
Schmoll 2006	Yes	Unclear	Yes	Yes	Yes	Yes
Warr 2005	Yes	NR	Yes	Yes	NR	Yes
Yeo 2009	Unclear; "according to an in-house blinding and allocation schedule"	Unclear	Yes	Yes	Yes	Yes

Author Year	Patient masked?	Reporting of attrition, crossovers, adherence, and contamination	Attrition: differential/high	Intention-to-treat (ITT) analysis	Post-randomization exclusions	Quality Rating	Funding
Campos 2001	Yes	Yes, No, No, No	Unclear/Unclear	No, but only excluded 8 (2%)	No	Fair	Merck
Chawla 2002	Yes	Yes, No, No, No	None	No, but only excluded 5 (1.3%)	No	Fair	Merck
de Wit 2003	Yes	Yes, No, No, No	No, No	No, but only excluded 3 (1.7%)	Unclear; 22% were excluded after receiving treatment due to the reason of "ineligible", which was not explained	Fair	Merck; 1st author is consultant for Merck
Herrington 2008	Yes	Yes, No, No, No	No, No	Implied, but not specifically described	None	Fair	MGI Pharma and Scott & White grant #R3429
Hesketh 2003	Yes	Yes, No, No, No	No loss to follow-up	No, but only excluded 6 (1.1%)	Unclear; 7.4% excluded due to reason "other"	Fair	Merck
Navari 1999	Yes	Yes, No, No, No	None	No, but only excluded 2 (1.2%)	No	Fair	NR, but 1st author is with Merck
Poli-Bigelli 2003	Yes	Yes, No, No, No	No, No (1 patient in each group)	No; excluded 9.2% (40 patients excluded from 1 site whose efficacy data were considered unreliable)	Yes	Fair	Merck
Rapoport 2010	Yes	Yes, No, Yes, No	No, No	No, but only excluded 16 (2%)	No	Fair	Merck
Schmoll 2006	Yes	Yes, No, Yes, No	No, No	No, excluded 5/489 (1%)	No	Fair	Merck & Co, Inc
Warr 2005	Yes	Yes, No, No, No	No loss to follow-up	No for efficacy (excluded 1%); yes for safety	No	Fair	Merck
Yeo 2009	Yes	Yes, No, Yes, No	No, No	No, excluded 3/127 (2%)	No	Fair	Merck Sharpe & Dohme (Asia) Ltd.

Evidence Table 3. Chemotherapy: Head-to-head trials

Author Year Setting Emetic potential	Design	Subpopulation	Intervention	Corticosteroid	Run-in/ Wash-out	Age Gender Ethnicity	Screened/ Eligible/ Enrolled	Withdrawn/ Lost to fu/ Analyzed	Other population characteristics
Granisetron vs Ondansetron									
Chiou 2000 Single Center Moderate/High	Open RCT Parallel	None	Ondansetron IV 24mg+10 .m.i.v. dex (N=26) Granisetron po 2mg +10 mg IV dex (N=26) 24hr	Initial dose given with dexamethasone IV 10 mg; dex not given with other doses	No/NR	Age 56.5 yrs Gender 63%male Ethnicity NR	NR/NR/51	0/0/51	Severely emetogenic chemo: 57% moderately emetogenic chemo: 43% Primary Tumor: Non-Hodgkin's lymphoma: 35% Unknown: 12% Urologic: 12% Gastrointestinal: 12% Breast: 6% Non-small-cell lung cancer: 10% Head and neck: 14%
Chua 2000 Single Center High	Open RCT Crossover	None	Granisetron IV 3mg +Dex 20 mg IV Tropisetron IV 24mg+ Dex 20mg IV Ondansetron IV 5mg+Dex 20 mg IV Dex given on Day 1 *this is a crossover study so all 89 patients were exposed to different treatments	dexamethasone 20 mg IV given with study antiemetics on day 1,	NR/NR	Age NR Gender 87%male Ethnicity Asian (Chinese), n= 89 (100%)	94/89/89	0/0/89	GRADEX vs TRODEX: 65% GRADEX vs ONDEX: 73% TRODEX vs ONDEX: 72% Primary Tumor: Nasopharynx: 80% Oral Cavity: 10% Hypopharynx: 8% Larynx: 1% Ear: 1% Chemo as part of : primary treatment: 55%; induction: 39%; adjuvant: 11%; concomitant chemoirradiations: 4% Chemo : as palliative: 45% Chemo : in combo w/radiation: 55% Chemo Cycle 1: 100% Chemo Cycle 2: 82% Chemo Cycle 3: 64% Antiemetic regimens: GRADEX: 76% Antiemetic regimens: TRODEX: 80% Antiemetic regimens: ONDEX: 90% Crossed over once: 18%; Crossed over twice: 64%
Fox-Geiman 2001 Single Center High	DB RCT Parallel	BMT; TBI	Ondansetron po 24mg (8 mg Q8)+ 10 mg Dex (N=34) Ondansetron IV 32mg qd+10 mg Dex (N=34) Granisetron po 2mg (1 mg Q12)+10 mg Dex (N=34)	Yes; all received dexamethasone 10 mg IV qd while receiving the 5-HT3 antagonist; also, benzodiazepines were allowed as needed for sleep.	NR/NR	Age 47 yrs Gender 28%male Ethnicity NR	NR/NR/102	6/0/102	Mean weight, kg: 78kg allogenic transplant 3% autologous transplant 97% Inpatient treatment setting 73% Outpatient treatment setting 27% History of moderate/severe nausea 72% History of vomiting: 57% History of anticipatory nausea/vomiting 12% Conditioning regimens: TBI-containing 26% Conditioning regimens: Chemo only 74% Preparative regimen: STAMP V: 33% TBI/VP/CY: 25% TANC: 15%; BU/CY: 11% BEAM: 4%; BCNU/VP/CY: 2% ICE: 2% Carboplatin/VP: 2% Carboplatin/MTZ/CY: 2% MMT: 2% Thiotepa/CY: 1% TBI/CY: 1%

