Drug Class Review
on
Newer Antiemetics

Final Report Evidence Tables

January 2006

A literature scan of this topic is done periodically

The purpose of this report is to make available information regarding the comparative effectiveness and safety profiles of different drugs within pharmaceutical classes. Reports are not usage guidelines, nor should they be read as an endorsement of, or recommendation for, any particular drug, use or approach. Oregon Health & Science University does not recommend or endorse any guideline or recommendation developed by users of these reports.

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Note: A scan of the medical literature relating to the topic is done periodically (see http://www.ohsu.edu/ohsuedu/research/policycenter/DERP/about/methods.cfm for scanning process description). The Drug Effectiveness Review Project governance group elected to proceed with another update of this report. Please see timeline on the DERP website for details on the date of its release.

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Author Year Setting Hesketh rating	Design	Subpopulation	Intervention	Allow other medication	Run-in/ Wash-out	Age Gender Ethnicity
Children						
Jaing 2004 Multicenter 3	Open RCT Crossover	children, females	granisetron po 0.5 or 1.0mg ondansetron iv 0.45mg/kg once	no other antiemetics allowed.	4 wk run-in with antiemetics acc. to rand. scheme/NR	7.8 64%male NR
Forni 2000 Not specified 5	DB RCT Parallel	children	Ondansetron iv 5.3mg/m2 Granisetron iv 2mg/m2 Tropisetron iv 3.3mg/m2	Antiemetics were given with dexamethasone 8 mg/m2 iv.	NR/NR	16.9 69%male NR

Evidence Table 1. Chemotherapy: head-to-head trials

Author Year Setting Hesketh rating	Screened/ Eligible/ Enrolled	Withdrawn/ Lost to fu/ Analyzed	Other population characteristics
Children			
Jaing 2004 Multicenter 3	35/33/33	0/0/33	Acute lymphoblastic leukemia: 100%
Forni 2000 Not specified 5	NR/NR/90	NR/0/90	NR

Evidence Table 1. Chemotherapy: head-to-head trials

Author Year Setting Hesketh rating	Results
Children	
Jaing **2004** Multicenter 3	Granisetron vs Ondansetron Complete response: no emetic episodes and no need for rescue medication: Within 24h: 60.6% vs 45.5%, NS Incomplete response: 39.4% vs 54.5%, NS Therapeutic success: 84.8% vs 87.9%, NS Failure: ≥ 3 vomiting episodes in 24h study period: 15% vs 12%, NS
Forni **2000** Not specified 5	Results given as Ondansetron vs Granisetron vs Tropisetron Complete response (no vomiting or retching) Complete response : 58.3% vs 62.9% vs 57.1%, NS Complete response: broken down by chemo regimen, not by study drug: 69% vs 44%, 0.0001 for ifos pts vs. cisplatin pts Partial response, % of patient days (1-4 episodes of vomiting/day): 34.2% vs 28.2% vs 38.3%, NS Failure (≥5 episodes of vomiting/day) % of patient days: 7.5% vs 8.9% vs 4.6%, NS

Evidence Table 1. Chemotherapy: head-to-head trials

Author Year Setting Hesketh rating	Adverse events	Comments
Children		
Jaing **2004** Multicenter 3	"The most frequently reported AEs were mild headache and constipation. The AEs were the same in both groups."	No concomitant antiemetic therapy apart from the study drugs was given to the patients.
Forni **2000** Not specified 5	All patient days Headache: 3.9% of 717 pt days, NR Headache was the only AE the authors reported; they stated that it was of mild intensity and its frequency was the same in all 3 treatment groups.	Population stratified by age owing to rarity of osteosarcoma; both pediatric and adult pts entered study. Nausea data not collected because pediatric pts deemed not able to give reliable nausea data. Withdrawal data: No cases of dose reduction of antiblastics; in 2 pts the ifosfamide (ifo) cycle was stopped (on days 4 & 5 of infusion) because of neurotoxicity. 717 pt-days of treatment evaluated for 90 pts; results were given in terms of pt days. 3 pt days not evaluable: 2 Gran pts were not given ifo for 3 days total due to neurological problems. Children not analyzed as a subpopulation. In cisplatin-Adriamycin cycles the complete protection (CP) rate decreased from 61% on day 1 to 27% on day 2. On the third day when Adriamycin was given, the total protection=44% (P<0.0001). During ifo cycles CP decreased from 95.5% on day1 to 43% on the last (P<0.0001). 10% of pts experienced CP on all treatment days during both chemo types. CP was achieved in 19% only for one type of chemo cycle; the remaining 71% experienced emesis in both cycles for at least 1 day.

Evidence Table 1. Chemotherapy: head-to-head trials

Author Year Setting Hesketh rating	Design	Subpopulation	Intervention	Allow other medication	Run-in/ Wash-out	Age Gender Ethnicity
White **2000** Multicenter 4, 5	DB RCT Parallel	children, kinetosis	Ondansetron iv 5mg/m2 Ondansetron po 8mg	Dexamethasone 2-4 mg po was given along with study antiemetics	No/NR	8 58%male NR

Evidence Table 1. Chemotherapy: head-to-head trials

Author Year Setting Hesketh rating	Screened/ Eligible/ Enrolled	Withdrawn/ Lost to fu/ Analyzed	Other population characteristics
White **2000** Multicenter 4, 5	NR/438/428	0/0/428	Mean weight (+/- SD) = 28.6 (+/- 12.2) kg Mean body surface area: (+/- SD) = 1.01 (+/- 0.30)m2 Previous motion sickness: yes: 3%

Evidence Table 1. Chemotherapy: head-to-head trials

Author Year Setting Hesketh rating	Results
White **2000** Multicenter 4, 5	Ond iv vs Ond po <u>Complete control of emesis (0 episodes)</u> Treatment phase A: 73% vs 71%, NS Overall (A+B): 62% vs 62%, NS Treatment Day 1: 81% vs 78%, NS <u>Major control of emesis (1-2 episodes):</u> Treatment A: 16% vs 17%, NS Overall (A+B): 23% vs 20%, NS Treatment Day 1: 10% vs 13%, NS <u>Mild Nausea</u> Treatment Day 1: 21% vs 21%, NS Phase A (a little bit nauseous): 26% vs 26%, NS Overall (A+B): 36% vs 33%, NS No nausea experienced: Treatment Day 1: 73% vs 70%, NS Overall (Phases A + B): 52% vs 56%, NS Phase A: 64% vs 64%, NS % with reduced appetite during treatment: increased by 7% from baseline vs increased by 12% from baseline, NS

Evidence Table 1. Chemotherapy: head-to-head trials

Author Year Setting Hesketh rating	Adverse events	Comments
White **2000** Multicenter 4, 5	Ond iv vs Ond po All Adverse Events: 20% vs 19%, NS Abdominal/ gastronintestinal discomfort and pain: 4% vs 3%, NS Fever/pyrexia: 3% vs 3%, NS Diarrhea and headaches: 2% vs 2%, NS Serious AEs: ≤2% vs ≤2%, NS	Ond po administered as an oral syrup, not a tablet. Study medication administered during 2 phases: phases A and B. Treatment phase A involved each of the days (max. 8 days) during which pts received moderately/highly emetogenic chemo. Ptsallowed to receive 1 or 2 single days of no or low emetogenic chemo in between the days that they received moderately/highly emetogenic chemo. interventions are given for Phase A. Treatment phase B defined as the 2 days immediately following cessation of moderately/highly emetogenic chemo (or if pts received chemo of low emetic potential for ≥2 consecutive days). All pts received Ond 4 mg po during phase B. All pts received Ond 4 mg po + Dex 2-4 mg po 6-8 h after receiving the IV. Dex given according to thebody surface area (BSA): 4mg/d for pts with BSA≤ 0.6 m2 and 8 mg/d for BSA >0.6 m2. This regimen was followed each day of moderate or highly emetogenic chemo. 483 pts originally enrolled; 9 did not receive mod./highly emetogenic chemo and another did not receive Ond iv; so 482 were considered the ITT population.

Evidence Table 1. Chemotherapy: head-to-head trials

Author Year Setting Hesketh rating	Design	Subpopulation	Intervention	Allow other medication	Run-in/ Wash-out	Age Gender Ethnicity
Orchard 1999 Single Center 5	DB RCT Parallel	children, BMT, TBI	Ondansetron iv mg Granisetron iv mg 7 days	All received dexamethasone iv 10 mg/m2/day (max 10 mg/day) for patients <18; and 10 mg/day IV for pts ≥18.	NR/NR	38.4 57%male NR

Evidence Table 1. Chemotherapy: head-to-head trials

Author Year Setting Hesketh rating	Screened/ Eligible/ Enrolled	Withdrawn/ Lost to fu/ Analyzed	Other population characteristics
Orchard **1999** Single Center 5	NR/NR/193	4/2/187	Conditioning regimen: Chemo only: 22% Chemo plus radiation: 75% Weight (range) = 72 kg (11-132 kg) Autologous transplant: 35% Allogeneic transplant: 26% Unrelated transplant: 35% Nonmalignancy: 16% Aplastic anemia: 7% Immune deficiency: 2% Metabolic disorder: 8% Acute lymphocytic leukemia: 3% AML/MDS: 21% Chronic myeloid leukemia: 25% Lymphoma: 10% Breast cancer: 6% Other malignancy: 15%

Evidence Table 1. Chemotherapy: head-to-head trials

Author Year Setting Hesketh rating	Results
Orchard **1999** Single Center 5	Ondansetron vs Granisetron Mean no. of emetic episodes: Day 0 of study (transplantation): 0.70 vs 0.75, NS Adults: pts ≥ 18 yrs, overall (Days -7 to Day +2 of study): 0.86 vs 0.80, NS No. of emetic episodes: Day -6 of study: 0.75 vs 0.65, NS Children: pts Day +2 of study: 1.30 vs 1.20, NS Day -7 of study: 0.50 vs 0.60, NS Episodes of emesis: All patients, overall (Days -7 to Day +2 of study): 0.86 vs 0.73, NS Major control of emesis: 1-2 emetic episodes in 24h of pt days: 27% pt days vs 27% pt days, NS Failure of control for emesis: >5 emetic episodes in 24h of pt days: 4% pt days vs 3% pt days, NS Minor control : 3-5 emetic episodes in 24h of pt days: 8% pt days vs 7% pt days, NS Complete control of emesis: No emetic episodes in 24h of pt days: 61% pt days vs 63% pt days, NS Mean nausea scores All patients, overall (Days -7 to Day 0): 1.29 vs 1.17, NS Day 0 of study: 1.30 vs 1.45, NS Day -1 of study: 1.45 vs 1.10, NS Day -6 of study: 1.30 vs 1.00, NS Adults: pts ≥ 18yrs, overall (Days -7 to Day 0): 1.36 vs 1.29, NS Children: pts Day -7 of study: 0.75 vs 0.75, NS Day -5 of study: 1.20 vs 0.9, NS Number of Daily Requests for Rescue Drugs 0 requests: 41% vs 40%, NS 1 request: 37% vs 38%, NS 2 requests: 20% vs 19%, NS 3 requests:1% vs 2%, NS

Evidence Table 1. Chemotherapy: head-to-head trials

Author Year Setting Hesketh rating	Adverse events	Comments
Orchard **1999** Single Center 5	Ondansetron vs Granisetron Headache: 13.4% vs 14.4%, NR Diarrhea: 2.1% vs 6.7%, Dizziness: 2% vs 4%, Joint pain: 1.0% vs 5.5%,	Patients were undergoing hematopoietic cell transplants; results were stratified by age (<18, n=51; ≥ 18 n=136) and analyzed. Of the 193 pts randomized, 4 withdrew within 48 h of randomization and 2 had inadequate data for analysis. The pediatric population of this study was receiving HSCT for nonmalignant conditions at a much higher percentage (51% vs. 4%) than the adult population; they also had a higher proportion of transplants from an unrelated donor than adults did (68% vs. 24%)

Evidence Table 1. Chemotherapy: head-to-head trials

Author Year Setting Hesketh rating	Design	Subpopulation	Intervention	Allow other medication	Run-in/ Wash-out	Age Gender Ethnicity
Adult						
Granisetron vs Ondansetron						
Barrajon 2000 Single Center 5	DB RCT Crossover	women, alcoholics, prior chemo	Tropisetron iv 5mg Granisetron iv + 3mg Ondansetron iv 24mg 10 min	All received 20 mg dexamethasone iv with the antiemetic; and then received it on a tapering oral schedule of 2mg bid for 2 days and then 1 mg bid for two days.	NR/NR	61 32%male NR
Chiou 2000 Single Center 4, 5	Open RCT Parallel	none	Ondansetron iv 24mg Granisetron po 2mg 24hr	Initial dose given with dexamethasone iv 10 mg; dex not given with other doses	No/NR	56.5 63%male NR

Evidence Table 1. Chemotherapy: head-to-head trials

Author Year Setting Hesketh rating	Screened/ Eligible/ Enrolled	Withdrawn/ Lost to fu/ Analyzed	Other population characteristics
Adult			
Granisetron vs Ondansetron			
Barrajon **2000** Single Center 5	NR/NR/136	16/0/120	Primary Tumor: Breast: 54% Primary Tumor: Lung: 12% Primary Tumor: Head and neck: 12% Primary Tumor: Gynacological: 9% Primary Tumor: Digestive: 6% Primary Tumor: Other: 8% Ethanol consumption >120g/day: 13% Previous chemo: 30% Chemo: CDDP + TAX: 26% Chemo: CDDP+5FU+/-MTX: 20% Chemo: CEI/PEI+/-VNR: 10% Chemo: FAC/FEC: 15% Chemo: CMF: 16% Chemo: Other: 13% Mean cisplatin dose = 74.7 Pts receiving Platinum-based chemo: 54% Pts receiving chemo for >24h: 29%
Chiou **2000** Single Center 4, 5	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%

Evidence Table 1. Chemotherapy: head-to-head trials

Author Year Setting Hesketh rating	Results
Adult	
Granisetron vs Ondansetron	
Barrajon **2000** Single Center 5	Ondansetron vs Granisetron vs Tropisetron Degree of nausea: (first cycle only) grades 0-3 1: 15.0% vs 13.0% vs 20.0%, NS 2: 20.0% vs 28.0% vs 13.0%, NS 3 (severe): 15.0% vs 18.0% vs 15.0%, NS No nausea (grade 0): 50.0% vs 43.0% vs 53.0%, NS Emesis: Complete control (for first cycle only) No emetic episodes experienced: 60% vs 63.0% vs 55.0%, NS Emesis: number of patients with ≥1 episodes (first cycle only): 40.0% vs 37.5% vs 45.0%, NS Emesis: number of episodes and mean (for the first cycle only) Total number of episodes of emesis per each treatment group: 84 vs 87 vs 100, NS Mean number of episodes (per pt expereiencing emesis): 2.1 vs 2.18 vs 2.5, NS Emesis: days with emesis and mean (first cycle only) Total days with emesis per treatment group: 33 vs 40 vs 44, NS Mean number of days with emesis per patient: 0.83 vs 1.0 vs 1.1, NS Patient preference (after crossovers): 45% vs 30% vs 25%, p
Chiou **2000** Single Center 4, 5	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

Evidence Table 1. Chemotherapy: head-to-head trials

Author Year Setting Hesketh rating	Adverse events	Comments
Adult		
Granisetron vs Ondansetron		
Barrajon 2000 Single Center 5	Ond vs Gran vs Trop % with headache, first cycle only: 10% vs12.5%vs 40%; NR Fluid administration all 3 courses: 8.3% vs 8.3% vs 8.3%; NR Need for rescue antiemetic (metoclopramide) No. of patients needing rescue: 6 vs 4 vs 6; NR Trop emergency admission for less than 24h: probably due to fluid loss: 2.5%	No stratification implemented. No correction made for paired data or for continuity. Rescue antiemetic was metoclopramide. 16 of 136 pts included in the initial rounds of randomization were not evaluable because they were not able to complete the anticipated treatment owing to progression of disease or intolerable toxicity that prevented further chemo at the same initial doses. Subgroup analysis: NSD in emesis depending on these risk factors: age, gender, chemo with cisplatin, or alcohol consumption. The factor clearly associated to a significant increase in emesis was chemo regimens >1day (complete protection for those with only 1 day chemo = 69% vs. 4% for >1day chemo, p<0.001).All efficacy measures are reported from the first cycle only, before any crossover occurred, unless otherwise noted. The authors state: an ITT analysis after the first course [ie, cycle] was not considered possible, as data were not available for 8 of 16 included pts. The preference for ondansetron appeared at the start of the trial and was maintained throughout the study. Cumulative preferences for Gran and Trop crossed each other throughout the study.
Chiou 2000 Single Center 4, 5	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.

Evidence Table 1. Chemotherapy: head-to-head trials

Author Year Setting Hesketh rating	Design	Subpopulation	Intervention	Allow other medication	Run-in/ Wash-out	Age Gender Ethnicity
Chua 2000 Single Center 5	Open RCT Crossover	none	granisetron iv 3mg tropisetron iv 24mg ondansetron iv 5mg	dexamethasone 20 mg iv given with study antiemetics on day 1,	NR/NR	NR 87%male Asian (Chinese), n= 89 (100%)
deWit 2001 NR 5	DB RCT Crossover	none	Granisetron iv 3mg Ondansetron iv 8mg once	dexamethasone 10 mg iv given with study medication	No/NR	46 10%male NR

Evidence Table 1. Chemotherapy: head-to-head trials

Author Year Setting Hesketh rating	Screened/ Eligible/ Enrolled	Withdrawn/ Lost to fu/ Analyzed	Other population characteristics
Chua **2000** Single Center 5	94/89/89	0/0/89	GRADEX vs TRODEX: 65% GRADEX vs ONDEX: 73% TRODEX vs ONDEX: 72% Primary Tumor: Nasopharnyx: 80%; Oral Cavity: 10%; Hypopharnx: 8%; Larnyx: 1%; Ear: 1% Chemo as part of : primary treatment: 55%; induction: 39%; adjuvant: 11%; concomitant chemoirradaiton: 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%
deWit **2001** NR 5	NR/45/40	0/0/40	cisplatin-based chemo: 33% cyclophosphamide-based chemo: 68% previous cycles: 10% Primary Tumor- Breast: 63% Primary Tumor- Ovarian: 10% Primary Tumor- Lung: 10% Primary Tumor- Other: 18%

Evidence Table 1. Chemotherapy: head-to-head trials

Author Year Setting Hesketh rating	Results
Chua **2000** Single Center 5	Ondansetron vs Granisetron vs Tropisetron Complete reponse: 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
deWit **2001** NR 5	Ondansetron vs Granisetron Results for Cisplatin-based chemotherapy pts Partial: 34% vs 34%, NS Failure: 67% vs 43%, NS Complete: 0% vs 29%, NS Results for Cyclophosphamide-based chemotherapy pts Failure to repsond: 73% vs 25%, NS Partial response: 20% vs 17%, NS Complete response : 7% vs 58%, NS Ond iv 8 vs Gran iv 3 Complete protection to failure to respond for total population Complete response:no vomiting and no/mild nausea : 4.8% vs 47.4%, 0.005 for Gran vs. Ond Failure to respond: ≥ 2 vomits or severe nausea (no significant intake possible), or nausea >4 hours : 67% vs 37%, NR Partial response: 0-1 vomits and/or moderate nausea during a max. of 4 hours: 29% vs 16%, NR

Evidence Table 1. Chemotherapy: head-to-head trials

Author Year Setting Hesketh rating	Adverse events	Comments
Chua **2000** Single Center 5	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.
deWit **2001** NR 5		45 pts randomized; 5 pts excluded at the study cycle: 2 had nausea prior to chemo; 2 had chemo dose reductions; and 1 used other antiemetics. The patients on cisplatin were in a highly emetogenic category (defined by Hesketh 1997); but the patients on cyclophosphamide had dosages ≥ 500 mg/m2, which can range from moderate (500-750 mg/m2 and 750-1500 mg/m2) emetogenicity to high emetogenicity (≥ 1500 mg/m2) per Hesketh 1997. The study did not specify which dosage the cyclophosphamide pts were receiving.