Author Year Setting Emetic potential	Results	Adverse events	Comments
Granisetron vs Ondansetron			
Chiou 2000 Single Center Moderate/High	Ondansetron vs Granisetron Complete control of vomiting/retching (no emesis) and nausea: acute and delayed No nausea in 24h (acute): 38.5% vs 56%, NS No nausea over 2-7 days (delayed): 34.6% vs 16%, NS No emesis in 24h (acute): 84.6% vs 84%, NS No emesis over 2-7 days (delayed): 19.2% vs 16%, NS Need of rescue medication Within 24h: 11.5% vs 12.0%, NS Within 2-7 days: 38.5% vs 56.0%, NS	Granisetron vs Ondansetron Diarrhea: 12.0% vs 0%, NR Constipation: 4.0% vs 23.1%, NR Headache: 4.0% vs 3.8%, NR Dizziness: 8.0% vs 3.8%, NR Restlessness: 8.0% vs 3.8%, NR	Moderate emetogenicity including non-cisplatin-based regimens, (CHOP, FAC, FEC). Sever emetogenicity including cisplatin (> 50 mg/m2)-based chemotherapy (CMV, EP, FP, FEP, and one case of high-dose chemotherapy with 4 g/m2 of cyclophosphamide.
Chua 2000 Single Center High	Ondansetron vs Granisetron vs Tropisetron Complete response: no nausea or vomiting, or mild nausea only in the 24h after starting chemo First cycle only: 74% vs 81% vs 75%, NS Pt preference: Gran vs Onda vs Trop vs no drug preference post-crossover: 14% vs 17.8% vs 15% vs 53%, NS	Headache vs Diarrhea vs Constipation All adverse events Patient: 14% vs 7% vs 4%, NS	Study antiemetics given on Day 1 only; the antiemetic regimen for days 2-6 was metoclopramide 80 mg/d + dex 8mg/d + alprazolam 500 micrograms/d. GRADEX= granisetron + dexamethasone; TRODEX= tropisetron + dexamethasone; ONDEX= ondansetron + dexamethasone. Data abstracted for Cycle 1 of the crossover study; this portion represented a parallel study. Chemo regimen: DAY 1: cisplatin 100 mg/m2 and DAYS 1-3: 5-FU 1000 mg/m2. All had prehydration with IV fluids for 1 day before chemo. Cisplatin was a 4-hr infusion, and 5-FU was administered as a continuous infusion.
Fox-Geiman 2001 Single Center High	Ond po 24 vs Ond IV 32 vs Gran po 2 Complete response (CR: no or mild nausea (pt able to eat; reasonable intake) and no rescue antiemetics used) Day 1: 95% vs 92% vs 92%, NS Day 2: 69% vs 69% vs 77%, NS Day 3: 73% vs 75% vs 81%, NS Day 4: 35% vs 32% vs 45%, NS Day 5: 27% vs 30% vs 25%, NS Day 6: : 32% vs 32% vs 25%, NS Day 7: 45% vs 31% vs 15%, NS Day 8: 35% vs 10% vs 8%, NS Composite score (overall - Days 1-8): 48% vs 49% vs 47%, NS Major Response score (1 vomiting episode or if no vomiting, moderate nausea (intake significantly decreased; pt can eat) with rescue allowed: Normalized for 8 days: 82% vs 81% vs 84%, NS Major response (MR): 1 episode of vomiting or moderate nausea (intake significantly decreased, but patient can eat) with rescue allowed Day 1: 2% vs 6% vs 8%, NS Day 2: 31% vs 24% vs 17%, NS Day 3: 21% vs 19% vs 11%, NS Day 4: 42% vs 42% vs 47%, NS Day 5: 58% vs 47% vs 55%, NS Day 6: 46% vs 41% vs 60%, NS Day 7: 28% vs 54% vs 57%, NS Day 8: 44% vs 65% vs 70%, NS Failure (>4 episodes of nausea regardless of nausea or rescue antiemetic use) Composite score: 4.0% vs 2.6% vs 3.3%, NS No. of patients requiring rescue antiemetics On ≥1 day of their antiemetic regimen: 91% vs 79% vs 85%, NS Nausea VAS score (0= no nausea to 100=extreme nausea): 32 vs 27 vs 32, NS	Total po pts vs Ond IV Total withdrawals: 7.3% vs 2.9%, NR Ond IV vs Ond po vs Gran po Withdrawals due to AEs: blurred vision: 2.9% vs 0% vs 0%, NR Blurred vision: 2.9% vs 0% vs 0%, NR No AEs discussed other than the IV pt who withdrew due to blurred vision on 2 occasions "attributed to dexamethasone". The additional 5 withdrawals "refused to continue the protocol due to poor nausea and/or emesis control."	Patients were stratified by gender and by TBI-containing vs. non-TBI-containing preparative regimens. Pt population was to receive chemo or chemoradiotherapy treatments prior to stem cell transplantation. Chemo regimens: Preparative regimens included STAMP V; TBI/etoposide (VP)/cyclophosphamide (CY); TANC (paclitaxel 700 mg/m^2 IV over 24 hours on day -9; mitoxantrone 30 mg/m^2 IV bolus on days -8, -6, and -4; and carboplatin [total area under curve (AUC)=28] continuous IV over 5 days on days -8, -7, -6, -5, and -4); busulfan (BU)/CY; BEAM (carmustine, etoposide, cytosine arabinoside, and melphalan); carmustine (BCNU)/VP/CY; ICE (ifosfamide, carboplatin, VP-16) (carboplatin dose modified to total AUC = 28); carboplatin/VP (carboplatin dose modified to a total AUC = 30; carboplatin/mitoxantrone (MTZ)/CY; MMT (paclitaxel 150 mg/m^2 per day continuous IV infusion [CIV] over 96 hours on days -6, -5, -4, and -3; mitoxantrone 30 mg/m^2 IV over 15 minutes on days -6, -5, and -4; and melphalan 90 mg/m^2 IV over 20 minutes on days -6 and -5); thiotepa/CY; and TBI/CY.