Evidence Table 1. Chemotherapy: head-to-head trials

Author Year Setting Hesketh rating	Design	Subpopulation	Intervention	Allow other medication	Run-in/ Wash-out	Age Gender Ethnicity
Del Favero 1995 Multicenter 5	DB RCT Parallel	kinetosis	Ondansetron iv 8mg Granisetron iv 3mg	all given dexamethasone (dex) 20 mg iv as a 15-min infusion 45 min before administration of cisplatin. All pts received Dex im and metoclopramide po on days 2-4.	NR/NR	61 68%male NR

Evidence Table 1. Chemotherapy: head-to-head trials

Author Year Setting Hesketh rating	Screened/ Eligible/ Enrolled	Withdrawn/ Lost to fu/ Analyzed	Other population characteristics
Del Favero 1995 Multicenter 5	NR/NR/973	6/1/966	Median dose of cisplatin (mg per square meter): 8% Dose of cisplatin: < 90 mg/m2: 63% ≥ 90 mg/m2: 37% Performance Status: 50-80: 35% 90-100: 65% Previous non-cisplatin chemo: Yes 7% No 92% Primary tumor: Ovary: 14% Lung: 38% Head-neck: 12% Bladder: 14% Other: 21% Kinetosis: Yes: 10% No: 89% Concomitant medications: Opioids: 4% H2 antagonists: 14% Benzodiazepines: 4% NSAID: 9%

Evidence Table 1. Chemotherapy: head-to-head trials

Author Year Setting Hesketh rating	Results
Del Favero **1995** Multicenter 5	*Data given as ond vs gran* Complete response: acute: no nausea and no vomiting, and no nausea+no vomiting No nausea: acute : 72.1% vs 71.8%, NS Complete response: Acute: 66.5% vs 67.3%, NS No vomiting: acute: 79.3% vs 79.9%, NS Mean number of emetic episodes: acute Only in patients who had vomiting: 4.04 vs 3.91, NS Acute (only in pts who had nausea; scale = 0:none to 3:severe) score: 1.47 vs 1.48, NS Complete protection from nausea: acute: 72.1% vs 71.8%, NS Complete protection from vomiting, days 2-6 Day 2: 81.9% vs 81.9%, NS Day 3: 82.8% vs 86.9%, NS Day 4: 85.5% vs 87.8%, NS Day 5: 88.5% vs 88.6%, NS Day 6: 92.0% vs 90.7%, NS Complete protection from nausea, Days 2-6 Day 2: 66.6% vs 63.1%, NS Day 3: 63.7% vs 67.5%, NS Day 4: 65.8% vs 70.7%, NS Day 5: 70.4% vs 73.4%, NS Day 6: 72.5% vs 75.7%, NS Complete protection from nausea and vomiting, days 2-6 Day 2: 61.8% vs 59.9%, NS Day 3: 60.3% vs 65.4%, NS Day 4: 63.0% vs 68.4%, NS Day 5: 68.3% vs 71.3%, NS Day 6: 71.4% vs 74.5%, NS

Evidence Table 1. Chemotherapy: head-to-head trials

Author Year Setting Hesketh rating	Adverse events	Comments
Del Favero **1995** Multicenter 5	granisetron vs ondansetron constipation:0.6% vs 0.4%, NS headache: 3.1% vs 3.1%; NS heartburn: 0.8% vs 0.2%, NS weakness: 2.3% vs 0.8%, NS epigastric pain: 1.0% vs 0.8%, NS nervousness: 0.2% vs 0.8%, NS hot flush: 2.9% vs 2.1%, NS hiccup: 2.3% vs 3.3%, NS sedation: 1.0% vs 0.4%, NS other AEs (not specified) : 4.1% vs 4.3%, NS	15 min after study drug administration finished, cisplatin infusion began and was given over 30 min. The other chemo agents were given immediately after the end of the cisplatin infusion. Food intake was not permitted until 8 hrs after cisplatin. To prevent cisplatin-induced delayed emesis, all pts received metoclopramide (meto) 20 mg po every 6 hrs on days 2 to 4, together with intramuscular dex 8 mg bid on days 2 and 3, and 4 mg bid on day 4. Gran and Ond given to patients on day 1 only; so day 1 was the head-to-head part of the trial for the study medication. The number of evaluable pts went from 483/group to Ond N= 476 and Gran N=474 (Total N=950). Causes of non-availability were: 2 pts died; 7 pts had failure of antiemetic treatment on day 1; 1 pt had failure of antiemetic treatment on day 2; 3 were lost to followup; 1 refused antiemetic therapy; 1 had AEs on day 1; 1 had AEs on day 2. By group: Ond: 1 pt: error in administered antiemetic reatment and case report form not completed; 1 pt refused chemo; 1 pt the administered chemo was different after randomization. Gran: 1 pt died during first 24 hours; 2 pts failed to receive antiemetic therapy after randomization; 1 pt was lost to

Evidence Table 1. Chemotherapy: head-to-head trials

Author Year Setting Hesketh rating	Design	Subpopulation	Intervention	Allow other medication	Run-in/ Wash-out	Age Gender Ethnicity
Fox-Geiman 2001 Single Center 5	DB RCT Parallel	BMT; TBI	Ondansetron po 24mg (8 mg Q8) Ondansetron iv 32mg qd Granisetron po 2mg (1 mg Q12)	Yes; all received dexamethasone 10 mg iv qd while receiving the 5-HT3 antagonist; also, benzodiazepines were allowed as needed for sleep.	NR/NR	47 28%male NR

Evidence Table 1. Chemotherapy: head-to-head trials

Author Year Setting Hesketh rating	Screened/ Eligible/ Enrolled	Withdrawn/ Lost to fu/ Analyzed	Other population characteristics
Fox-Geiman 2001 Single Center 5	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%

Evidence Table 1. Chemotherapy: head-to-head trials

Author Year Setting Hesketh rating	Results
Fox-Geiman **2001** Single Center 5	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 Reponse 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

Evidence Table 1. Chemotherapy: head-to-head trials

Author Year Setting Hesketh rating	Adverse events	Comments
Fox-Geiman 2001 Single Center 5	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 were 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 carboplatine [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) (carboplatine dose modified to total AUC = 28); carboplatin/VP (carboplatin dose modified to a total AUC = 30; carboplatine/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.

Evidence Table 1. Chemotherapy: head-to-head trials

Author Year Setting Hesketh rating	Design	Subpopulation	Intervention	Allow other medication	Run-in/ Wash-out	Age Gender Ethnicity
Gebbia 1994a Single Center 5	Open RCT Parallel	none	ondansetron iv 24mg granisetron iv 3mg	No	NR/NR	59 64%male NR
Gebbia 1994b Single Center 3	Open RCT Parallel	none	ondansetron iv 16mg Granisetron iv 3mg	No	NR/NR	56 21%male NR

Evidence Table 1. Chemotherapy: head-to-head trials

Author Year Setting Hesketh rating	Screened/ Eligible/ Enrolled	Withdrawn/ Lost to fu/ Analyzed	Other population characteristics
Gebbia 1994a Single Center 5	NR/NR/182	16/0/166	Delayed: 91% Primary tumor: head and neck 47% lung 16% urinary bladder 7% ovary 7% stomach 6% endometrium 6% vulva 7% breast 3% testis 1% sarcoma 1%
Gebbia 1994b Single Center 3	NR/NR/164	8/0/158	Primary Tumor: Breast 60% Lung 15% Ovary 8% Stomach 6% Non-Hodgkin lymphoma 9% Melanoma 1%

Evidence Table 1. Chemotherapy: head-to-head trials

Author Year Setting Hesketh rating	Results
Gebbia **1994a** Single Center 5	Ondansetron vs Granisetron <u>Acute emesis response rates: complete, major, minor, and failure</u> Major response: 29% vs 24%, NS Minor response: 14% vs 12%, NS Failure: 5% vs 15%, NS Complete response: no emesis(acute): 52% vs 49%, NS <u>Delayed emesis response rates: complete, major, minor, and failure</u> Complete response : 39% vs 36%, NS Major response : 24% vs 22%, NS Minor response : 21% vs 28%, NS Failure: 16% vs 14%, NS <u>Nausea severity</u> No nausea: acute: 74% vs 79%, NS No or mild nausea: delayed: 53% vs 45%, NS <u>Complete response in pts undergoing fractionated chemo</u> No emesis in pts undergoing fractionated chemo: Days 2-5 : 43% vs 35%, NS
Gebbia **1994b** Single Center 3	Ondansetron vs granisetron <u>Acute emesis reponse rates: Complete, major, minor, failure</u> Failure: ≥ 6 emetic episodes: 3% vs 4%, NS Minor response: 3-5 emetic episodes: 6% vs 10%, NS Major response: 1-2 emetic episodes: 22% vs 19%, NS Complete response: no emetic episodes: 69% vs 67%, NS <u>Delayed emesis response rates: Complete, major, minor, failure</u> Major response, days 2-5: 15% vs 20%, NS Complete response: no emesis days 2-5: 45% vs 52%, NS <u>Pts experiencing no nausea</u>: Acute: 50% vs 45%, NS Delayed: 31% vs 37%, NS

Evidence Table 1. Chemotherapy: head-to-head trials

Author Year Setting Hesketh rating	Adverse events	Comments
Gebbia **1994a** Single Center 5	*data given as Ond iv 24 vs Gran iv 3* Headache:9% vs 4%, NS Constipation: 17% vs 7%, NS	Pts stratified according to length of chemo (single day vs. fractionated). Cisplatin was given as a single dose on day 1. Pts with fractionated chemo recevied Ond po 8 mg bid (total= 16 mg) or Gran iv 3 mg on the days with chemo after day 1.
Gebbia **1994b** Single Center 3		All pts were required to receive epidoxorubicin ≥ 75 mg/m2, doxorubicin ≥ 40 mg/m2, cyclophosphamide ≥ 600 mg/m2 iv, IFX ≥ 3 g/m2 (study 2). In Study 2, most patients received a CMF regimen (cyclophosphamide 600 mg/m2, methotrexate 40 mg/m2, and 5-fluorouracil [5-FU] 600 mg/m2), FAC/FEC regimen (5-FU 600 mg/m2, cyclophosphamide 600 mg/m2, epidoxorubicin 75-90 mg/m2 or doxorubicin 40-60 mg/m2), or ifosfamide 3-5 g/m2 plus vinorelbine 25-30 mg/m2.

Evidence Table 1. Chemotherapy: head-to-head trials

Author Year Setting Hesketh rating	Design	Subpopulation	Intervention	Allow other medication	Run-in/ Wash-out	Age Gender Ethnicity
Gralla 1998 Multicenter 5	DB RCT Parallel	corticosteroids	Ondansetron iv 32mg + dex or m-prednisolone Granisetron po 2mg + dex or m-prednisolone	Corticosteroids (dexamethasone or methylprednisolone) could be given as replacement or maintenance therapy up to an equivalent total daily dose of 10mg prednisone, or as part of prophylactic antiemetic pretherapy ≤ 8 hours before chemo with cisplatin.	NR/NR	61.7 66%male NR

Evidence Table 1. Chemotherapy: head-to-head trials

Author Year Setting Hesketh rating	Screened/ Eligible/ Enrolled	Withdrawn/ Lost to fu/ Analyzed	Other population characteristics
Gralla **1998** Multicenter 5	NR/NR/1054	13/0/1054	Mean body weight = 74 kg Mean alcohol units/week = 6.7 units/wk Pts using corticosteroids: 79% Respiratory and intrathoracic cancers: 61% Genitourinary cancers: 13% Other cancers (incl. head and neck): 9%

Evidence Table 1. Chemotherapy: head-to-head trials

Author Year Setting Hesketh rating	Results
Gralla **1998** Multicenter 5	Ondansetron vs Granisetron Total control (no emesis, no nausea of any severity, and no use of antiemetic rescue medication) over 24h post cisplatin administration) For all patients: 58.3% vs 54.7%, NS Females only: 52.0% vs 46.3%, NS Patients using corticosteroids: 61.5% vs 58.8%, NS Patients not using corticosteroids: 45.8% vs 40.2%, NS Males only: 61.5% vs 59.3, NS Complete control of emesis Total population: 61.2% vs 67.1%, NS No Corticosteroid Added: 57.9% vs 46.2%, NS Corticosteroid Added: 69.5% vs 65.5%, NS Females: 60.0% vs 53.7%, NS Males: 70.7% vs 65.3%, NS Complete control of nausea Total population: 59.0% vs 55.4%, NS Females: 53.1% vs 46.8%, NS Corticosteroid Added: 62.0% vs 59.5%, NS Males (Ond n = 345; Gran n = 346): 62.0% vs 60.1%, NS No Corticosteroid Added: 47.7% vs 41.0%, NS Use of antiemetic rescue medication Total % of patients (both study drugs combined): 28.2% Use of antiemetic rescue medication Total % of patients: 25.2% vs 31.1%, NS

Evidence Table 1. Chemotherapy: head-to-head trials

Author Year Setting Hesketh rating	Adverse events	Comments
Gralla **1998** Multicenter 5	Ondansetron vs Granisetron Asthenia: 18.5% vs 18.0%, NS Constipation: 12.1% vs 15.7%, NS Headache: 14.0% vs 15.5%, NS Decreased Appetite: 13.7% vs 12.5%, NS Diarrhea: 9.8% vs 10.7%, NS Patients experiencing any AE: 85.8% vs 87.1%, NS Total withdrawals: 1.4% vs 0.94%, NR Both drugs Withdrawals due to AEs: not stratified by drug: 0.38%, NA	Patients were required to receive IV cisplatin of ≥ 60 mg/m2 over a period not exceeding 3 hours. No additional cisplatin was administered until 24 hours had elapsed. The timing of all post-chemo assessments and procedures was based on the time when cisplatin administration began. All patients had the same drug schedule: if they received Ond iv, they also received 2 placebo tablets at the same time as the Gran pts; and if they received Gran tablets, they received placebo (i.e., saline) via iv 30 minutes before chemo like the Ond pts. This study only reported numbers for AEs that occurred in at least 10% of each drug's population. They state that "there were no notable difference between the treatment groups in the types of events reported or their incidences". The two most commonly used antiemetic rescue medications used were prochlorperazine and dexamethasone, respectively. 1053 of 1054 pts received cisplatin (one ineligible pt was enrolled in error and greceived Gran but not cisplatin).

Evidence Table 1. Chemotherapy: head-to-head trials

Author Year Setting Hesketh rating	Design	Subpopulation	Intervention	Allow other medication	Run-in/ Wash-out	Age Gender Ethnicity
Herrington 2000 Multicenter 4	Open RCT Parallel	women	Ondansetron po 16mg Granisetron po 1mg	Yes: study drug given concomitantly with dexamethasone (dex) 12 mg po	No/NR	60.6 25%male NR
Jantunen 1993 Multicenter 3, 4	Open RCT Crossover	none	Ondansetron iv 8mg Granisetron iv 3mg Tropisetron iv 5mg	First 24h: no other medication allowed; but from Day 2 onward, pts received metoclopramide (10 mg 6-hourly po) if experiencing nausea.	no/no	50.6 16%male NR

Evidence Table 1. Chemotherapy: head-to-head trials

Author Year Setting Hesketh rating	Screened/ Eligible/ Enrolled	Withdrawn/ Lost to fu/ Analyzed	Other population characteristics
Herrington 2000 Multicenter 4	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%
Jantunen 1993 Multicenter 3, 4	NR/NR/166	34/2/130	Previous Chemo:yes: 70% Previous Chemo:no: 30% Breast cancer: 64% Gastrointestinal cancer: 16% Lymphoma: 9% Lung cancer: 4% Head and neck cancer: 2% Mesothelioma: 2% Other malignancies: 2% Chemo: CMF: 34% Chemo: FAC/FEC: 14% Chemo: C+mitoxantrone+5-FU: 5% Chemo: other cyclophsophamide containing: 7% Chemo: A/E+MTX+5-FU: 14% Chemo: other antracycline-containing: 9% Chemo:carboplatin-containing: 5% Chemo: Mitomycin + MTX+mitoxantrone: 5% Chemo: DTIC-containing: 2% Chemo: cisplatin Chemo: other: 4%

Evidence Table 1. Chemotherapy: head-to-head trials

Author Year Setting Hesketh rating	Results
Herrington 2000 Multicenter 4	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
Jantunen 1993 Multicenter 3, 4	Ondansetron vs Granisetron vs Tropisetron Control of vomiting during the first 24h (for Cycle 1 of 3) Complete control: no vomiting or retching; Cycle 1 (N = 161 of 166) (p-value gran vs. other drug): 60.7% (<0.01 Partial control: 1-2 episodes of vomiting or retching: Cycle 1 (N = 161 of 166) (p-value gran vs. other drug): 21.4% (NS) vs 14.0% (NA) vs 12.7%(NS), NS Failure: >2 episodes of vomiting or retching: Cycle 1 (N = 161 of 166)(p-value gran vs. other drug): 17.9%(<0.01 Ondansetron vs Granisetron vs Tropisetron vs no preference Patient preference (after all 3 cycles (ie, everyone had tried all 3 drugs) were completed): 16.9% vs 41.5% vs 15.4% vs 26.2%, NR

Evidence Table 1. Chemotherapy: head-to-head trials

Author Year Setting Hesketh rating	Adverse events	Comments
Herrington **2000** Multicenter 4	ondansetron vs granisetron <u>Overall AEs</u> 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.
Jantunen **1993** Multicenter 3, 4	Ondansetron vs Granisetron vs Tropisetron <u>Headache</u> (no. of pts analyzed not given, nor is it stated if these are for all 3 cycles): 35% vs 35% vs 34%,	Patients crossed over twice after receiving their original study drug; only the results from Cycle 1 are given in this evidence table (130/166 patients were analyzed for all 3 cycles; 161/166 were in analyzed for Cycle 1). C=cyclophosphamide; M=methotrexate; F or 5-FU = 5-fluourouracil; A = doxorubicin; E = epirubicin MTX - methotrexate; DTIC - ductual carcinoma in situ. Withdrawal information: In cycle 1, data was given for 161 of 166 pts (no reasons given as to why those 5 not accounted for); for all 3 cycles, there were 36 pts total who could not evaluated in the cross-over analysis of response. Of these, 18 had their chemo changed due to progressive disease and no longer fit the inclusion criteria; 4 had chemo dose reductions due to low blood counts; 5 had incomplete data on emesis; 4 requested to be withdrawn after Cycle 1 due to inadequate control of emesis (2 in Ond, 2 in Trop); 2 emigrated and were lost to F/u; 1 did not fit inclusion criteria (astrocytoma); 1 received Trop 2X which was considered to be a major violation of study protocol; 1 requested to be withdrawn after random