Author Year Setting Emetic potential	Design	Subpopulation	Intervention	Corticosteroid	Run-in/ Wash-out	Age Gender Ethnicity	Screened/ Eligible/ Enrolled	Withdrawn/ Lost to fu/ Analyzed	Other population characteristics
Gibbs 1996 Single Center High	Open RCT Parallel	Total body irradiation	Granisetron IV 3 mg (N=13) Ondansetron PO 8 mg BID (N=13) Dexamethasone PO 4 mg BID for 3 days (all patients received this)	Dexamethasone PO 4 mg BID for 3 days	NR/NR	Age NR Gender NR Ethnicity NR	NR/NR/26	1/0/25	None reported
Herrington 2000 Multicenter Moderate	Open RCT Parallel	women	Ondansetron po 16mg+oral dex 12 mg (N=33) Granisetron po 1mg+ oral dex 12 mg (N=28)	Yes: study drug given concomitantly with dexamethasone (dex) 12 mg po	No/NR	Age 60.6 yrs Gender 25%male Ethnicity NR	65/61/61	0/0/61	Primary Tumor- Breast: 63%; Lymphoma: 20%; Multiple myeloma: 7%; Other: 12% Chemo: cyclophosphamide-doxorubicin: 66%; cyclophosphamide: 21%; doxorubicin: 7%; other: 7%
Dolasetron vs Granisetron									
Tan 2004 Single Center Moderate/High	Open CT Parallel	none	Dolasetron po 100mg+ 20 mg IV dex (N=13) Granisetron po 2mg+20 mg IV dex (N=13)	All received 20 mg of IV dexamethasone with the antiemetic.	NA/NA	Age 57.5 yrs Gender 38%male Ethnicity NR	NR/NR/26	0/0/26	Primary Cancer Site Lymphoma: 46% Lungs: 15% Larynx: 15% Uterus: 12% Other sites: 12% Patients receiving highly emetogenic chemo: 92%

Author Year Setting Emetic potential	Results	Adverse events	Comments
Gibbs 1996 Single Center High	Granisetron compared to ondansetron: Complete response Acute: 42% vs 46%, *P-value* NR Delayed: 42% vs 46%, *P-value* NR	NR	None
Herrington 2000 Multicenter Moderate	Ond po 16 vs Gran po 1 Total control of nausea and emesis Total control of nausea and emesis (over 24 hours): 45% vs 46%, NS Severity of nausea Severe: 9% vs 14%, NS Mild: 18% vs 25%, NS Moderate: 15% vs 14%, NS None: 58% vs 46%, NS Emetic episodes None: 76% vs 82%, NS 1: 12% vs 14%, NS 2-3: 3% vs 4%, NS 4 or more: 9% vs 0%, NS Rescue antiemetics administered: 42% vs 54%, NS	Ondansetron vs Granisetron Overall AEs constipation: 3.0% vs 7.1%, NS flushing: 6.1% vs 10.7%, NS diarrhea: 12.1% vs 3.6%, NS dry mouth: 15.1% vs 7.1%, NS headache: 27.2% vs 42.8%, NS no adverse event: 52% vs 32%, NS	65 patients were enrolled, but only 61 were analyzed: 2 pts took prophylactic phenothiazines although they experienced no nausea or emetic symptoms, and 2 pts received drugs listed in the exclusion criteria before receiving study drugs.
Dolasetron vs Granisetron			
Tan 2004 Single Center Moderate/High	Dolasetron vs Granisetron Total control: no nausea, no emesis, no need for rescue antiemetic Within 24h following chemo: 69.2% vs 23.1%, Vomiting: no. of pts who had vomiting episodes: 53.8% vs 7.7%, Nausea: no. of pts who experienced nausea: 76.9% vs 30.8%, Nausea intensity: Score: ++ (3-5 episodes/d) vs + (Pts requiring rescue antiemetic: 76.9% vs 23.1%, Mean no. of doses of rescue antiemetic: 7.0 vs 1.0,	NR	All chemo-naïve patients were 5-HT3 antagonist naïve, but this was not stated if it was an eligibility criterion. No specific data on adverse events given for the total population nor for either study group; a general statement that patients in both groups complained of occasional headaches but no statistically significant differences were found between groups was all that was stated pertaining to AEs. nausea intensity scale: + : <2 episodes/d (mild); ++ : 3-5 episodes/d (moderate); +++ : >5 episodes/d (severe)

Evidence Table 4. Quality assessments of chemotherapy head-to-head trials

Author Year	Randomization	Allocation	Groups similar at baseline	Eligibility criteria specified	Care provider masked	Patients masked	Attrition Crossover Adherence Contamination	Loss to follow-up
Granisetron vs Ondansetron								
Chiou 2000	NR	NR	Yes	Yes	No	No	Yes No No No	No
Chua 2000	Yes, computer-generated code	NR	Unclear; crossover study with no comparison of baseline characteristics based on order of randomization	Yes	No	No	Yes No No No	Unable to determine
Fox-Geiman 2001	Yes	Yes	Yes	Yes	Yes	Yes	Yes No No No	No
Gibbs 1996	Yes; six-sided dice	Yes; study officer enrolling patients had to telephone an independent doctor who had not seen or admitted patient	Unclear; not reported	Yes	No	No	Yes No Yes No	No
Herrington 2000	NR	NR	Unable to determine (reported for evaluated pts)	Yes	No	No	No No No Yes	No
Dolasetron vs Granisetron								
Tan 2004	Not randomized; patients admitted in February received dolasetron and those admitted in March received granisetron	NR	Yes for age, gender, emetogenicity; unclear for others	Yes	No, open-label	No, open-label	No No No No	No

Author Year	Intention-to-treat analysis	Postrandomization exclusions	Quality rating	Controlled group standard of care	Funding
Granisetron vs Ondansetron					
Chiou 2000	Yes	No	Fair	Yes	SmithKline Beecham Taiwan supplied granisetron for the study.
Chua 2000	No; 5/94 (5%) excluded	Yes	Fair	Yes	NR
Fox-Geiman 2001	Unable to determine	No	Fair	Yes	Supported in part by an educational grant from Glaxo-Wellcome, Inc.
Gibbs 1996	No; 1/26 (4%)	No	Poor	Yes	NR
Herrington 2000	No; excluded 4/65 (6%) due to protocol violations (e.g., use of drugs listed in exclusion criteria)	Yes	Fair	Yes	Funded in part by SmithKline Beecham Pharmaceuticals
Dolasetron vs Granisetron					
Tan 2004	Yes	Unable to determine	Poor	Yes	Roche Laboratories