Evidence Table 1. Chemotherapy: head-to-head trials

Author Year Setting Hesketh rating	Design	Subpopulation	Intervention	Allow other medication	Run-in/ Wash-out	Age Gender Ethnicity
Kalaycio **1998** NR 5	DB RCT Parallel	ASCT, women	Granisetron iv 0.5mg Ondansetron iv 8mg 8 days	All pts received dexamethasone 10 mg iv for 7 days	NR/NR	43 0%male NR
Leonardi **1996** Multicenter 3, 4, 5	NR RCT Crossover	none	Ondansetron iv 0.45mg/kg Granisetron iv 0.04mg/kg	No	NR/NR	51 41%male NR

Evidence Table 1. Chemotherapy: head-to-head trials

Author Year Setting Hesketh rating	Screened/ Eligible/ Enrolled	Withdrawn/ Lost to fu/ Analyzed	Other population characteristics
Kalaycio **1998** NR 5	48/48/48	3/45/45	Primary Tumor: Breast: 100% Chemotherapy Non-Naïve: 100% History of alcohol use: 18% History of emesis: 38% History of ondansetron: 62% History of granisetron: 31%
Leonardi **1996** Multicenter 3, 4, 5	NR/NR/118	3/0/118	Patients receiving moderately emetogenic chemo: 41% Pts receiving highly emetogenic chemotherapy: 59% ECOG Performance Status 0-3: 100% Breast cancer: 36% Lung cancer: 24% Hodgkins or non-Hodgkins lymphoma: 16% Other malignancies: 24%

Evidence Table 1. Chemotherapy: head-to-head trials

Author Year Setting Hesketh rating	Results
Kalaycio **1998** NR 5	Granisetron vs Ondansetron Mean number of salvage anti-emetics: 15.8 vs 15.8, NS Mean days to first salvage anti-emetic: 2.8 vs 2.9, NS Mean emetic episodes per day: 5.6 vs 7.0, NS No emetic episodes: 17.4% vs 9.1%, NS
Leonardi **1996** Multicenter 3, 4, 5	Ondansetron vs Granisetron Complete control: no vomiting and no nausea, or only mild nausea after initial administration of antiemetic therapy Pts receiving highly emetogenic chemo:54.3% vs 61.7%, NS Pts receiving moderately emetogenic chemo: 67% vs 72.8%, NS All patients combined: 62.1% vs 68.4%, NR Major control: moderate to severe nausea, or just one episode of vomiting All patients: 15.5% vs 12.8%, NR Pts receiving highly emetogenic chemo: 13% vs 12.7%, NS Pts receiving moderately emetogenic chemo: 17% vs 12.8%, NS Minor control: 2-5 episodes of vomiting, regardless of nausea rating All patients: 16.4% vs 14.5%, NR Pts receiving moderately emetogenic chemo: 12.8% vs 10%, NS Pts receiving highly emetogenic chemo: 21.7% vs 21.2%, NS Failure: >5 vomiting episodes, regardless of nausea rating Pts receiving highly emetogenic chemo: 8.7% vs 2.1%, NS Pts receiving moderately emetogenic chemo: 2.8% vs 4.3%, NS All patients: 5.2% vs 5.1%, NR No. of cycles with vomiting episodes Pts receiving highly emetogenic chemo: 41.3% vs 38.3%, NS Pts receiving moderately emetogenic chemo: 31.4% vs 27.1%, NS All patients: 35.3% vs 31.6%, NR Patient preference: Preference: 22% vs 38%, 0.05 No preference: 40%, NR

Evidence Table 1. Chemotherapy: head-to-head trials

Author Year Setting Hesketh rating	Adverse events	Comments
Kalaycio **1998** NR 5	Granisetron vs Ondansetron headache: 36% vs 39%, NS diarrhea: 36% vs 39%, NS creatinine (mean): 0.73 vs 0.60, NS bilirubin (mean): 0.60 vs 0.59, NS	All pts received an infusion of autologous stem cells 3 days after the chemo regimen was complete. All pts received hematopoietic growth factors after ASCT until engraftment was achieved. 2 pts were disqualified for being on antiemetics at the time of study entry and 1 pt was excluded for absence of her chart.
Leonardi **1996** Multicenter 3, 4, 5	Death: Both drugs:1.7% Ondansetron vs Granisetron Headache: 24% vs 23%, NS Lightheadedness: 13% vs 18%, NS Constipation: 11% vs 6%, NR Other AEs (not specified): 6% vs 6%, NR Number of cycles without any AEs: 62% vs 68%, NS	Moderately emetogenic (ME) chemo: a regimen containing adriamycin >25 mg/m2 or epidoxorubicin >40 mg/m2 and/or cyclophosphamide >500 mg/m2 in combination with other agents except cisplatin. Highly emetogenic (HE) chemo: a regimen containing cisplatin >50 mg/m2 alone or in association with other antiblastic agents. Data is presented as a result of cycles, not patients; Ond was first administered in 65 patients and Gran in 53 patients. There were a total of 233 cycles (3 patients did not complete a second cycle - 2 died before the second cycle began and one refused a second cycle) evaluated for the 118 patients. There were 93 HE cycles (40%) and 140 ME cycles (60%); and there were 116 cycles with Ond and 117 with Gran.

Evidence Table 1. Chemotherapy: head-to-head trials

Author Year Setting Hesketh rating	Design	Subpopulation	Intervention	Allow other medication	Run-in/ Wash-out	Age Gender Ethnicity
Mantovani 1995 Single Center 5	Open RCT Parallel	none	Ondansetron iv 24mg Granisetron iv 3mg Tropisetron iv 5mg	Not explicitly stated unless pt had severe nausea.	NR/NR	58.2 97%male NR
Martoni 1995 Single Center 5	Open RCT Crossover	none	Ondansetron iv 24mg Granisetron iv 3mg	No other antiemetic drugs allowed, including corticosteroids.	NR/NR	62 75%male NR

Evidence Table 1. Chemotherapy: head-to-head trials

Author Year Setting Hesketh rating	Screened/ Eligible/ Enrolled	Withdrawn/ Lost to fu/ Analyzed	Other population characteristics
Mantovani 1995 Single Center 5	NR/NR/117	0/0/117	No. of cycles with Gran. used = 165 cycles No. of cycles with Ond. used = 150 cycles No. of cycles with Trop. used = 148 cycles ECOG performance status = 0: 60% ECOG performance status = 1: 31% ECOG performance status = 2: 8% ECOG performance status =3: 2% Cancer Stage II: 5% Cancer Stage III: 25% Cancer Stage IV: 70% Site of primary tumor: oral cavity: 27%; oropharynx; 24%; hypopharynx: 9%; Larynx: 37%; maxillary sinus: 2%; upper esophagus: 2% Crossed over once (ie, to a second drug): 16% Crossed to a third drug: 2% Mean no. of chemo cycles/patient = 3.9
Martoni 1995 Single Center 5	NR/NR/124	0/0/124	Outpatients: 20% Inpatients: 80% Karnofsky perfm score median (range) = 80 (50-100) Primary tumor: NSCLC: 61% Primary tumor: Bladder: 27% Primary tumor: Ovary: 6% Primary tumor: Others: 6% Previous emesis (kinetosis, during pregnancy): 5% Alcohol use: 20% Chemo: CP (60) + VNR (25): 44% Chemo: CP (60) + EPI (120): 18% Chemo: CP (60) + EPI (60): 6% Chemo: CP (50) + EPI (50) + CTX (500): 6% Chemo: CP (70) + EPI (60) + MTX (40): 27%

Evidence Table 1. Chemotherapy: head-to-head trials

Author Year Setting Hesketh rating	Results
Mantovani **1995** Single Center 5	Ondansetron vs Granisetron vs Tropisetron Complete response (CR): no nausea of vomiting or only mild nausea in the 24h after starting chemo: 82.4% vs 84.2% vs 72.5%, NS Major response (MR): single vomiting episode in the 24h after chemo; or no vomiting but moderate to severe nausea: 17.9% vs 10.5% vs 15.0%, NS Major efficacy (CR+MR): Complete and Major response combined: 100.0% vs 94.7% vs 87.5%, Minor response (MiR): 2-4 vomiting episodes in the 24h after starting chemo: 0.0% vs 2.6% vs 7.5%, Failures (F): >4 vomiting episodes in the 24h after starting chemo: 0.0% vs 2.6% vs 5.0%,
Martoni **1995** Single Center 5	Ondansetron vs Granisetron <u>First cycle outcomes, including complete response (no nausea and no vomiting)</u> No nausea: 60% vs 64%, NS No vomiting: 74% vs 76%, NS Complete response: No nausea and no vomiting: 59% vs 62%, NS <u>Patient preference</u> For study drug: 24.8% vs 44.6%, 0.003 Neither drug preferred: 30.6%, NR

Evidence Table 1. Chemotherapy: head-to-head trials

Author Year Setting Hesketh rating	Adverse events	Comments
Mantovani **1995** Single Center 5	All 3 drugs were well tolerated and no severe AEs were observed during treatment. Headache, a common complaint among pts receiving 5-HT3 antagonists, was <10% and not significantly different in any of the 3 treatment arms. No other relevant side effects were observed in any of the pts during treatment	All pts were on study drugs for multiple courses of chemotherapy. 40 pts had al-Sarraf's classical chemo: 100 mg/m2 cisplatin (CDDP) iv over 2h using a standard pre- and post- hydration protocol with forced diuresis by 250 cc of 18% mannitol on Day 1 + 1000 mg/m2 of 5-fluourouracil (5-FU) iv, continuous infusion for 120H on Days 1-5. 77 pts had: 80 mg/m2 CDDP iv over 2 h according to standard pre- and post- hydration protocol with forced diuresis by 250 cc of 18% mannitol on Day 1; 600 mg/m2 of 5-FU infused during a period of 4h on days 2-5; and 20 mg/m2 of vinorelbine iv over 20 min on days 2 and 8. Response data given for the first chemo cycle only (data for all 3 cycles given in paper). Pts did not know to which antiemetic they had been assigned, even if they were crossed over to a different antiemetic due to failure. Significance was between Ond vs. Trop for CR+MR and Gran and Ond vs.Trop for MiR. P-values for all other comparisons were NS. Data was given mostly in terms of number of cycles, not number of pts. It appears there were 117 pts in cycle 1, 104 pts in cycle 2, and 87 pts in cycle 3; but withdrawal rates and reasons not given.
Martoni **1995** Single Center 5	Ondansetron vs Granisetron Headache: Data from both cycles combined/after crossover: 18.3% vs 12.7%, NS First cycle only: 15.5% vs 13.6%, NS Constipation: data for both cycles/ after crossover: 4.3% vs 2.7%, NS Diarrhea: data from both cycles combined (ie, after crossover): 0.87% vs 2.7%, NS	Eligible pts randomized to Ond or Gran at the first cycle; they crossed over to second drug at the second cycle. Just before the third cycle, they were asked which antiemetic they preferred. We report only data from the first antiemetic drug used for the first cycle. Chemo included 5 different regimens containing CP (median dose = 60 mg/m2; dose range = 50-70 mg/m2) and 1 or 2 other drugs including epirubicin (EPI; 50-120 mg/m2) or cyclophosphamide (CTX; 500 mg/m2) or methotrexate (MTX; 40 mg/m2) or vinorelbine (VNR; 25 mg/m2). All regimens were administered IV on Day 1 and repeated every 21-28 days. Alcohol use ≥0.75 liters/day of wine. Pt preference for drugs was conditioned by which antiemetic the pt first received: only 7 (13%) patients preferred Ond vs. 25 (48%) who preferred Gran and 20 (38%) who had no preference when Gran was administered as the first cycle (p=0.019). 23 pts not evaluable at the 2nd cycle: 13 (6 on Gran and 7 on Ond) had a reduced dose of cytotoxic drugs; 9 (2 on Gran and 7 on Ond) did not receive the 2nd cycle at all; and 1 Gran had protocol violation. Cross-over analysis carried out on 101 pts who received both cycles.

Evidence Table 1. Chemotherapy: head-to-head trials

Author Year Setting Hesketh rating	Design	Subpopulation	Intervention	Allow other medication	Run-in/ Wash-out	Age Gender Ethnicity
Massidda 1996b NR 3	NR RCT Parallel	women	Ondansetron iv 8mg Granisetron iv 3mg Tropisetron iv 5mg short	No	NR/NR	51.7 0%male NR
Navari 1995 Multicenter 5	DB RCT Parallel	women	Ondansetron iv 0.45 mg/kg Granisetron iv 10 mcg/kg Granisetron iv 40 mcg/kg 15min	No	NR/NR	62.3 64%male NR

Evidence Table 1. Chemotherapy: head-to-head trials

Author Year Setting Hesketh rating	Screened/ Eligible/ Enrolled	Withdrawn/ Lost to fu/ Analyzed	Other population characteristics
Massidda 1996b NR 3	NR/NR/60	NR/NR/60	Performance status: 0: 42% Performance status: 1: 58% Kinetosis: yes: 7%; no: 93% Alcohol use: > 150ml of table-wine or equivalent: 57% Benzodiazepines concomitant use: 10% H2 antagonists concomitant use: 5% Chemo: Epirubicin high dose: 27%; mitomycin C + methotrexate + mitoxantrone: 15%; cyclophosphamide regimens: 58%
Navari 1995 Multicenter 5	NR/NR/994	7/0/987	Mean weight - 73.43 kg Weight range = 36.3 to 148.8 kg: 0% Mean alcohol consumption = 15.2 units/wk Mean body surface area (m2) = 1.84 Mean cisplatin dose = 81.5 mg/m2 Range of cisplatin doses = 50 to 126 mg/m2 Patients receiving a high dose of cisplatin ≥100mg: 27%

Evidence Table 1. Chemotherapy: head-to-head trials

Author Year Setting Hesketh rating	Results
Massidda **1996b** NR 3	Ond iv 8 vs Gran iv 3 vs Trop iv 5 <u>Complete response: absence of vomiting and none or mild nausea</u> Acute (within 24 h of chemo): 74% vs 58.6% vs 50.8%, NR Delayed (within days 2-5 of chemo): 64% vs 63.7% vs 47.3%, NR <u>Complete protection from nausea: no episodes of nausea</u> Delayed: 50% vs 35% vs 27%, ond. vs gran; p=0.104 Acute: 56% vs 37% vs 20%, ond vs gran: p=0.018 <u>Complete protection from vomiting: no episodes of vomiting</u> Acute: 75% vs 70% vs 72%, NS Delayed: 70% vs 82% vs 27%, NS
Navari **1995** Multicenter 5	Ondansetron vs Granisetron 10 vs Granisetron 40 <u>Total control rate (TCR) (pts did not experience any vomiting, retching, or nausea of any severity and who received no rescue med)</u> Total N of patients: 39% vs 38% vs 41%, NS Females: 28% vs 33% vs 28%, NS High dose of Cisplatin patients: 25% vs 28% vs 33%, NS Males: 46% vs 48% vs 40%, NS <u>No emesis - pts who did not vomit, retch, or receive any rescue medication</u> Total N of patients: 51% vs 47% vs 48%, NS High dose of Cisplatin patients: 35% vs 38% vs 37%, NS Males: 59% vs 50% vs 56%, NS Females: 37% vs 42% vs 34%, NS <u>No nausea - pts who did not experience nausea and did not receive rescue med</u> Total N of patients: 25% vs 28% vs 33%, NS Females: 28% vs 33% vs 29%, NS High dose of Cisplatin patients: 28% vs 28% vs 36%, NS Number of Males: 47 vs 42 vs 49, NS

Evidence Table 1. Chemotherapy: head-to-head trials

Author Year Setting Hesketh rating	Adverse events	Comments
Massidda 1996b NR 3	AE data given: "AEs correlated with the 3 antiemetics were mild and reversible and essentially represented by constipation, headache, and diarrhea."	The only p-values of significance were for Ond vs. Gran (p=0.018) and Ond vs. Trop (p=0.05) in acute nausea; and in delayed nausea: Ond vs. Gran (p=0.104) and Ond vs. Trop (p=0.01).
Navari 1995 Multicenter 5	All treatment groups, data recorded day of treatment and throughout the 5-11 day follow-up period Headache: for total N: 20%, NS Diarrhea: for total N: 17%, NS Constipation: for total N: 14%, NS Fever: for total N: 12%, NS Anorexia: for total: 11%, NS Fatigue: for total: 10%, NS There were no significant differences between treatment groups for incidence or type of AE reported. Changes in vital signs and clinical lab parameters were comparable across study groups and were considered the result of the underlying disease or cytotoxic treatment rather than a consequence of the study drugs.	To maintain blinding, placebo administered as iv 4 & 8 h after chemo in both gran groups. All iv administrations occurred over a 15 min infusion rather than recommended 5-min infusion for granisetron. Alcohol unit - 150 mL wine, 0.25L beer, or 50 mL liquor. Mean values are average units/week over the previous 12 months. The outcomes for the subgroup of patients receiving a high cisplatin dose were further stratified by gender (but we do not report these results in our tables). There were no differences in % of pts who received rescue medication; in each group 43% of patients received additional antiemetics. Time to first nausea and time to first emesis were similar for all treatment groups (data given as graphical representation).

Evidence Table 1. Chemotherapy: head-to-head trials

Author Year Setting Hesketh rating	Design	Subpopulation	Intervention	Allow other medication	Run-in/ Wash-out	Age Gender Ethnicity
Noble **1994** Multicenter 3	DB RCT Crossover	none	Ondansetron iv 24mg/d (8 mg tid) Granisetron iv 3mg/d 5 days	no	none/NR	51.8 77%male NR
Oge **2000** NR 4, 5	NR RCT Parallel	none	ondansetron iv 8mg granisetron iv 3mg Tropisetron iv 5mg	No other antiemetics were given within the first 24 h; after Day2, pts experiencing nausea received metoclopramide 10mg/6hr po.	NR/NR	50.17 64%male NR

Evidence Table 1. Chemotherapy: head-to-head trials

Author Year Setting Hesketh rating	Screened/ Eligible/ Enrolled	Withdrawn/ Lost to fu/ Analyzed	Other population characteristics
Noble **1994** Multicenter 3	NR/NR/359	0/0/359	Mean weight = 67.4 kg (range 39-118 kg) Head and neck cancer: 25% Lung cancer: 18% Ovarian and cervical cancer: 8% Testical cancer: 17% Other cancer: 32% Pts receiving cisplatin in Cycle 1: 83% Mean cis. dose, C.1 (range) = 19.25 (11.3-37.9) Pts receiving ifosfamide in Cycle 1: 17% Mean ifo. dose, for C.1 (range) = 1392 (1018-2455)
Oge **2000** NR 4, 5	NR/NR/106	0/0/106	Primary Tumor: __ Lung: 29%; Nasopharynx: 20% Metastatic carcinoma: 12% Cervix: 8% Larynx: 4% Testis: 3% Adrenal: 3% Ovary: 3% Breast: 2% Thyroid: 2% Primary Tumor: Lymphoma: 2% Primary Tumor: Bladder: 2% Primary Tumor: Other: 11% Chemo: Cisplatin + 5FU: 33%; Cisplatin+ Etoposide: 18%; EAP: 11%; CIF: 7%; Cisplatin+Vinalbine: 5%; BEP: 4%; MIC: 4%; Cisplatin+Gemsitabine: 3%; Other chemo: 16%

Evidence Table 1. Chemotherapy: head-to-head trials

Author Year Setting Hesketh rating	Results
Noble **1994** Multicenter 3	Granisetron vs Ondansetron vs undecided Patient preference: 34% vs 25.6% vs 39.2%, p=0.048 Ondansetron vs Granisetron Other efficacy results: No vomiting and treatment failure, cycle 1 No vomiting: (0-24h): 90.7% vs 94.9%, NS 0-5 days: 45.4% vs 44.3%, NS Treatment failure (>4 vomits): 0-24h: 2.2% vs 2.3%, NS 0-5 days: 21.3% vs 20.5%, NS
Oge **2000** NR 4, 5	*ond iv 8 vs gran iv 3 vs Tropisetron* Complete response (CR): no vomiting or retches Acute (24h): 51.4% vs 65.7% vs 61.1%, NS Delayed (24-72h): 48.5% vs 55.5% vs 48.5%, NS Partial response (PR): 1-2 vomits, or mild to moderate nausea, or 1-3 retches Acute (24h): 22.8% vs 22.8% vs 19.4%, NS Delayed (24-72h): 22.8% vs 25% vs 37.1%, NS Failure: >2 vomits or >3 retches or severe nausea Acute (24h): 25.7% vs 11.4% vs 19.4%, NS Delayed (24-72h): 28.5% vs 19.4% vs 14.2%, NS

Evidence Table 1. Chemotherapy: head-to-head trials

Author Year Setting Hesketh rating	Adverse events	Comments
Noble **1994** Multicenter 3	Ondansetron vs Granisetron <u>Any adverse event, cycle 1</u> Any serious AE (non-specific): 6.0% vs 6.3%, NS Any AE (non-specific): 67.8% vs 67.6%, NS <u>Specific adverse events for Cycle 1</u> Pain: 12.0% vs 14.8%, NS Insomnia: 6.0% vs 5.1%, NS Headache: 19.1% vs 18.2%, NS Constipation: 18.0% vs 19.9%, NS Hypertension: 6.0% vs 4.5%, NS Decreased Appetite: 6.0% vs 2.8%, NS Diarrhea: 7.7% vs 4.5%, NS	Double dummy study. After cross-over, pts received other antiemetic therapy. 5% of patients in both groups discontinued treatment due to poor antiemetic efficacy at cycle 1 [approx. Ond = 9 pts (of 183) and Gran = 9 pts (of 176)]. Pts who experienced breakthrough nausea and/or vomiting received up to 2 further blinded doses of Gran 3mg iv (pts receiving gran) or placebo Gran (pts receiving Ond). Any subsequent uncontrolled nausea and vomiting was treated with a standard antiemetic of the MD's choice and the pt was withdrawn from that cycle. These pts were eligible for inclusion in the second treatment cycle. Pts were in hospital for each of the 5-day chemo cycles. Data for Cycle 1 and cycle 2 reported in study; we only looked at Cycle 1 data (i.e., pre-cross-over data). Cycle 1 contained 359 pts; cycle 2 contained 309 pts. Times to first vomiting episode and first use of rescue were significantly longer in Cycle 1 than cycle 2 (p=0.029 and p=0.036, respectively) and approached significance for time to first episode of moderate or severe nausea (p=0.074).
Oge **2000** NR 4, 5	All drugs combined <u>Headache</u>: 3.8%, NR <u>Constipation</u>: 0.94%, NR	E= etoposide; P= Cisplatin; B= Bleomycin; D= doxorubicin; I= Ifosfamide; M= mitomycin; C= cisplatin (?); F= 5-Fluourouracil. No pts were excluded from the study due to adverse effects. There were no differences in adverse effects in the 3 different drug groups.

Evidence Table 1. Chemotherapy: head-to-head trials

Author Year Setting Hesketh rating	Design	Subpopulation	Intervention	Allow other medication	Run-in/ Wash-out	Age Gender Ethnicity
Park 1997 Single Center 5	Open CT Parallel	none	Granisetron iv 3mg 1 day Ondansetron iv + po 24mg 5 day	No	No/NR	51 53%male NR
Perez 1998 Multicenter 4	DB RCT Parallel	women, corticosteroid use	Ondansetron iv 32mg Granisetron po 2mg 15min	Prednisone ≤ 10 mg daily (or other equivalent corticosteroid dose) was allowed at any time. Prophylactic dexamethasone and methylprednisolone were allowed as a component of pretherapy.	Dexamethasone and methylprednisolone was permitted/NR	55.6 20%male NR

Evidence Table 1. Chemotherapy: head-to-head trials

Author Year Setting Hesketh rating	Screened/ Eligible/ Enrolled	Withdrawn/ Lost to fu/ Analyzed	Other population characteristics
Park 1997 Single Center 5	NR/NR/97	2/NR/95	Primary Tumor: Head and neck: 19% Stomach: 33% Esophagus: 3% Colorectal: 14% Breast: 20% Gynecologic: 2% Soft tissue sarcoma: 4% Pancreatcobilary: 3% Other: 2% Chemo: Cisplatin 80mg/mean: 85% Cisplatin 100mg/mean: 67% Chemo: Adriamycin: 15% Chemotherapy naïve: 74% Chemotherapy non-naïve: 26%
Perez 1998 Multicenter 4	NR/NR/1085	16/1/1085	Breast cancer: 60% Lymphatic/hematologic malignancies: 13% Respiratory/intrathoracic malignancies: 13% IV Dexamethasone mean dose = 15.2 mg Oral dexamethasone mean dose = 15.3 mg Using prophylactic corticosteroids: 81%

Evidence Table 1. Chemotherapy: head-to-head trials

Author Year Setting Hesketh rating	Results
Park **1997** Single Center 5	Ondansetron vs Granisetron Complete Response: no vomiting and no use of rescue medication Acute (within 24h): 45.8% vs 53.2%, NS Days 2-7: 27.1% vs 29.8%, NS Major response: 1-2 episodes of vomiting or moderate to severe nausea Acute (within first 24 hours): 27.1% vs 23.4%, NS Days 2-7: 27.1% vs 29.8%, NS Minor response: 2-4 vomiting episodes, regardless of nausea Acute (within first 24 hours): 20.8% vs 17.0%, NS Days 2-7: 33.3% vs 34.0%, NS Failure: >4 episodes of vomiting Days 2-7: 12.5% vs 14.9%, NS Acute (within first 24 hours): 6.3% vs 6.4%, NS Need for rescue treatment Acute: 14.6% vs 14.9%, NS Delayed: 27.7% vs 31.3%, NS
Perez **1998** Multicenter 4	Ondansetron iv vs Granisetron po Total control (no emesis (vomiting or retching), no nausea of any severity, and no use of any rescue medication: Total control for 0-24h after study period 0: Users of dexamethasone/methylprednisolone: 59.8% vs 61.9%, NS Males: 74.8% vs 75.0%, NS Carboplatin pts: 72.6% vs 74.0%, Cyclophosphamide pts: 54.2% vs 55.3% Nonusers of dexamethasone/methylprednisolone: 50% vs 48.5%, NS All pts: 58.0% vs 59.4%, NS Total control for 0-48h after study period 0: Cyclophosphamide pts: 39.8% vs 41.5%, NA Nonusers of dexamethasone/methylprednisolone: 40% vs 39.6%, NS Users of dexamethasone/methylprednisolone: 44.7% vs 48.3%, NS Females: 66.4% vs 65.2%, NS All pts: 43.8% vs 46.7%, NS Carboplatin pts: 57.5% vs 63.9%, NA Patients who were emesis free (ie, incidence of emesis measurement) All pts (0-24h): 72.6% vs 71.0%, NS Females (0-24h): 69.7% vs 67.7%,

Evidence Table 1. Chemotherapy: head-to-head trials

Author Year Setting Hesketh rating	Adverse events	Comments
Park **1997** Single Center 5	Gran iv 3 vs Ond iv 32 All Adverse events Headache: 6.4% vs 8.3%, NS Dyspepsia: 4.3% vs 2.1%, NS Diarrhea: 4.3% vs 6.3%, NS Decreased Appetite: 0% vs 2.1%, NS Agitation: 0% vs 0%, NS Somnolence: 0% vs 0%, NS Constipation: 10.6% vs 8.3%, NS	Pts were to receive 80-100 mg/m2 of cisplatin or 40 mg/m2 doxorubicin.
Perez **1998** Multicenter 4	Ondansetron iv vs Granisetron po Any adverse event experienced: 76.2% vs 77.1%, NR Headache: 21.0% vs 20.6%, NR Asthenia: 18.0% vs 16.2%, NR Constipation: 10.9% vs 12.9%, NR Diarrhea: 6.3% vs 6.6%, NR Dizziness: 9.6% vs 5.4%, 0.011 Insomnia: 4.8% vs 5.2%, NR Dyspepsia: 5.2% vs 5.0%, NR Decreased Appetite: 5.0% vs 4.6%, NR Abnormal Vision: 4.2% vs 0.6%, p<0.001 Total withdrawals: 2.6% vs 0.55%, Withdrawals due to AEs: Total patients Wtihdrawals due to AEs - drug group not specified: 0.28%,	Double-dummy study. The prophylactic corticosteroid (dexamethasone or methylprednisolone) usage was equivalent between the two study groups. One alcohol unit = 5.07 oz wine; 8.46 oz beer; 1.69 oz spirits. Mild nausea = easily tolerated by pt, causing minimal discomfort and not interfering with normal everyday activities. Moderate nausea = sufficiently discomforting to interfere with normal everyday activities. Severe nausea = incapacitating and prevented normal everyday activities. P-values are NS unless a value or NR ("not reported") is given. Withdrawals are given, but it is not stated when these withdrawals occurred, and if the total N=1085 includes these 17 withdrawals or not. Dexamethasone and methylprednisolone was permitted as a prophylactic component of pretherapy.

Evidence Table 1. Chemotherapy: head-to-head trials

Author Year Setting Hesketh rating	Design	Subpopulation	Intervention	Allow other medication	Run-in/ Wash-out	Age Gender Ethnicity
Perez 1998a Multicenter 3, 4	DB RCT Crossover	women, breast cancer	Granisetron iv 0.01mg/kg 30 sec Ondansetron iv 32mg 15 min	Dexamethasone (Dex) or methylprednisolone permitted at physician's discretion; if given in cycle1, the same medication and dose was required to be given in cycle 2.	No/NR	51.6 0%male White: 439 (76.6) Black: 85 (14.8) Asian: 11 (1.9) Other: 38 (6.6%)
Poon 1997 Single Center 4	DB RCT Crossover	women, breast cancer	Ondansetron iv 16mg Granisetron iv 3mg	Not allowed	NR/NR	47 0%male Chinese = 100%

Evidence Table 1. Chemotherapy: head-to-head trials

Author Year Setting Hesketh rating	Screened/ Eligible/ Enrolled	Withdrawn/ Lost to fu/ Analyzed	Other population characteristics
Perez 1998a Multicenter 3, 4	NR/NR/623	//623	Mean body weight (+/- SD) = 75.3 kg (+/- 18.5) (Body weight range = 37.3 - 166.8 kg) Mean alcohol units/week = 2.00 units/week (range = 0 - 73.4 units/wk)
Poon 1997 Single Center 4	NR/NR/20	0/0/20	Breast cancer: 100% Radical mastectomy: 90% Wide local excision plus axillary dissection: 10%

Evidence Table 1. Chemotherapy: head-to-head trials

Author Year Setting Hesketh rating	Results
Perez **1998a** Multicenter 3, 4	Ondansetron vs Granisetron Emesis-free and nausea-free patients at 24 h Emesis free pts at 24h (both cycles combined): 62.7% vs 58.6%, NS Emesis free pts at 48h (both cycles combined): 45.0% vs 42.2%, NS Nausea free pts at 24h (both cycles combined): 48.5% vs 44.0%, 0.034 Nausea free pts at 48h (both cycles combined): 31.0% vs 26.7%, 0.021 Patient preference for study medication Patient preference for study medication: 50.9% vs 49.1%, NR Total control during 48 h period: no nausea, emesis, or antiemetic rescue Total emetic control at 24h (both cycles combined): no nausea, emesis, or antiemetic rescue: 48.3% vs 44.0%, 0.04 Total emetic control at 48h (both cycles combined): no nausea, emesis, or antiemetic rescue: 30.5% vs 26.2%, 0.024
Poon **1997** Single Center 4	Ondansetron vs Granisetron Acute vomiting: complete, major, minor responses, and failure Failure (>5 vomiting episodes): 5% vs 5%, NS Complete response (no vomiting): 67.5% vs 72.5%, NS Minor response (3-5 vomiting episodes): 5% vs 7.5%, NS Major response (1-2 vomiting episodes): 22.5% vs 25%, NS Delayed vomiting: complete, major, minor responses, and failure Failure (>5 vomiting episodes): 12.5% vs 10%, NS Minor response (3-5 vomiting episodes): 15% vs 17.5%, NS Complete response (0 vomiting episodes): 55% vs 52.5%, NS Major response (1-2 vomiting episodes): 17.5% vs 20%, NS Acute nausea: no, mild, moderate, and severe nausea Severe nausea (bedridden because of nausea): 10% vs 10%, NS Moderate nausea (interfereswith daily life): 10% vs 15%, NS Mild nausea (interferes with eating): 45% vs 37.5%, NS No nausea: 35% vs 37.5%, NS Acute nausea: Mean VAS score (range): 2.5(0-8) vs 2.2(0-9), NS Delayed nausea: no, mild, moderate, and severe nausea Moderate nausea (interferes with daily life): 15% vs 22.5%, NS Severe nausea (beridden because of nausea): 7.5% vs 10%, NS Mild nausea (interferes with eating): 52.5% vs 40%, NS No nausea: 25% vs 27.5%, NS Delayed nausea: Mean VAS score (range): 2.8 (0-9) vs 2.9 (0-9), NS

Evidence Table 1. Chemotherapy: head-to-head trials

Author Year Setting Hesketh rating	Adverse events	Comments
Perez **1998a** Multicenter 3, 4	Ondansetron vs Granisetron vs both drugs All adverse events >5% (excluding death) Diarrhea: 5.9% vs 7.7% vs 2.8%, Abnormal vision: 6.3% vs 0.4% vs 0%, p=0.001 Constipation: 6.3% vs 5.1% vs 3%, Dizziness: 14.0% vs 5.2% vs 2.8%, Fatigue: 14.3% vs 11.3% vs 5.2%, Headache: 14.3% vs 15.7%, Patients experiencing any AE: 75.4% vs 72.1% vs 42.9%, Anorexia: 5.4% vs 3.6% vs 0.9% An AE that began in cycle1 and continued unchanged was not considered an AE in cycle 2.	573/623 pts crossed over to both drugs. An alcohol unit is equivalent to 5.07 fl oz wine, 8.46 fl oz of beer, or 1.69 fl oz of spirits. Cycle 1: Dex and Pred were given to 82.3% of Gran pts and 79.8% of Ond pts; in cycle 2, those numbers were 80.1% and 82.1% Mean cyclophosphamide dose was 591.3 (Gran) and 575.1 (Ond) mg/m2 for cycle 1 and 572.2 (Gran) and 589.6(Ond) mg/m2 for cycle 2. Mean doxorubicin dose range was 53.7(Gran) and 53.9(Ond) mg/m2 for cycle 1 and 53.5(Gran) and 53.7(Ond) mg/m2 for cycle 2. A cycle effect was seen at 48 hours (p=0.024) with higher total control rates during Cycle 2 than during cycle 1.
Poon **1997** Single Center 4	Ondansetron vs Granisetron Constipation: 30% vs 20%, NS Headache: 25% vs 20%,	The first two cycles of chemo for each pt were used for the trial. Pts were randomized to receive either Gran on Day 1 followed by Ond on Day 8 or Ond on Day 1 and Gran on Day 8. The order of the drugs were reversed in the second cycle. A total of 40 cycles were analyzed; and the data is given in terms of these cycles. Acute vomiting/nausea = in the first 24 h after chemo; delayed nausea vomiting = in the following 7 days after chemo. Chemo given after resection of breast cancer.

Evidence Table 1. Chemotherapy: head-to-head trials

Author Year Setting Hesketh rating	Design	Subpopulation	Intervention	Allow other medication	Run-in/ Wash-out	Age Gender Ethnicity
Raynov 2000 Single Center 5	Open RCT Parallel	none	MCL- day 1: 2mg/kg MCL- days 2-6: 1mg/kg Ondansetron: 8 mg all days Granisetron: 3mg all days Tropisetron: 5mg all days	yes, for some arms.	NR/NR	49 89%male NR
Ruff 1994 Multicenter 5	DB RCT Parallel	none	Ondanstron iv 8mg Ondansetron iv 32mg Granisetron iv 3mg once	No	No/NR	55 56%male NR
Slaby 2000 Single Center 5	not specified RCT Parallel	ASCT	Ondansetron iv 16mg Granisetron iv 3mg Tropisetron iv 5mg 7 days	20 mg iv dexamethasone was added to antiemetics in case of its failure.	NR/NR	38.0 67%male NR

Evidence Table 1. Chemotherapy: head-to-head trials

Author Year Setting Hesketh rating	Screened/ Eligible/ Enrolled	Withdrawn/ Lost to fu/ Analyzed	Other population characteristics
Raynov 2000 Single Center 5	NR/NR/72	0/0/72	Primary Tumor- Lung: 54% Primary Tumor- Testis: 31% Primary Tumor- Ovary: 11% Primary Tumor- Head and Neck: 4% Chemo: Cisplatin monotherapy (120 mg/m2): 25% Chemo: Cisplatin (≥ 50) + Cycophosphamide (≥500): 75% Chemo: Cisplatin (≥ 50) + Doxorubicin (≥ 50): 8% Chemo: Cisplatin (≥ 50) + Vinblastine (5): 31% Chemo: Cisplatin (≥ 50) + Bleomycin (30 flat dose): 31% Mean cisplatin dose = 75 mg/m2
Ruff 1994 Multicenter 5	NR/NR/NR	1/NR/Various	Age: 30-65: 75% Age: >66: 20% Alcohol use: current> 4units/day: 9% previous> 4units/day: 15% cisplatin dose: >100 mg/m2: 14% emetic potential: none: 25%; low: 42%; moderate: 32% Primary tumor: Gynecolgical: 30% Lung; 25%; Head and neck: 23%; Genitourinary: 9% Gastrointestinal: 8%; Bone/soft tissue: 2% Median cisplatin dose = 78 mg/m2 Mean body surface area = 1.73 m2
Slaby 2000 Single Center 5	NR/NR/45	0/0/45	BEAM 200: 67% BEAM 400: 33% Lineages of previous therapy = 2%; range = 1%-5% Previous chemo-induced nausea: 91% Previous chemo-induced vomitus (emesis): 73%

Evidence Table 1. Chemotherapy: head-to-head trials

Author Year Setting Hesketh rating	Results
Raynov **2000** Single Center 5	MCL vs MCL + CS vs OND vs Ond + CS vs Granisetron Need for Rescue Therapy: 29% vs 16% vs 6% vs 3% vs 22.2%, NR Ondansetron vs Ond + CS vs Gran vs Gran + CS vs Tropisetron Complete response for vomiting: No emetic episodes Acute: 63.9% vs 85.7% vs 22.2% vs 100% vs 45.4%, NR Delayed: Overall and major response for vomiting Major response for vomiting (1-2 emetic episodes): acute: 16.7 % vs 8.6% vs 33.3% vs 0% vs 27.3%, NR Overall response for vomiting (no episodes (CR) plus 1-2 emetic episodes): acute: 80.6% vs 94.3% vs 55.6% vs 100% vs 72.7%, NR No nausea: acute: 63.9% vs 85.7% vs 22.2% vs 84.7% vs 45.4%, NR Mild nausea and overall (mild+none) response for nausea Mild Nausea: acute: 22.1% vs 7.3% vs 33.3% vs 14.3% vs 40.9%, NR Overall response: no nausea + mild nausea: acute: 86% vs 93% vs 55.6% vs 100% vs 86.4%, NR
Ruff **1994** Multicenter 5	Ond 8 mg vs Ond 32 mg vs Gran 3 mg Complete response: no emetic episodes: 59% vs 51% vs 56%, NS Ondansetron 8 mg vs Ondansetron 32 m vs Gransetron 3 mg Moderate response: 1-2 emetic episodes: 17% vs 23% vs 22%, NS Nausea: none and/or mild Mild: 15% vs 21% vs 17%, NS Either none or mild combined: 71% vs 69% vs 73%, NS None: 56% vs 48% vs 56%, NS Gran 3 vs Ond 8 vs Ond 32 Pt satisfaction scores: 0= not at all satisfied to 100=completely satisfied: 89 vs 91 vs 85, NS
Slaby **2000** Single Center 5	Ondansetron vs Granisetron vs Tropisetron Nausea and/or emesis control failure (for 6 and 10 days) 10 days: 80% vs 46.7% vs 33.3%, Gran and Trop vs. ond: p=0.03 6 days: 26.7% vs 33.3% vs 13.3%, NS Emesis control failure (6 and 10 days) Emesis control failure (6 and 10 days) 10 days: 46.7% vs 26.7% vs 6.7%, Gran and trop vs. Ond; p=0.04 6 days: 6.7% vs 0% vs 0%, NS

Evidence Table 1. Chemotherapy: head-to-head trials

Author Year Setting Hesketh rating	Adverse events	Comments
Raynov 2000 Single Center 5		Rescue medication was given to pts with ≥ 2 episodes of vomiting or severe chemo-induced nausea.
Ruff 1994 Multicenter 5	Ond 8 mg vs Ond 32 mg vs Gran 3 mg Overall Constipation: 0.61% vs 0% vs 2.4%, NS Diarrhea:1.2% vs 3.1% vs 0%, NS Headache: 12.1% vs 9.8% vs 6.5%, NS Total number of patients experiencing AEs: 14.5% vs 15.3% vs 14.7%, NS Dizziness: 0.61% vs 1.8% vs 0.59%, NS	
Slaby 2000 Single Center 5	Ondansetron vs Granisetron vs Tropisetron Headache: 53.3% vs 33.3% vs 20%, NS Total patients: Asthenia: 4.4%, NR	BEAM conditioning regimen consists of 4 cytotoxic drugs: Day 1 = carmustine 300 mg/m2; Day 2-5: etoposide 200 or 400 mg/m2/day; Day 2-5: cytosine arabinoside 400 mg/m2/day; Day 6: melphalan 140 mg/m2. Thus, two separate regimens: BEAM 200 (etoposide 200 mg/m2/day) and BEAM 400 (etoposide 400 mg/m2/day). The highest incidence of nausea and/or emesis control failures occurred on Day 3 (6 pts) and on Day 7 (7 pts). The maximum incidence of vomiting was observed from Days 7-10 (the post-chemo period). Constipation was not markedly pronounced in the pts.