Evidence Table 5. Long-term uncontrolled intervention studies of safety and adverse events

Author Year Country	Population	Antiemetic	Hesketh Score Primary malignancy	Outcomes
Hamadani 2007	Adults with no history of anticipatory N/V receiving highly to moderately emetogenic chemotherapy (cisplatin, carboplatin, or oxaliplatin).	ondansetron granisetron dolasetron All + dexamethasone	NR - cisplatin containing regimens 40% non-small cell lung CA 13% small cell lung CA 21% head and neck CA	No difference between groups in age, race smoking atratus, alcohol consumption, or ECOG performance status at baseline. Details of analysis NR.
The Italian Group for Antiemetic Research 2004	In or outpatients receiving single-day chemotherapy without concomitant radiation, excluding patients with leukemia, high-dose chemotherapy, or bone marrow transplantation.	5HT2 antagonist alone or + steroid Steroids Benzamine alone or + steroid	High to moderate Taxanes: breast CA 74% Gemcitabine Lung CA 54% Irinotecan Colorectal CA 97%	5HT2 antagonists were used in 87% Taxanes, 60% gemcitabine, 97% Irinotecan patients. Analysis indicated the choice of drug did not depend on previous experience of chemotherapy induced emesis. Details of analysis not reported.
Mertens 2003	Adults who had received highly emetogenic chemotherapy including cisplatin and non cisplatin based regimens using ACSO guidelines, in an ambulatory oncology infusion suite.	Not specified, other than 5HT3 antagonist, and dexamethasone, metoclopramide given post-chemotherapy	16% cisplatin, 22% paclitaxel/carboplatin, 34% doxorubicin/cyclophosphamide NR	52% treated post-chemo with 5HT3 antagonist. No difference in 5HT3 receptor antagonist use and prior chemotherapy induced N/V, not stratified by specific drug.
The Italian Group for Antiemetic Research 2001	In or outpatients receiving 5-flourauracil +/- folinic acid without concomitant radiation	5HT2 antagonist + steroid or other drug Steroids metoclopramide steroids + antidopaminergic drug	5-flourouracil +/- folinic acid: 'low to moderate risk of emetogenicity' NR	Prescription of a particular class of antiemetics or no treatment not significantly related to prior experience of nausea and vomiting, sex, age or alcohol intake. Data for 5HT3 antagonists not reported by specific drug.
The Italian Group for Antiemetic Research 1998	In or outpatients receiving chemotherapy without concomitant radiation, excluding patients with leukemia or those 'already in the study'	5HT2 antagonist alone or + steroid Steroids Benzamine alone or + steroid	7% high, 38% moderate, 17% low Single-day chemo Breast CA 51% Multi-day chemo colorectal 42%	Previous experience with chemotherapy induced N/V was not found to be associated with regimen selected. Centers with antiemetic clinical trial experience used 5HT2+steroid regimens more often than those without in highly emetogenic regimens (92% vs 64%, P<0.001 - cisplatin based regimens), and moderately emetogenic regimens (47% vs 38%, P<0.001).

Evidence Table 6. Quality assessment of long-term uncontrolled intervention studies of safety and adverse events

Author Year	Non-biased selection?	Low overall loss to follow-up?	Outcomes pre-specified and defined?	Ascertainment techniques adequately described?	Non-biased and adequate ascertainment methods?	Statistical analysis of potential confounders?	Overall quality
The Italian Group for Antiemetic Research 2001	Yes	Unclear	Some	Moderately well described	No, unclear that ascertainment was done in blinded fashion	Confounders considered and reported to be NS, but details of analysis NR	Fair
Hamandi 2007	Unclear	Yes	No	Unclear	No, unclear that ascertainment was done in blinded fashion	Confounders considered and reported to be NS, but details of analysis NR	Poor
The Italian Group for Antiemetic Research 2004	Yes	Unclear	Some	Moderately well described	No, unclear that ascertainment was done in blinded fashion	Confounders considered and reported to be NS, but details of analysis NR	Fair
The Italian Group for Antiemetic Research 1998	Yes	Unclear	Some	Moderately well described	No, unclear that ascertainment was done in blinded fashion	Confounders considered and reported to be NS, but details of analysis NR	Fair
Mertens 2003	Unclear	Unclear	Some	Unclear	No, unclear that ascertainment was done in blinded fashion	Only prior chemotherapy induced N/V considered and reported to be NS, but details of analysis NR	Poor