Evidence Table 1. Chemotherapy: head-to-head trials

Author Year Setting Hesketh rating	Design	Subpopulation	Intervention	Allow other medication	Run-in/ Wash-out	Age Gender Ethnicity
Spector 1998 Multicenter 5	DB RCT Parallel	none	Ondansetron po (tablet) 24mg Granisetron i.v. 0.10 mg/kg	No concurrent use of corticosteroids (including dexamethasone) allowed.	None/None	64.05 56%male Caucasian = 90%

Evidence Table 1. Chemotherapy: head-to-head trials

Author Year Setting Hesketh rating	Screened/ Eligible/ Enrolled	Withdrawn/ Lost to fu/ Analyzed	Other population characteristics
Spector **1998** Multicenter 5	NR/NR/371	//371	Mean height = 169.4 cm: Mean weight = 72.55 kg Mean cisplatin dose = 65.4 mg/m2 Median cisplatin dose = 70 mg/m2 Range of cisplatin dosage = 31-100 mg/m2 Lung cancer: 59% Gynecological cancer: 10% Genitourinary cancer: 9% Gastrointestinal cancer: 8% Head/neck cancer: 7% Other cancer types: 7%

Evidence Table 1. Chemotherapy: head-to-head trials

Author Year Setting Hesketh rating	Results
Spector **1998** Multicenter 5	Ondansetron po vs Granisetron iv Therapeutic failures Withdrawal prior to failure: 1% vs 1%, >5 emetic episodes over 24 h: 27% vs 35%, Number with need for rescue therapy due to severity of nausea or vomiting: 50 vs 64, NS Complete response (CR): no emetic episodes and no use of rescue medications Males: 67% vs 59%, NS Females: 46% vs 41%, NS No emetic episodes and no use of rescue medication: 58% vs 51%, NS Major response MR (1-2 emetic episodes): 11% vs 10%, NS Minor response (3-5 emetic episodes): 3% vs 3%, NS Patient Assessments Of Nausea: no nausea over 24h (complete control: no nausea, rescue, or withdrawal): 43% vs 35%, NS Of Appetite: Worse than usual at 24h: 43% vs 44%, NS Of Appetite: As usual at 24h: 53% vs 52%, NS Of Appetite: Better than usual at 24h: 4% vs 4%, NS Patient Satisfaction with Antiemetic Therapy at 24h: very plus somewhat satisfied: 88% vs 83%, NS CR + MR CR + MR: 68% vs 61%, NS

Evidence Table 1. Chemotherapy: head-to-head trials

Author Year Setting Hesketh rating	Adverse events	Comments
Spector **1998** Multicenter 5	Ondansetron vs Granisetron <u>Adverse events</u> Fever: 3% vs 1%, NS Diarrhea: 3% vs 0.5%, NS Malaise/fatigue: 3% vs 4%, NS Constipation: 0.5% vs 2%, NS Any adverse event experienced: 24% vs 28%, NS Headache: 7% vs 12%, NS	Study protocol amended after the study initiation to allow use of carboplatin at a dose of >200 mg/m2 instead of cisplatin. P-values NS if no value specified. Chemo: cisplatin 50-75 mg/m2 administered as a single iv infusion over a period of ≤ 3 hrs (co-administration of other chemo agents was permitted at the discretion of the investigator, with the exception of cyclophosphamide at a dose of ≥500 mg/m2, nitrogen mustard, dacarbazine (DTIC), procarbazine, carmustine, and ifosfamide). No statistically significant differences existed between treatment groups for time to treatment failure. Of pts who failed treatment, few did so within the first 3h; most failed between 6-24h after the start of chemo. N of pts who finished appetite survey at 24h: Ond = 136/184 (73.9%) and Gran = 129/187 (69.0%). No explanation or reason given as to why drop in numbers occurred for this part of the study.

Evidence Table 1. Chemotherapy: head-to-head trials

Author Year Setting Hesketh rating	Design	Subpopulation	Intervention	Allow other medication	Run-in/ Wash-out	Age Gender Ethnicity
Stewart, A. 1995 Multicenter 4	DB RCT Parallel	women	Ondansetron iv+po 16mg Ondansetron po only 16mg Granisetron iv only 3mg 5 days	NR	NR/NR	50.3 0%male NR

Evidence Table 1. Chemotherapy: head-to-head trials

Author Year Setting Hesketh rating	Screened/ Eligible/ Enrolled	Withdrawn/ Lost to fu/ Analyzed	Other population characteristics
Stewart, A. **1995** Multicenter 4	NR/NR/514	16/10/488	Mean surface area = 1.70 m2: 95% Chemo: cyclophosphamide: 1% Chemo: CMF: 45% Chemo: AC combinations: 3% Chemo: EC combinations: 33% Other Cyclophosphamide combinations: 12%

Evidence Table 1. Chemotherapy: head-to-head trials

Author Year Setting Hesketh rating	Results
Stewart, A. **1995** Multicenter 4	Ondiv +po vs Ond po vs Gran iv Emesis control: Acute (day 1) Results No. of pts with no emetic episodes: Complete response: acute: 77.7% vs 78.1% vs 77.2%, NS No. of pts for whom data were missing: acute: 0.6% vs 6.4% vs 3.6%, NS No. of pts with 1-2 emetic episodes: acute: 10.8% vs 8.4% vs 9.6%, NS Rescued/withdrawan due to lack of response: acute: 1.8% vs 7.7% vs 4.2%, 0.014 Emesis control: Worst Day of Days 1-5 Results No emetic episodes days 1-5: Complete response: delayed: 58.1% vs 58.1% vs 52.4%, NS No. of pts for whom data were missing: 0.6% vs 0% vs 3.6%, NR Rescue/withdrawn due to lack of response days 1-5: 16.8% vs 20% vs 25.3%, P 1-2 emetic episodes days 1-5: 16.8% vs 10.9% vs 12.0%, NS Nausea control: Acute (day 1) Results No. of pts with moderate nausea episodes: acute: 12.6% vs 10.9% vs 15.1%, NS No. of pts with mild nausea episodes: acute: 28.1% vs 21.9% vs 18.7%, NS Severe nausea or rescued/withdrawn due to lack of response: acute: 8.4% vs 11.6% vs 9.6%, NS No. of pts for whom data was missing: acute: 0.6% vs 0.6% vs 4.8%, NR No. of pts with no nausea episodes: acute: 50.3% vs 54.8% vs 51.8%, NS Nausea control: worst day of Days 1-5 No. of pts experiencing no nausea days 1-5: 32.9% vs 33.5% vs 24.1%, see note No. of pts experiencing mild nausea: 29.3% vs 18.1% vs 23.5%, NS No. of pts experiencing moderate nausea: 18.0% vs 16.8% vs 18.7%, NS Severe nausea or rescued/withdrawn due to lack of response: 19.2% vs 31.0% vs 30.1%, NS No. of pts for whom data were missing: 0.6% vs 6.4% vs 3.6%, NR Gran iv vs Ond iv/po vs Ond po Global satisfaction with treatment Global satisfaction with treatment median score: 89% vs 91% vs 93%, NS

Evidence Table 1. Chemotherapy: head-to-head trials

Author Year Setting Hesketh rating	Adverse events	Comments
Stewart, A. **1995** Multicenter 4	Ond iv+po vs Ond po only vs Gran Constipation: 11.1% vs 6.3% vs 7.8%, NS Headache: 7.8% vs 9.5% vs 8.4%, NS The most common AEs occurred in >1% of the study population according to treatment group.	Adverse events analyses were for all 514 patients randomized; ITT analysis (488 of 514) excluded 26 pts: 16 received incorrect antiemetics treatment prior to chemo and 10 received antiemetic treatment that was not clearly documented. CMF = cyclophosphamide + methotrexate + 5-fluorouracil; AC combinations = adriamycin + cyclophosphamide + others (e.g., 5-fluorouracil, vincristine); EC combinations = epirubicin + cyclophosphamide + others (e.g., 5-fluorouracil, vincristine). For nausea control, the severity of nausea was significantly reduced with both Ond regimens compared to the Gran group (p=0.009) over the 5 day period.

Evidence Table 1. Chemotherapy: head-to-head trials

Author Year Setting Hesketh rating	Design	Subpopulation	Intervention	Allow other medication	Run-in/ Wash-out	Age Gender Ethnicity
Stewart L. 2000 Single Center 5	DB RCT Crossover	none	Ondansetron iv 8mg Granisetron iv 3mg	8-mg IV bolus of dexamethasone was given with the antiemetic on Day1; and 4 mg dex po was given tid on days 2-4 and/or metoclopramide 0 or 20 mg orally on days 2-4.	NR/NR	56 43%male NR
Yalcn 1999 Single Center 3	NR RCT Parallel	women	Granisetron iv 3mg Tropisetron iv 5mg Ondansetron iv 8mg	No	No/NR	44.0 2%male NR
Zeidman 1998 Single Center 3, 4, 5	NR RCT Parallel	none	ondansetron iv & po 16mg granisetron iv 3mg	No	none/none	55 71%male NR

Evidence Table 1. Chemotherapy: head-to-head trials

Author Year Setting Hesketh rating	Screened/ Eligible/ Enrolled	Withdrawn/ Lost to fu/ Analyzed	Other population characteristics
Stewart L. 2000 Single Center 5	NR/NR/21	5/NR/16	Cisplatin mean dose 74 mg/m2 (range: 59-100 mg/m2)
Yalcn 1999 Single Center 3	NR/NR/54	0/0/54	Breast Cancer: 100% Chemo: CMF: 31% Chemo: CAF: 33% Chemo: CEF: 35%
Zeidman 1998 Single Center 3, 4, 5	NR/NR/60	2/0/58	hematological neoplasms: 81% lymphoproliferative disorders: 53% multiple myeloma: 16% acute myeloid leukemia: 12% solid tumors: 19% Highly emetogenic chemo: adriamycin-cisplatin group: 55% Moderately emetogenic chemo regimens: 45%

Evidence Table 1. Chemotherapy: head-to-head trials

Author Year Setting Hesketh rating	Results
Stewart L. **2000** Single Center 5	Ondansetron vs Granisetron <u>Severity of nausea</u> Day 1 mean nausea score (scale: 0-3): 0.65 vs 0.44, NS Day 2 mean nausea score (scale: 0-3): 1.0 vs 1.48, NR Day 7 mean nausea score (scale: 0-3): 0.7 vs 0.8, NR % of courses where pts had no nausea or mild nausea on day 1 Number(% of courses): 36 cycles(90%) vs 46 cycles(94%), NR <u>Number of episodes of retching or vomiting</u> Day 1 mean no. of vomiting episodes: 0.68 vs 0.43, NR Day 2 mean no. of vomiting episodes: 2.50 vs 0.8, NR Day 7 mean no. of vomiting episodes: 0.55 vs 0.60, % of course where pts suffered from no vomiting on day 1: 77.5% vs 88%, NR
Yalcn **1999** Single Center 3	
Zeidman **1998** Single Center 3, 4, 5	Adriamycin/cis. vs Moderate regimens <u>Sensation of nausea</u> Nausea, stratified by chemo type: 15.6% vs 11.5%, NR Sensation: 25% vs 7%, NR Ondansetron vs Granisetron <u>Episodes of vomiting</u> Episodes: 29% vs 13.3%, NR Vomiting, stratified by chemo type: 22% vs 8%, NR

Evidence Table 1. Chemotherapy: head-to-head trials

Author Year Setting Hesketh rating	Adverse events	Comments
Stewart L. **2000** Single Center 5		The study was designed with a random allocation using a Latin square design in sets of four. First day was a head-to head of the study drugs; days 2-4 only corticosteroids (not the study drugs) were administered. No data on adverse events were given. Data on days 2-4, though given in study, are not reported here. Dex = dexamethasone; meto = metoclopramide. Emesis control info was colledted for 16 pts (10 women, 6 men) who had received >1 treatment each of Ond and Gran. 40 course of Ond and 49 course of Gran were studied. Citerion for success would be that pts would suffer no more than mild nausea on Day 1.
Yalcn **1999** Single Center 3	No details on adverse events other than "the adverse events, includig headaches, constipation, diarrhea, and insomnia, were rare and mild in all groups" given.	Chemo treatment: Cyclophosphamide, adriamycin, 5-fluorouracil (CAF); Cyclophosphamide, epirubicin, 5-fluorouracil (CEF); Cyclophosphamide, methotrexate, 5-fluorouracil (CMF); all were single day chemotherapy.
Zeidman **1998** Single Center 3, 4, 5	AE data: "There were no significant side effects in either antiemetic regimen".	2 pts who withdrew from the original 60 pts randomized were "withdrawn from the study because of refusal to continue". One came from each antiemetic group, and their genders were not specified. This left a group of 58 patients who were analyzed. There were 41 men and 17 women in these 58 patients.

Evidence Table 1. Chemotherapy: head-to-head trials

Author Year Setting Hesketh rating	Design	Subpopulation	Intervention	Allow other medication	Run-in/ Wash-out	Age Gender Ethnicity
Walsh 2004 Multicenter 5	DB RCT Parallel	HSCT	Granisetron iv 0.01mg/kg Ondansetron iv 0.45mg/kg 24hr	All received 10 mg dexamethasone (Dex) iv daily and lorazepam 1 mg iv every 8 hours.	No/NR	52 84%male NR

Evidence Table 1. Chemotherapy: head-to-head trials

Author Year Setting Hesketh rating	Screened/ Eligible/ Enrolled	Withdrawn/ Lost to fu/ Analyzed	Other population characteristics
Walsh **2004** Multicenter 5	NR/NR/110	14/0/96	Primary Cancer- Non-Hodgkin's lymphoma/Hodgkins: 35% Primary Cancer- Breast: 14% Primary Cancer- Other: 14% Primary Cancer- Myeloma: 28% Emesis w/ previous chemo: none-mild: 69% Emesis w/ previous chemo: mod-severe: 17% Emesis w/ previous chemo: unknown: 1% Alcohol intake: none-minimal: 57% Alcohol intake: mod-heavy: 27% Alcohol intake: unk: 3% Chemo: BuCy: 21% Chemo: CBV: 32% Chemo: Melphalan: 15% Chemo: Other: 19%

Evidence Table 1. Chemotherapy: head-to-head trials

Author Year Setting Hesketh rating	Results
Walsh **2004** Multicenter 5	Granisetron vs Ondansetron Complete response: no emetic episodes and none-to-mild nausea Day 1: 83% vs 90%, NS; Day 2: 70% vs 84%, NS; Day 3: 69% vs 79%, NS; Day 4: 54% vs 56%, NS; Day 5: 48% vs 71%, NS; Day 6: 50% vs 46%, NS Major Response: 1-2 emetic episodes and none-to-moderate nausea; or no emetic episodes and moderate nausea Day 1: 13% vs 6%, NS Day 2: 18% vs 10%, NS Day 3: 17% vs 9%, NS Day 4: 23% vs 25%, NS Day 5: 35% vs 18%, NS Day 6: 14% vs 46%, NS Minor Response: 3-5 emetic epsiodes and any degree of nausea; or 0-2 emetic episodes and severe nausea Day 6: 36% vs 8%, NS; Day 5: 17% vs 12%, NS Day 4: 17% vs 17%, NS Day 3: 14% vs 9%, NS Day 2: 7% vs 4%, NS Day 1: 2% vs 2%, NS Failure: ≥6 emetic episodes and nay degree of nausea Day 1: 2% vs 2%, NS Day 2: 5% vs 2%, NS Day 3: 0% vs 2%, NS Day 4: 6% vs 3%, NS Day 5: 0% vs 0%, NS Day 6: 0% vs 0%, NS

Evidence Table 1. Chemotherapy: head-to-head trials

Author Year Setting Hesketh rating	Adverse events	Comments
Walsh **2004** Multicenter 5	Granisetron vs Ondansetron Overall Diarrhea: 9% vs 12%, NS Hypersensitivity: 7% vs 2%, NS Sedation: 9% vs 4%, NS Tremors: 4% vs 2%, NS Other: 9% vs 12%, NS Constipation: 2% vs 4%, NS Hiccups: 26% vs 34%, NS Headache: 2% vs 10%, NS Total withdrawals __ Study drugs combined: 12.7%, Withdrawals due to AEs: 0% vs 0%,	Other meds allowed: antihistamines as premedication for blood transfusions; triazolam or diphenhydramine for insomnia. Chemo: Pts who received bisulfan + cyclophosphamide as regimen did not begin study drug until cycloph. administered since bisulfan has little emetogenic potential. The total days of study drug depended on type of chemo administered; so # of pts reporting data varied/day Rescue medication: prochlorperazine 10mg iv every 6 hrs as needed (if the pts had 3-5 emetic episodes in 24h or if the pt requested it). Pts were removed from study if they experienced a Southwestern Oncology group (SWOG) grade 3 or 4 toxiticy, other than myelotoxicity, unless it was unrelated to the study medication. Reasons 14/110 pts withdrawn after randomization: 5 pts had baseline nausea or vomiting prior to first dose of study drug ; 5 pts received medication with antiemetic activity not permitted during the study period; 1 pt received wrong study drug; 1 pt developed severe opiate-induced confusion and hand tremors (unable to complete the VAS); 2 pts received the scheduled antiemetics incorrectly.

Evidence Table 1. Chemotherapy: head-to-head trials

Author Year Setting Hesketh rating	Design	Subpopulation	Intervention	Allow other medication	Run-in/ Wash-out	Age Gender Ethnicity
Dolasetron vs Ondansetron						
Hesketh 1996 Multicenter 5	DB RCT Parallel	prior chemo	Dolasetron iv 1.8mg/kg Dolasetron iv 2.4mg/kg Ondansetron iv 32mg once	Dex not allowed; for other drugs, see comment	No/NR	62 62%male NR

Evidence Table 1. Chemotherapy: head-to-head trials

Author Year Setting Hesketh rating	Screened/ Eligible/ Enrolled	Withdrawn/ Lost to fu/ Analyzed	Other population characteristics
Dolasetron vs Ondansetron			
Hesketh 1996 Multicenter 5	NR/NR/609	51/NR/558	previous chemotherapy: 8% history of heavy alcohol use: 16% Cancer Site- Lung: 55% Cancer Site- Gastrointestinal: 11% Cancer Site- Gynecologic: 10% Cancer Site- Head/Neck: 11% Cancer Site- Other: 14%

Evidence Table 1. Chemotherapy: head-to-head trials

Author Year Setting Hesketh rating	Results
Dolasetron vs Ondansetron	
Hesketh **1996** Multicenter 5	Dolasetron 1.8 vs Dolasetron 2.4 vs Ondansetron Antiemetic Efficacy: complete response and other parameters Received rescue medication: 33.8% vs 42.0% vs 37.4%, NS Complete + major response: 63.1% vs 54.1% vs 59.2%, NS No emetic episodes and no rescue medication in 24h: 44.4% vs 40.0% vs 42.7%, NS Lower cisplatin dose stratum: 49.2% vs 45.6% vs 50.4%, NS Higher cisplatin dose stratum: 36.8% vs 31.3% vs 31.8%, NS Complete Response by Subgroup No previous chemotherapy: 46% vs 39% vs 42%, NR Narcotic analgesic use: 37.5% vs 34% vs 37%, NR Use of benzodiazepines: 50% vs 18% vs 43%, NR Previous chemotherapy: 27% vs 47% vs 50%, NR Patient ≥ 65 years age: 44% vs 46% vs 45%, NR History of heavy alcohol use: 66% vs 60% vs 56%, NR Female: 21% vs 25% vs 27%, NR Male: 58% vs 49% vs 54%, NR No use of benzodiazepines: 44% vs 42% vs 43%, NR No narcotic analgesic use: 48% vs 44% vs 46%, NR No history of heavy alcohol use: 40% vs 37% vs 40%, NR Median time to the first emetic episode or to rescue medication: 21.5 h vs 19.75 hvs 21.21 h, NS Patient VAS scores for nausea and general satisfaction

Evidence Table 1. Chemotherapy: head-to-head trials

Author Year Setting Hesketh rating	Adverse events	Comments
Dolasetron vs Ondansetron		
Hesketh 1996 Multicenter 5	Dolasetron 1.8 vs Dolasetron 2.4 vs Ondansetron 32 Overall rales: 3% vs 1% vs 2%, NR diarrhea: 14% vs 13% vs 6%, NR fever: 7% vs 6% vs 7%, NR chills: 3% vs 1% vs 2%, NR loose stools: 1% vs 2% vs 2%, NR light-headed feeling: 1% vs 1% vs 2%, NR hypertension: 2% vs 2% vs 2%, NR fluid overload: 1% vs 2% vs 3%, NR AST increased: 2% vs 2% vs 2%, NR headache: 22% vs 22% vs 18%, NR ALT increased: 2% vs 2% vs 2%, NR	These benzodiazepine treatments were permitted: alprazolam if initiated 48h beforestudy; midazolam during 24h before but not during study; temazepam or traizolam 24 h before and during the study. Lorazepam was not allowed during 24h before or during the study except as a rescue. Dexamethasone only allowed as a rescue medication. Pts were stratified into 2 groups: those receiving between 70-91 mg/m2 of cisplatin (mean dose for this group = 74.7 mg/m2) and those receiving cisplatin ≥ 90 mg/m2 (mean dose for this group = 100.6 mg/m2); all cisplatin doses were administered over ≤ 3 hours. Rescue medication was given if a pt requested it or if a pt experienced >2 emetic episodes during the 24h study period. Abstinence from narcotic analgesics, male gender, and a history of heavy alcohol use (present or past use of ≥ 5 drinks/day) were statistically significant predictors of a higher CR rate across all 3 treatment groups.

Evidence Table 1. Chemotherapy: head-to-head trials

Author Year Setting Hesketh rating	Design	Subpopulation	Intervention	Allow other medication	Run-in/ Wash-out	Age Gender Ethnicity
Fauser 1996 Multicenter 3, 4	DB RCT Parallel	women, prior chemo	Dolasetron po 25mg Dolasetron po 50mg Dolasetron po 100mg Dolasetron po 200mg Ondansetron po 32mg	No	NR/NR	53.2 39%male NR

Evidence Table 1. Chemotherapy: head-to-head trials

Author Year Setting Hesketh rating	Screened/ Eligible/ Enrolled	Withdrawn/ Lost to fu/ Analyzed	Other population characteristics
Fauser 1996 Multicenter 3, 4	NR/399/399	1/0/398	Mean height = 165.3 cm Mean weight = 70.7 kg Karnofsky Mean index = 89.0 Non-smoker: 69%; Ex-smoker: 12%; Smoker: 18% Alcohol use - no: 45%; rarely: 39%; occasionally: 12%; regularly: 5% Chemo-naïve: 42% Breast cancer: 57% Lung cancer: 8% Bladder cancer: 5% Colon cancer: 4% Rectal cancer: 3% Small-cell lung cancer: 3% Gastric cancer: 3% Mean Karnofsky status (+/- SD) = 91.4% (+/-10.9) Previous chemo: yes: 54% Chemo: cyclophosphamide: 28%; doxorubicin: 23%; carboplatin: 21%; platinum-based, alone or in combination: 28%; multiple moderately emetogenic non-platinum: 37% Primary neoplasm: breast cancer: 40%; lung cancer: 21%

Evidence Table 1. Chemotherapy: head-to-head trials

Author Year Setting Hesketh rating	Results
Fauser **1996** Multicenter 3, 4	Dol po 25 vs Dol po 50 vs Dol po 100 vs Dol po 200 vs Ond po 32 Complete response (no emetic episodes and no need for rescue medication): All pts: 45.0% vs 49.4% vs 60.5% vs 76.3% vs 72.3%, p Dolasetron 25 vs Dolasetron 50 vs Dolasetron 100 vs Dolasetron 200 vs Ond po 32 Complete + major response: 57.5% vs 59.5% vs 72.4% vs 85.0% vs 78.3%, p Dolasetron 25 vs Dolasetron 50 vs Dolasetron 100 vs Dolasetron 200 vs Ondansetron No response: >2 emetic episodes; received escape antiemetic medicaiton; or did not have data for ≥ 23.5h after chemo: 42.5% vs 40.5% vs 27.6% vs 15.0% vs 21.7%, NS Median time to first emetic episode (hours): 19.58 vs 21.75 vs >24.00 vs >24.00 vs >24.00, NS Patient VAS evaluation of nausea (median change from baseline at 24h) Score: 29.0 vs 31.0 vs 3.5 vs 0.0 vs 3.0, p=0.0061 for Dol 200 vs. ond Dolasetron 25 vs Dolasetron 50 vs Dolasetron 100 vs Dolasetron 200 vs Ond po 32 Complete response: subgroup analyses Prior chemo = yes: 50.0% vs 39.0% vs 64.9% vs 72.3% vs 67.4%, NR Female: 38.8% vs 41.7% vs 51.2% vs 73.5% vs 67.4%, NR Prior chemo = no: 39.5% vs 60.5% vs 56.4% vs 81.8% vs 78.4%, NR Age ≥65 years: 50.0% vs 58.3% vs 80.0% vs 95.0% vs 78.9%, NR Male: 54.5% vs 61.3% vs 72.7% vs 80.6% vs 77.8%, NR Dolasetron groups' range vs Ondansetron Overall satisfaction (VAS) Median scores (0mm=not satisfied to 100mm=completely satisfied): 54mm to 99mm vs 98mm, NR Dolasetron 25 vs Dolasetron 50 vs Dolasetron 100 vs Dolasetron 200 vs Ondansetron No nausea present By investigator report: 45.6% vs 36.7% vs 53.3% vs 69.9% vs 57.3%, NS

Evidence Table 1. Chemotherapy: head-to-head trials

Author Year Setting Hesketh rating	Adverse events	Comments
Fauser **1996** Multicenter 3, 4	Doln 25 vs Dol 50 vs Dol 100 vs Dol 200 vs Ond All Adverse Events (AEs) Headache: 11.3% vs 8.8% vs 19.7% vs 18.8% vs 14.5%, NS Overall AEs experienced: 25.0% vs 37.5% vs 39.5% vs 33.8% vs 36.1%, NS Dizziness: 0% vs 2.5% vs 3.9% vs 1.3% vs 0%, NS Diarrhea: 0% vs 3.8% vs 2.6% vs 5.0% vs 1.2%, NS Death: .6% vs 1.2%, NR Fever: 1.3% vs 1.3% vs 0% vs 0% vs 4.8%, NS Fatigue: 0% vs 0% vs 2.6% vs 1.3% vs 3.6%, NS Weakness: 1.3% vs 3.8% vs 1.3% vs 0% vs 1.2%, NS Drowsiness: 0% vs 2.5% vs 3.9% vs 3.8% vs 2.4%, NS Constipation:0% vs 3.8% vs 1.3% vs 1.3% vs 0%, NS Withdrawals: 0% vs 1.3% vs 0% vs 0% vs 0%, NR Adverse events were reported if experienced by ≥3% of patients.	Note: 21 of the 83 Ondansetron patients received only 24 mg of the drug instead of the 32 mg. The one-post randomization withdrawal occurred when a pt received the study drug but not the chemo drugs they had been scheduled to receive. Patients were stratified by gender and prior chemo status and then randomized. The p-values for the complete response stratified by subgroup were as follows: males vs. females receiving dolasetron (p=0.0015); Chemo naïve vs non-naïve patients receiving dolasetron (p=0.0212); and pts <65 yrs. vs. pts ≥ 65 yrs receiving dolasetron (p=0.0078). P=NS for complete responders in the following variables: use of narcotics, use of steroids, use of benzodiazepines, or type of chemo regimen employed during study.

Evidence Table 1. Chemotherapy: head-to-head trials

Author Year Setting Hesketh rating	Design	Subpopulation	Intervention	Allow other medication	Run-in/ Wash-out	Age Gender Ethnicity
Lofters, Pater (2 papers on 1 trial) 1997 Multicenter 3	RCT Parallel	corticosteroids	Ondansetron iv 32mg Dolasetron iv 2.4mg/kg	Medication given along with dexamethasone 8 mg po, or dex alone for days 2-7	NR/NR	%male
Dolasetron vs Granisetron						
Audhuy 1996 Multicenter 5	DB RCT Parallel	women, prior chemo	dolasetron iv 1.8mg/kg dolasetron iv 2.4mg/kg granisetron iv 3mg	No	NR/NR	55 66%male NR
Tan 2002 Single Center 4, 5	Open CT Parallel	none	Dolasetron po 100mg Granisetron po 2mg	All received 20 mg of iv dexamethasone with the antiemetic.	NA/NA	57.5 38%male NR

Evidence Table 1. Chemotherapy: head-to-head trials

Author Year Setting Hesketh rating	Screened/ Eligible/ Enrolled	Withdrawn/ Lost to fu/ Analyzed	Other population characteristics
Lofters, Pater (2 papers on 1 trial) **1997** Multicenter 3	NR/NR/407	//	NR
Dolasetron vs Granisetron			
Audhuy **1996** Multicenter 5	NR/NR/476	2/0/474	Previous chemo naïve: 60% Previous chemo non-naïve: 40% Chemo naïve: male: 45% Chemo naïve: female: 15% Chemo non-naïve: male: 22% Chemo non-naïve: female: 18%
Tan **2002** Single Center 4, 5	NR/NR/26	0/0/26	Lymphoma (primary cancer site): 46% Lungs (primary cancer site): 15% Larynx (primary cancer site): 15% Uterus (primary cancer site): 12% Other sites: 12% Patients receiving highly emetogenic chemo: 92%

Evidence Table 1. Chemotherapy: head-to-head trials

Author Year Setting Hesketh rating	Results
Lofters, Pater (2 papers on 1 trial) **1997** Multicenter 3	Dex added vs No dex added Complete protection: no episodes of emesis, no rescue medication, no data missing Dexamethasone (dex) added vs. no dex added for 24h: 67% vs 55%, 0.001 Dexamethasone (dex) added vs. no dex added for 7 days: 48% vs 28%, <0.001 Dol (arms 1-3) vs. Ond (arms 4-6) for 7 days: 39% vs 36%, NS Dol (arms 1-3) vs. Ond (arms 4-6) for 24h: 67% vs 57%, 0.013
Dolasetron vs Granisetron	
Audhuy **1996** Multicenter 5	Dol iv 1.8 vs Dol iv 2.4 vs gran iv 3 Complete Response: overall population: no emetic episodes and no use of rescue antiemetics: 54% vs 47% vs 48%, NS Complete response: stratified by gender and/or chemo-naïve status Male naïve: 71% vs 57% vs 63%, NS Male non-naïve: 59% vs 58% vs 55%, NS Male: 67% vs 57% vs 60%, NS Female non-naïve: 20% vs 21% vs 30%, NS Female naïve: 43% vs 27% vs 17%, NS Female: 31% vs 24% vs 24%, NS Chemo-naïve: 63% vs 51% vs 51%, NS Chemo non-naïve: 42% vs 40% vs 43%, NS Patient Nausea score (VAS) Mean and median scores on scale 0 to 100 Mean score(Median score): 34(19) vs 38(26) vs 36(18), NS Number with no nausea: 41% vs 41% vs 41%, NS Investigators assessment of maximum nausea on scale 0 = none to 3 = severe mean score: 1.1 vs 1.2 vs 1.2, NS Patients with no nausea: 43% vs 44% vs 42%, NS
Tan **2002** Single Center 4, 5	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,

Evidence Table 1. Chemotherapy: head-to-head trials

Author Year Setting Hesketh rating	Adverse events	Comments
Lofters, Pater (2 papers on 1 trial) **1997** Multicenter 3		
Dolasetron vs Granisetron		
Audhuy **1996** Multicenter 5	*data given as Dol 1.8 vs Dol 2.4 vs Gran 3* <u>AEs reported by ≥ 3% of all patients</u> headache: 28% vs 22% vs 23%, NS diarrhea:13% vs 11% vs 6%, NS abdominal pain: 6% vs 1% vs 3%, NS epigastric pain: 2% vs 1% vs 3%, NS hypertention: 2% vs 7% vs 4%, NS abnormal hepatic function: 9% vs 6% vs 3%, NS extrasystoles: 3% vs 1% vs 1%, NS athenia: 3% vs 1% vs 1%, NS fever: 2% vs 3% vs 3%, NS Overall AEs: 58% vs 55% vs 45%, NS Severe AEs: 6% vs 7% vs 5%, NS Serious AEs considered to be possibly related to the study medication were angina/myocardial infarction/ acute pulmonary edema in 1 pt and fever/abdominal pain in 1 pt - both pts in Gran 3 group	2 pts assigned to treatment out of 476 did not receive study medication and were excluded. Pts stayed in the hospital for at least 8h after the start of chemo; most were hospitalized for the entire 24h study period. Mean cisplatin dose was significantly different among all groups (p= 0.0389) , the 2 mg/m2 magnitude of difference was not considered to be clinically significant.
Tan **2002** Single Center 4, 5		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 tor AEs. ausea intensity scale: + : <2 episodes/d (mild); ++ : 3-5 episodes/d (moderate); +++ : >5 episodes/d (severe)

Evidence Table 1. Chemotherapy: head-to-head trials

Author Year Setting Hesketh rating	Design	Subpopulation	Intervention	Allow other medication	Run-in/ Wash-out	Age Gender Ethnicity
Palonsetron						
Gralla 2003 Multicenter 4	DB RCT Parallel	none	Palonosetron iv 0.25mg Palonosetron iv 0.75mg Ondansetron iv 32mg	No other medications allowed; no pt was allowed pretreatment with corticosteroids.	None/NA	55.4 28%male Caucasian = 557 (98.9%) Hispanic = 2 (0.36%) Asian = 2 (0.36%) Other = 2 (0.36%) Black = 0

Evidence Table 1. Chemotherapy: head-to-head trials

Author Year Setting Hesketh rating	Screened/ Eligible/ Enrolled	Withdrawn/ Lost to fu/ Analyzed	Other population characteristics
Palonsetron			
Gralla **2003** Multicenter 4	NR/NR/570	12/0/563	Mean height = 165.3 cm Mean weight = 70.7 kg Karnofsky Mean index = 89.0 Non-smoker: 69% Ex-smoker: 12% Smoker: 18% Alcohol use - no: 45% Alcohol use - rarely: 39% Alcohol use - occasionally: 12% Alcohol use - regularly: 5% Chemo-naïve: 42% Chemo non-naïve: 58% Breast cancer: 57% Lung cancer: 8% Bladder cancer: 5% Colon cancer: 4% Rectal cancer: 3% Small-cell lung cancer: 3% Gastric cancer: 3%

Evidence Table 1. Chemotherapy: head-to-head trials

Author Year Setting Hesketh rating	Results
Palonsetron	
Gralla **2003** Multicenter 4	Palon 0.25 vs Ondansetron <u>Complete response; no emeit episodes and no rescue medication (all time periods)</u> During 0-24h following chemo: 81.0% vs 68.6%, 0.0085 During 0-24h following chemo: 73.5% vs 68.6%, NS During 24-120h (delayed period) following chemo: 74.1% vs 55.1%, p<0.001 During 24-120h (delayed period) following chemo: 64.6% vs 55.1%, NS Overall (0-120h) following chemo: 69.3% vs 50.3%, p<0.001 Overall (0-120h) following chemo: 58.7% vs 50.3%, NS Palonosetron vs Ondansetron <u>Complete control: study days 1-5</u> Delayed (24-120h): 66.7% vs 50.3%, 0.001 Overall (0-120h): 63.0% vs 44.9%, 0.001 <u>Ondansetron vs Palon 0.25 vs Palon 0.75</u> <u>No. of pts requiring rescue medication</u> Overall (0-120h): 27.0% vs 18.5% vs 23.8%, NS Delayed (24-120h): 24.3% vs 15.9% vs 22.8%, NS

Evidence Table 1. Chemotherapy: head-to-head trials

Author Year Setting Hesketh rating	Adverse events	Comments
Palonsetron		
Gralla **2003** Multicenter 4	Palon 0.25 vs Palon 0.75 vs Ond 32 Headache: 4.8% vs 5.3% vs 5.3%), Dizziness: 0.5% vs 0% vs 3.2%, Constipation: 1.6% vs 3.2% vs 1.6%, Ondansetron vs Palon 0.25 vs Palon 0.75 Adverse reactions (ie, AE;s considered to be treatment related) : 16% vs 16% vs 13.9%, NR Serious AEs: 2.7% vs 2.6% vs 2.6%, NS Ondansetron vs Palon 0.75 Withdrawals due to AEs: 0.5% vs 0.5%, NS Deaths: all groups Total deaths in study: 0.7% Ondansetron vs Palon 0.25 vs Palon 0.75 All pts experiencing >1 AE: 64.2% vs 61.0% vs 66.5%, NS	Double-dummy technique used for study medications. Pts stratified at randomization by gender and prior chemotherapy experience. Complete control: Data given for delayed and overall intervals, with both Palonosetron groups combined. The rest of this data was given as: Palon. 0.25mg was superior to Ond on Study Days 2 (p=0.001), 3 (p=0.001), and 4 (p=0.003) with Palon 0.75mg superior to Ond on Days 3 (p=0.004) and 4 (p=0.006). On all ot6her days, both Palon. doses were as effective as Ond. Time to treatment failure: Palon 0.25 vs. Ond: p<0.001. Median time to treatment failure was >120h in all treatment groups. First quartile of Palon 0.25mg = 46.5h vs. Ond =19.5h. one pt who died during the study (in the Ond group) had a pulmonary embolism that resulted in death. The other 3 deaths were not specified.

Evidence Table 1. Chemotherapy: head-to-head trials

Author Year Setting Hesketh rating	Design	Subpopulation	Intervention	Allow other medication	Run-in/ Wash-out	Age Gender Ethnicity
Eisenberg 2003 Multicenter 3	DB RCT Parallel	none	Palonosetron iv 0.25mg Palonosetron iv 0.75mg Dolasetron iv 100mg 30 sec infusion	20mg dexamethasone iv or po, or 125 mg methylprednisolone iv allowed 15 min before chemo.	NR/NR	54.0 18%male White: 178 (31.3%) Black: 30 (5.3%) Hispanic: 344 (60.4%) Asian: 13 (2.3%) Other: 4 (0.70%)

Evidence Table 1. Chemotherapy: head-to-head trials

Author Year Setting Hesketh rating	Screened/ Eligible/ Enrolled	Withdrawn/ Lost to fu/ Analyzed	Other population characteristics
Eisenberg 2003 Multicenter 3	NR/NR/592	23/0/569	Chemotherapy naïve: 67% Chemotherapy nonnaive: 33% Corticosteroid use: yes; 5% Corticosteroid use: no: 95% Alcohol use: none: 67% Alcohol use: rare: 14% Alcohol use: occasional: 13% Alcohol use: regular: 5% Breast carcinoma: 61% Lung carcinoma: 8% Non Hodgkins lymphoma: 4%

Evidence Table 1. Chemotherapy: head-to-head trials

Author Year Setting Hesketh rating	Results
Eisenberg **2003** Multicenter 3	Pal 0.25 vs Pal 0.75 vs Dolasetron CR: during the first 24 h after chemo, delayed (24-120h), overall (0-120h), and by each 24h period Overall (97.5% CI =Pal minus Dol; Pal 0.25 vs. Dol; and Pal 0.75 vs. Dol): 46.0% vs 47.1% vs 34.0%, for Pal 0.25 and 0.75 vs Dol: p=0.021 and p=0.012 Delayed (97.5% CI =Pal minus Dol; Pal 0.25 vs. Dol; and Pal 0.75 vs. Dol): 54.0% vs 56.6% vs 38.7%, for Pal 0.25 and 0.75 vs Dol: 0.004 and p<0.001 First 24h after chemo (97.5 % CI = Pal minus Dol): 63.0% vs 57.1% vs 52.9%, NS Complete control: acute, delayed, overall, and by day Day 2: (p-value: P vs. Dol): 40.3%(NA) vs 55.0%(0.004) vs 57.7%(0.001), see table Day 3: (p-value: P vs. Dol): 48.2%(NA) vs 62.4%(0.005) vs 68.3%(0.001), see table Overall (0-120h): (p-value: P vs. Dol): 30.9%(NA) vs 41.8%(0.027) vs 42.9%(0.016), see table Delayed (24-120h): (p-value: P vs. Dol): 36.1%(NA) vs 48.1%(0.018) vs 51.9%(0.002), see table Median times to treatment failure and to first emetic episode Treatment failure: 24.6 h vs 51.1 h vs 52.8 h, p First emetic episode: 41.5 h vs >120 h vs >120 h, p Complete response rates for subpopulations: Chemo-naïve patients (0-24 h): 60.5% vs 46.4% vs 55.7%, NR Non-chemo-naïve patients(0-24 h): 67.7% vs 65.2% vs 60.3%, NR Corticosteroid-using patients (0-24 h): 62.5% vs 72.7% vs 50.0%, NR Non-corticosteroid-using patients(0-24 h): 52.5% vs 62.4% vs 57.6%, NR

Evidence Table 1. Chemotherapy: head-to-head trials

Author Year Setting Hesketh rating	Adverse events	Comments
Eisenberg 2003 Multicenter 3	Palonosetron 0.25 vs Palonosetron 0.75 vs Dolasetron Headache (total: treatment and non-treatment related): 26.4% vs 24.1% vs 26.8%, NS Constipation (total: treatment and non-treatment related): 11.9% vs 14.9% vs 9.3%, NS Fatigue (total: treatment and non-treatment related): 21% vs 26% vs 24%, NS Death: 0.52% vs 1.03% vs 0%, NS Serious AEs (not specified as to what these are): 2.1% vs 6.7% vs 4.6%, NS Anxiety: treatment related: 2.1% vs 0% vs 0%, NS Diarrhea: treatment related: 1.6% vs 1.5% vs 2.1%, NS Dizziness: treatment related: 1.6% vs 1.0% vs 2.1%, NS Asthenia: treatment related: 0.5% vs 2.1% vs 0.5%, NS	569 patients analyzed for efficacy; 582 patients analyzed for adverse events. Of the original 592 who were randomized, 9 did not receive treatment, which leaves a group of 583, and one person in this group was excluded from ITT analysis because they had chemo with unacceptably low emetogenic potential. Of the remaining 582 patients, 13 were excluded post-randomization because they enrolled at a disqualified investigative site. Thus, the study reports its ITT cohort as 569 patients

Evidence Table 1. Chemotherapy: head-to-head trials

Author Year Setting Hesketh rating	Design	Subpopulation	Intervention	Allow other medication	Run-in/ Wash-out	Age Gender Ethnicity
Granisetron iv vs Granisetron po						
1	DB RCT Parallel	BMT, PBPCT, women	granisetron iv 2mg granisetron po 2mg 10 days	Lorazepam iv or po 2 mg/day	nr/nr	49.2 35%male Caucasian: n=55 (92%) Non-Caucasian: n=5 (8%)

Evidence Table 1. Chemotherapy: head-to-head trials

Author Year Setting Hesketh rating	Screened/ Eligible/ Enrolled	Withdrawn/ Lost to fu/ Analyzed	Other population characteristics
Granisetron iv vs Granisetron po			
1	NR/NR/60	9/0/51	Primary Tumor: Non-Hodgkin's disease: 25% Hodgkin's disease: 10% Breast: 47% Chronic myelogenous leukemia: 5% Multiple myeloma: 3% Lymphoma: 3%; Testicular: 2% Waldenstrom macroglobuliemia: 2% Chemo: Etoposide/carmustine/cyclophophamide: 41% Cyclophosphamide/carboplatin/etoposide: 49% Busulfan/cyclophosphamide: 12% Peripheral blood progenitor transplant: 83% Allogeneic bone marrow transplant: 15% Autologous bone marrow transplant: 2%

Evidence Table 1. Chemotherapy: head-to-head trials

Author Year Setting Hesketh rating	Results
Granisetron iv vs Granisetron po	
1	Gran po vs Gran iv Complete response (CR): no emesis All patients: 9.1% vs 6.9%, NS Female: 8.3% vs 5%, NS Male: 10% vs 11.1%, NS Partial response (PR): 1-2 episodes of emesis Females only: 58.3% vs 35%, NS Males only: 30% vs 33.3%, NS All patients: 45.5% vs 34.5%, NS Failure: ≥ 3 episodes of emesis Males only: 60% vs 55.6%, NS Females only: 33.3% vs 60.0%, NS All patients: 45.5% vs 58.6%, NS No. of emetic episodes Day 10: 0 vs 1.3, Day 9: 3.0 vs 6.0, Day 8: 4.0 vs 8.0, Day 7: 5.3 vs 14.3, Day 6: 4.0 vs 15.3, NR Day 5: 6.0 vs 15.3, NR Day 4: 5.0 vs 13.0, NR Day 3: 10.0 vs 13.0, NR Day 2: 12.3 vs 15.3, NR Day 1: 1.0 vs 4.0, NR Total number, over 10 days: 50 vs 104, p=0.0008 Gran po vs Gran iv

Evidence Table 1. Chemotherapy: head-to-head trials

Author Year Setting Hesketh rating	Adverse events	Comments
Granisetron iv vs Granisetron po		
1	Gran po 1 vs Gran iv 2 Headache: 8% vs 8%, NS Sedation: 4% vs %, NS Diarrhea: 4% vs 9%, NS Hypertension: 2% vs 2%, NS Hypotension: 3% vs 0%, NS Insomnia: 3% vs 3%, NS Jittery/EPS: 3% vs 6%, NS Hiccups: 1% vs 6%, NS Anxiety: 2% vs 4%, NS Sinus congestion: 2% vs 1%, NS Indigestion: 1% vs 3%, NS Mucositis: 1% vs 2%, NS Death: 0% vs 6.9%, NS Confusion: 0% vs 2%, NS Constipation: 0% vs 2%, NS Total withdrawals: 18.5% vs 9.1%, NS	Pts undergoing peripheral blood progenitory cell and bone marrow transplantation; chemo was administered for 10 days. Pts were stratified based on transplant type and and conditioning regimen. Balance between the two groups was obtained through random blocks of two. Pts received Gran (+placebo) every 12h until either the day of marrow or stem cell infusion (day 0), or until the pt experienced 3 ≥ emetic episodes within any 24h period. Administration of prochloroperazine, lorazepam, and promethazine permitted during study. Withdrawals: 8 pts (Gran po= 5 pts and Gran iv = 3 pts had emesis prior to study medication and were excluded from analysis. One pt, initally randomized, received therapy for 9 days and then voluntarily withdrew [study did not say why] and was censored from the efficacy analysis.

Evidence Table 2. Quality assessments of chemotherapy head-to-head trials

Author Year Setting Type of Chemo	Subpopulation	Exclusion criteria	Run-in/Wash out	Screened/ Eligible/ Enrolled	Withdrawn/ Lost to fu/ Analyzed
Children					
Forni 2000 Not specified 5	children	NR	NR/NR	NR/NR/90	NR/0/90
Jaing 2004 Multicenter 3	children, females	Patients were excluded if they were younger than 3 or older than 18, weighed <25 kg, suffered from primary or secondary brain tumors, had preexisting chronic nausea or vomiting problems, or suffered from gastrointestinal tumors that appeared likely to lead to bowl obstruction. The coadministration or corticosteroids (including dexamethasone) was prohibited during this study.	4 wk run-in with antiemetics acc. to rand. scheme/NR	35/33/33	0/0/33
Orchard 1999 Single Center 5	children, BMT, TBI	NR	NR/NR	NR/NR/193	4/2/187
White 2000 Multicenter 4, 5	children, kinetosis	Pts were excluded if they had a body surface area >1.6m2, severe concurrent illness other than neoplasia, or illness associated with nausea and vomiting (e.g., gastrointestinal obstruction, active peptic ulcer disease, hypercalcemia, or primary or secondary tumors of the CNS). Pts were excluded if they had experienced emesis (retching and/or vomiting) or severe nausea in the 24h before chemo. were receiving antiemetic medication other than the study medication either concurrently or during the 24h preceding chemo, were pregnant or likely to become pregnant, or had contraindications to either ondansetron or dexamethasone (dex). Pts were not allowed benzodiazepines or systemic steroids unless these were part of the chemo regimen. Inhaled corticosteroids were permitted.	No/NR	NR/438/428	0/0/428

Evidence Table 2. Quality assessments of chemotherapy head-to-head trials

Author Year Setting Type of Chemo	Randomization	Allocation	Groups similar at baseline	Eligibility criteria specified	Care provider masked	Patients masked	Attrition Crossover Adherence Contamination	Loss to follow up	Intention-to-treat analysis
Children									
Forni 2000 Not specified 5	NR	NR	Inadequate data	Yes	Yes, but not described	Yes, but not described	NR No No No	Unable to determine	Yes
Jaing 2004 Multicenter 3	NR	NR	NR	Yes	No	No	Yes No No No	Unable to determine	No
Orchard 1999 Single Center 5	NR	NR	Yes	Yes	Yes, but not described	Yes, but not described	Yes No No No	Unable to determine	No
White 2000 Multicenter 4, 5	Yes	NR	Yes	Yes	Yes	Yes	Yes No No No	Unable to determine	Yes

Evidence Table 2. Quality assessments of chemotherapy head-to-head trials

Author Year Setting Type of Chemo	Postramdomization exclusions	Quality rating	Controlled group standard of care	Funding	Relevance
Children					
Forni 2000 Not specified 5	No	Fair	Yes	NR	Yes
Jaing 2004 Multicenter 3	Yes	Poor	Yes	Supported in part by a grant from the Childhood Cancer Foundation of Taiwan.	Yes
Orchard 1999 Single Center 5	Yes	Fair	Yes	Children's Cancer Research Fund and the Bone Marrow Transplant Research Fund.	Yes
White 2000 Multicenter 4, 5	No	Fair	Yes	Supported by a grant from Glaxo Wellcome Research & Development	Yes

Evidence Table 2. Quality assessments of chemotherapy head-to-head trials

Author Year Setting Type of Chemo	Subpopulation	Exclusion criteria	Run-in/Wash out	Screened/ Eligible/ Enrolled	Withdrawn/ Lost to fu/ Analyzed
Adults					
Granisetron vs Ondansetron					
Barrajon 2000 Single Center 5	women, alcoholics, prior chemo	Patients with other severe conditions were excluded, as were patients with vomiting, prior to chemotherapy, from other causes: hypercalcaemia, intracranial hypertension, abdominal pathology, active peptic ulcers, etc. No dose modification was allowed. Patients not able to continue chemotherapy at same dose and schedule were excluded and replaced by other incoming patients.	NR/NR	NR/NR/136	16/0/120
Chiou 2000 Single Center 4, 5	none	Patients with any of the following were not eligible: 1) participation in any trial in which the patient received an investigative drug within 30 days or five half-lives preceding the screening phase of the study; 2) vomiting or having used antiemetic drugs within 24 hours or chronic use (> 1 month) before chemotherapy; 3) primary or secondary brain neoplasm with signs of increased intracranial pressure or requiring treatment within 30 days of entry; 4) severe hepatic, renal, or cardiac disease; 5) signs of bowel obstruction; 6) radiation therapy to any abdominal field within 24 hours before the dose of the study medication or during the study period; or 7) using corticosteroids or benzodiazepines.	No/NR	NR/NR/51	0/0/51
Chua 2000 Single Center 5	none	No significant cardiac, hepatic, or renal disease. Patients with gastrointestinal obstruction, brain tumor, increase in intracranial pressure or preexisting nausea or vomiting were excluded.	NR/NR	94/89/89	0/0/89
Del Favero 1995 Multicenter 5	kinetosis	Criteria for exclusion before randomization were: the presence of nausea and vomiting or the use of antiemetics in the 24 hours before cisplatin chemotherapy; severe concurrent illness other than neoplasia; other causes for vomiting (e.g. gastrointestinal obstruction, central nervous system metastases, hypercalcemia); contraindications to dexamethasone administration (active peptic ulceration or previous gastrointestinal bleeding due to peptic ulcer); concurrent therapy with corticosteroids (unless given as physiological supplements) or benzodiazepines (unless given for night sedation) and abdominal radiotherapy or pregnancy. A 10% error in the dose of administered cisplatin was acceptable, so only pts receiving <45 mg/m2 of cisplatin were excluded,	NR/NR	NR/NR/973	6/1/966

Evidence Table 2. Quality assessments of chemotherapy head-to-head trials

Author Year Setting Type of Chemo	Randomization	Allocation	Groups similar at baseline	Eligibility criteria specified	Care provider masked	Patients masked	Attrition Crossover Adherence Contamination	Loss to follow up	Intention-to-treat analysis
Adults									
Granisetron vs Ondansetron									
Barrajon 2000 Single Center 5	Yes	Yes	Yes	Yes	Yes	Yes	Yes No No No	No	No
Chiou 2000 Single Center 4, 5	NR	NR	Yes	Yes	No	No	Yes No No No	No	Yes
Chua 2000 Single Center 5	Yes	NR	NR	Yes	No	No	Yes No No No	Unable to determine	No
Del Favero 1995 Multicenter 5	Yes	NR	Yes	Yes	Yes	Yes	Yes No No No	No	No

Evidence Table 2. Quality assessments of chemotherapy head-to-head trials

Author Year Setting Type of Chemo	Postramdomization exclusions	Quality rating	Controlled group standard of care	Funding	Relevance
Adults					
Granisetron vs Ondansetron					
Barrajon 2000 Single Center 5	Yes	Fair	Yes	NR	Yes
Chiou 2000 Single Center 4, 5	No	Fair	Yes	SmithKline Beecham Taiwan supplied granisetron for the study.	Yes
Chua 2000 Single Center 5	Yes	Poor	Yes	NR	Yes
Del Favero 1995 Multicenter 5	Yes (7/973)	Fair	Yes	Supported in part by a grant from the Umbrian Cancer Association (A.U.C.C.)	Yes

Evidence Table 2. Quality assessments of chemotherapy head-to-head trials

Author Year Setting Type of Chemo	Subpopulation	Exclusion criteria	Run-in/Wash out	Screened/ Eligible/ Enrolled	Withdrawn/ Lost to fu/ Analyzed
deWit 2001 NR 5	none	Eligibility also required that there were no planned dose attenuations, no use of other antiemetic agents, benzodiazepines, or opiates and no emesis in the 24 hours preceding the study cycle.	No/NR	NR/45/40	0/0/40
Fox-Geiman 2001 Single Center 5	BMT; TBI	NR	NR/NR	NR/NR/102	6/0/102
Gebbia 1994a Single Center 5	none	Patients were excluded if they had a clinically detectable brain metastasis; the presence of neoplastic involvement of the stomach and bowel that could lead to partial obstruction; a history of non-neoplastic severe gastric or bowel diseases; a concomitant treatment with other antiemetic drugs, including steroids; a anticipatory emesis; a concomitant severe neurologic, hepatic, or renal diseases; and drug abuse or long term use of psychotropic drugs.	NR/NR	NR/NR/182	16/0/166
Gebbia 1994b Single Center 3	none	Patients were excluded if they had a clinically detectable brain metastasis; the presence of neoplastic involvement of the stomach and bowel that could lead to partial obstruction; a history of non-neoplastic severe gastric or bowel diseases; a concomitant treatment with other antiemetic drugs, including steroids; a anticipatory emesis; a concomitant severe neurologic, hepatic, or renal diseases; and drug abuse or long term use of psychotropic drugs.	NR/NR	NR/NR/164	8/0/158
Gralla 1998 Multicenter 5	corticosteroids	Patients with any of the following conditions were excluded: participation in any drug trial in which they received an investigational drug within 30 days or 5 half-lives (whichever was longer) of screening for this study; severe hepatic insufficiency; a primary or metastatic brain neoplasm (which signs or symptoms of increased intracranial pressure or metastases that required treatment within 30 days of entry into the study, or with signs or symptoms of cerebral edema); known hypersensitivity to any 5HT3 receptor antagonist; radiation therapy to any abdominal field within 24 h before the administration of study medication or during the 24h following chemo; and nausea within 1 hour or emesis (vomiting or retching) within 24 hours before administration of study medication. Eligible pts could not have received chronic (>1month) or concurrent (day 0 and through 24 h) treatment with agents with probable antiemetic activity, which included antihistamines, antipsychotics, cannabinoids, and metoclopramide.	NR/NR	NR/NR/1054	13/0/1054

Evidence Table 2. Quality assessments of chemotherapy head-to-head trials

Author Year Setting Type of Chemo	Randomization	Allocation	Groups similar at baseline	Eligibility criteria specified	Care provider masked	Patients masked	Attrition Crossover Adherence Contamination	Loss to follow up	Intention-to-treat analysis
deWit 2001 NR 5	NR	NR	Yes	Yes	Yes	Yes	Yes No No Yes	No	No
Fox-Geiman 2001 Single Center 5	Yes	Yes	Yes	Yes	Yes	Yes	Yes No No No	No	Unable to determine
Gebbia 1994a Single Center 5	NR	NR	Yes	Yes	NR	NR	Yes No No No	No	No
Gebbia 1994b Single Center 3	NR	NR	Yes	Yes	NR	NR	Yes No No No	No	No
Gralla 1998 Multicenter 5	NR	NR	Yes	Yes	Yes, but not described	Yes, but not described	Yes No No No	No	Yes

Evidence Table 2. Quality assessments of chemotherapy head-to-head trials

Author Year Setting Type of Chemo	Postramdomization exclusions	Quality rating	Controlled group standard of care	Funding	Relevance
deWit 2001 NR 5	Yes	Fair	Yes	NR	Yes
Fox-Geiman 2001 Single Center 5	No	Fair	Yes	Supported in part by an educational grant from Glaxo-Wellcome, Inc.	Yes
Gebbia 1994a Single Center 5	Yes	Fair	No	University of Palermo; Palermo, Italy	Yes
Gebbia 1994b Single Center 3	Yes	Fair	No	University of Palermo; Palermo, Italy	Yes
Gralla 1998 Multicenter 5	No	Fair	Yes	SmithKline Beecham Pharmaceuticals	Yes

Evidence Table 2. Quality assessments of chemotherapy head-to-head trials

Author Year Setting Type of Chemo	Subpopulation	Exclusion criteria	Run-in/Wash out	Screened/ Eligible/ Enrolled	Withdrawn/ Lost to fu/ Analyzed
Herrington 2000 Multicenter 4	women	Patients receiving paclitaxel, and late docetaxel, were not included because of the possible antiemetic effects of high dosage corticosteroid premedication required with these drugs. Patients were excluded if they had received emetogenic chemotherapy; had an unstable medical disorder, severe hepatic insufficiency, primary or secondary brain neoplasm, and intestinal diseases or disorders that may inhibit digestion or absorption of oral agents; received long-term or concurrent (within 24 hrs of first dose of study drug) treatment with agents known to have significant antiemetic activity (antihistamines, phenothiazines, butryophenones, cannabinoids, corticosteroids, metoclopramide); had radiation therapy to any abdominal field (T10-L5) within 24 hrs before the dose of study drug was given or during the 24-h assessment period (study days 0-1); had hypersensitivity to any 5-HT3-receptor antagonist or corticosteroid; or experienced nausea within 1 hr and/or emesis (vomiting and/or retching) within 24 hrs before dosing with study drug.	No/NR	65/61/61	0/0/61
Kalaycio 1998 NR 5	ASCT, women	Patients with central nervous system disease and patients receiving anti-emetics at the time of study entry were excluded. Patients with active peptic ulcer disease, uncontrolled diabetes mellitus, or other contraindications for corticosteroids were also excluded.	NR/NR	48/48/48	3/45/45
Jantunen 1993 Multicenter 3, 4	none	Vomiting or the use of any antiemetic drugs within 24h prior to chemo; signs of bowel obstruction; verified or suspected CNS tumor or metastases; severe concurrent illness other than neoplasia; use of corticosteroids unless as part of the chemo regimen; and use of benzodiazepines, except when given for night sedation. Patients regarded as having a very high alcohol intake (abusers) were excluded.	no/no	NR/NR/166	34/2/130
Leonardi 1996 Multicenter 3, 4, 5	none	see eligible criteria.	NR/NR	NR/NR/118	3/0/118
Mantovani 1995 Single Center 5	none	Pts could have no history of non-neoplastic severe gastric of bowel diseases; no concomitant treatment with other antiemetic drugs, including steroids; no anticipatory emesis; no concomitant severe neurologic, hepatic, or renal diseases, and no drug abuse or long-term use of psychotropic drugs.	NR/NR	NR/NR/117	0/0/117

Evidence Table 2. Quality assessments of chemotherapy head-to-head trials

Author Year Setting Type of Chemo	Randomization	Allocation	Groups similar at baseline	Eligibility criteria specified	Care provider masked	Patients masked	Attrition Crossover Adherence Contamination	Loss to follow up	Intention-to-treat analysis
Herrington 2000 Multicenter 4	NR	NR	unable to determine (reported for evaluated pts)	Yes	No	No	No No No No	No	No
Kalaycio 1998 NR 5	NR	NR	Yes	Yes	Yes	Yes	Yes No No No	Unable to determine	No
Jantunen 1993 Multicenter 3, 4	Yes	Yes	NR	Yes	No	No	Yes No No No	Yes 36/166 not evaluated	No
Leonardi 1996 Multicenter 3, 4, 5	NR	NR	NR	Yes	NR	NR	Yes No Yes No	Unable to determine	Yes
Mantovani 1995 Single Center 5	NR	NR	Yes	Yes	NR	Yes, but not described	No Yes No No	No	Yes

Evidence Table 2. Quality assessments of chemotherapy head-to-head trials

Author Year Setting Type of Chemo	Postramdomization exclusions	Quality rating	Controlled group standard of care	Funding	Relevance
Herrington 2000 Multicenter 4	Yes	Poor	Yes	Funded in part by SmithKline Beecham Pharmaceuticals	Yes
Kalaycio 1998 NR 5	Yes	Poor	Yes	NR	Yes
Jantunen 1993 Multicenter 3, 4	Yes	Poor	Yes	NR	Yes
Leonardi 1996 Multicenter 3, 4, 5	No	Poor	Yes	NR	Yes
Mantovani 1995 Single Center 5	No	Fair	Yes	The authors state that no support for this study came directly from a pharmaceutical company.	Yes

Evidence Table 2. Quality assessments of chemotherapy head-to-head trials

Author Year Setting Type of Chemo	Subpopulation	Exclusion criteria	Run-in/Wash out	Screened/ Eligible/ Enrolled	Withdrawn/ Lost to fu/ Analyzed
Martoni 1995 Single Center 5	none	Pts with gastrointestinal or symptomatic brain metastases or vomiting in the previous week were excluded.No other antiemetic drugs including corticosteroids were allowed.	NR/NR	NR/NR/124	0/0/124
Massidda 1996b NR 3	women	Patients were excluded if any of the following applied: serious disease other than the cancer being treated; nausea and vomiting caused by other than the chemotherapy; a clinical hepatic disorder; chronic alcoholism; emesis or antiemetic treatment during the 24h preceding entry into this study.	NR/NR	NR/NR/60	NR/NR/60
Navari 1995 Multicenter 5	women	Pts with any unstable systemic medical disorder, cerebral edema, primary or secondary brain neoplasm with signs or symptoms of intracranial pressure, and/or brain metastases that required treatment within 30 d of study entry; with nausea or emesis of any severity within 24 h before or 24 h after antiemetic treatment; and who were being treated with agents having significant antiemetic activity (e.g., benzodiazepines) either on a continuous basis for ≥3 months or concurrently with study; and pts receiving CNS agents without significant antiemetic activity for which dosage had been changed within 1 week of study.	NR/NR	NR/NR/994	7/0/987
Noble 1994 Multicenter 3	none	Patients with marked hepatic dysfunction, congestive heart failure, active peptic ulcer, gastrointestinal obstruction, primary or secondary brain tumors, pre-existing or chronic nausea and/or vomiting, and who (with the exception of short-acting benzodiazepines) had recently had a change in medication with central nervous system (CNS) activity.	none/NR	NR/NR/359	0/0/359
Oge 2000 NR 4, 5	none	Use of any antiemetic drug within 24 hours prior to chemotherapy, diagnosed or suspected central nervous system tumor or metastasis, any concomitant severe illness other than neoplasm, use of corticosteroids (unless as part of the chemotherapy) and use of benzodiazepines.	NR/NR	NR/NR/106	0/0/106
Park 1997 Single Center 5	none	Patients who met any of the following criteria were excluded: Abnormal liver or renal function; Nausea and vomiting within 7 days; Active ulcer disease; Concomitant treatment with other drugs, including benzodiazepines, psychotropics, and major tranquilizers; Scheduled to take any other antiemetics or to receive concomitant radiotherapy during the study periods.	No/NR	NR/NR/97	2/NR/95

Evidence Table 2. Quality assessments of chemotherapy head-to-head trials

Author Year Setting Type of Chemo	Randomization	Allocation	Groups similar at baseline	Eligibility criteria specified	Care provider masked	Patients masked	Attrition Crossover Adherence Contamination	Loss to follow up	Intention-to-treat analysis
Martoni 1995 Single Center 5	NR	NR	NR	Yes	No	No	Yes NR NR NR	No	Yes
Massidda 1996b NR 3	NR	NR	Yes	Yes	NR	NR	No No No No	Unable to determine Results appear to be based on 60 'evaluable' patients	NR
Navari 1995 Multicenter 5	NR	NR	Some differences (NS)	Yes	Yes	Yes, but not described	Yes Not relevant Not relevant No	Unable to determine	No
Noble 1994 Multicenter 3	NR	NR	Yes	Yes	Yes, but not described	Yes, but not described	Yes NA No No	No	No
Oge 2000 NR 4, 5	NR	NR	NR	Yes	NR	NR	Yes No No No	No	Yes
Park 1997 Single Center 5	NR	NR	Yes	Yes	NR	NR	Yes No No No	No	No

Evidence Table 2. Quality assessments of chemotherapy head-to-head trials

Author Year Setting Type of Chemo	Postramdomization exclusions	Quality rating	Controlled group standard of care	Funding	Relevance
Martoni 1995 Single Center 5	No	Poor	Yes	NR	Yes
Massidda 1996b NR 3	NR	Poor	Yes	Not stated	Yes
Navari 1995 Multicenter 5	Yes	Fair	Yes	Two authors are employees of SmithKline Beecham Pharamaceuticals	Yes
Noble 1994 Multicenter 3	No	Fair	Yes	One author is an employee at Smith Kline Beecham Pharmaceuticals, UK	Yes
Oge 2000 NR 4, 5	No	Fair	Yes	NR	Yes
Park 1997 Single Center 5	Yes	Fair	Yes	NR	Yes

Evidence Table 2. Quality assessments of chemotherapy head-to-head trials

Author Year Setting Type of Chemo	Subpopulation	Exclusion criteria	Run-in/Wash out	Screened/ Eligible/ Enrolled	Withdrawn/ Lost to fu/ Analyzed
Perez 1998 Multicenter 4	women, corticosteroid use	Patients with any of the following were excluded: prior history of emetogenic chemo; any unstable medical disorder; severe hepatic insufficiency (evidenced by ascites, encephalopathy, coagulopathy, or jaundice); primary or secondary brain neoplasm that required treatment within 30 days of study entry or caused signs or symptoms of increased intracranial pressure; pts who had received radiation therapy to any abdominal field within 24h before a dose of study medication or during the 48h assessment period following chemo; pts with known hypersensitivity to any 5-HT3 receptor antagonist; with nausea within 1 h before administration of study medication; with vomiting or retching within 24h before study medication; or who were unwilling or unable to comply with protocol. Pts were excluded if they had participated in any drug trial in which they received and investigational drug within 30 d of study entry or 5 half-lives of the investigational drug (whichever was longer) before screening or if they had received chronic (>1 month) or concurrent (day 0-48 hours) treatment with agents known to have significant antiemetic activity (antih	Dexamethasone and methylprednisolone was permitted/NR	NR/NR/1085	16/1/1085
Perez 1998a Multicenter 3, 4	women, breast cancer	Pts were not eligible if they had received an investigational drug within 30 days or 5 half-lives (whichever was longer) before the screening phase or if they had any unstable medical disorder, severe hepatic insufficiency, primary or secondary brain neoplasm with signs or symptoms of increased intracranial pressure, or brain metastases requiring treatment within 30 days of study entry. They could not receive chronic (>1 month) or concurrent (between Day 0 and 48 hrs after treatment) therapy with agents known to have significant antiemetic activity (antihistamines, antipsychotics, cannabinoids, corticosteroids, metodopramide) and could not receive radiation therapy to any abdominal field within 24h before each dose of study medication or during the 48h assessment period after each cycle. Pts were also excluded if they were know to be hypersensitive to any 5-HT3 receptor antagonist, were unwilling or unable to comply with the protocol, or experienced any nausea within 1h or vomiting or retching within 24h before administration of the study medication.	No/NR	NR/NR/623	//623
Poon 1997 Single Center 4	women, breast cancer	Pts with brain or gastrointestinal diseases that might lead to nausea or vomiting.	NR/NR	NR/NR/20	0/0/20

Evidence Table 2. Quality assessments of chemotherapy head-to-head trials

Author Year Setting Type of Chemo	Randomization	Allocation	Groups similar at baseline	Eligibility criteria specified	Care provider masked	Patients masked	Attrition Crossover Adherence Contamination	Loss to follow up	Intention-to-treat analysis
Perez 1998 Multicenter 4	NR	NR	Yes	Yes	Yes	Yes	Yes No No No	No	Yes
Perez 1998a Multicenter 3, 4	Yes	NR	Yes	Yes	Yes	Yes	Yes No No No	Unable to determine	No
Poon 1997 Single Center 4	NR	NR	Yes	Yes	Yes	Yes	No No No No	No	Yes

Evidence Table 2. Quality assessments of chemotherapy head-to-head trials

Author Year Setting Type of Chemo	Postramdomization exclusions	Quality rating	Controlled group standard of care	Funding	Relevance
Perez 1998 Multicenter 4	No	Fair	Yes	SmithKline Beecham Pharmaceuticals	Yes
Perez 1998a Multicenter 3, 4	No	Poor	Yes	Funded by SmithKline Beecham Pharmaceuticals	Yes
Poon 1997 Single Center 4	No	Fair	Yes	NR	Yes

Evidence Table 2. Quality assessments of chemotherapy head-to-head trials

Author Year Setting Type of Chemo	Subpopulation	Exclusion criteria	Run-in/Wash out	Screened/ Eligible/ Enrolled	Withdrawn/ Lost to fu/ Analyzed
Raynov 2000 Single Center 5	none	Patients with disease dissemination in the gastrointestinal tract or CNS. Personal history for severe nausea and vomiting.	NR/NR	NR/NR/72	0/0/72
Ruff 1994 Multicenter 5	none	Patients were excluded if they had received non-cisplatin chemotherapy during the previous 6 months, had a severe concurrent illness (other than cancer), had other etiologies for emesis (e.g. gastrointestinal obstruction, central nervous system metastases), had received anti-emetic therapy concurrently or in the 24 h before chemotherapy, had received benzodiazepines (except when given for night sedation) or concurrent corticosteroids (except for physiological supplementation, bone metastases or respiratory problems), had vomited in the 24 h prior to chemotherapy or were pregnant.	No/NR	NR/NR/NR	1/NR/Various
Slaby 2000 Single Center 5	ASCT	NR	NR/NR	NR/NR/45	0/0/45
Spector 1998 Multicenter 5	none	Patients were excluded if they had a Karnofsky performance status of <60%; had received an investigational drug within the previous 30 days (or were scheduled to receive an investigational drug during the study); were scheduled to receive any additional highly emetogenic chemotherapeutic agents; had chronic nausea and/or vomiting, or experienced retching, vomiting, or uncontrolled nausea within 24h prior to administration of study drug. Medications with antiemetic properties were not allowed within 24h prior to or during study period. Pts could not undergo radiation therapy to the abdomen or pelvis within 48h prior to or during the study period.	None/None	NR/NR/371	//371
Stewart L. 2000 Single Center 5	none	Hypersensitivity to ondansetron, granisetron, or related substances.	NR/NR	NR/NR/21	5/NR/16

Evidence Table 2. Quality assessments of chemotherapy head-to-head trials

Author Year Setting Type of Chemo	Randomization	Allocation	Groups similar at baseline	Eligibility criteria specified	Care provider masked	Patients masked	Attrition Crossover Adherence Contamination	Loss to follow up	Intention-to-treat analysis
Raynov 2000 Single Center 5	NR	NR	NR	Yes	No	No	No No No No	Unable to determine	Unable to determine
Ruff 1994 Multicenter 5	NR	NR	NR	Yes	Yes	Yes	No No No No	No	No
Slaby 2000 Single Center 5	NR	NR	Yes	Yes	NR	NR	No No No No	No	Yes
Spector 1998 Multicenter 5	NR	NR	Yes	Yes	Yes	Yes	No No No No	NR	Yes
Stewart L. 2000 Single Center 5	NR	NR	NR	Yes	Yes	Yes	Yes No No No	None	No

Evidence Table 2. Quality assessments of chemotherapy head-to-head trials

Author Year Setting Type of Chemo	Postramdomization exclusions	Quality rating	Controlled group standard of care	Funding	Relevance
Raynov 2000 Single Center 5	Unable to determine	Poor	Yes	NR	Yes
Ruff 1994 Multicenter 5	Unable to determine	Poor	Yes	NR, but 4 authors are employed by Glaxo.	Yes
Slaby 2000 Single Center 5	No	Fair	Yes	NR	Yes
Spector 1998 Multicenter 5	No	Fair	Yes	Supported by a grant from Glaxo Wellcome Inc.	Yes
Stewart L. 2000 Single Center 5	No	Poor	Yes	NR	Yes

Evidence Table 2. Quality assessments of chemotherapy head-to-head trials

Author Year Setting Type of Chemo	Subpopulation	Exclusion criteria	Run-in/Wash out	Screened/ Eligible/ Enrolled	Withdrawn/ Lost to fu/ Analyzed
Stewart, A. 1995 Multicenter 4	women	Pts were excluded if any of the following applied: receipt of multiday chemotherapy, concurrent administration of cisplatin, decarbazine, high-dose melphalan or ifosfamide; radiotherapy to the pelvic or abdominal region in the 48h before study start or scheduled to receive such treatment during the study period; other etiologies for vomiting including central nervous system (CNS) metastases, gastrointestinal obstruction or hypercalcaemia; concurrent systemic corticosteroids unless administered for the purposes of physiological supplementation or for bone metastases or for respiratory disorders (e.g.., chronic obstructive airway disease); concurrent antiemetics or anti-emetic therapy in the 24h before the start or the study; vomiting in the 24h before chemotherapy; concurrent medication with benzodiazepines (e.g.., lorazepam, diazepam) except when given for night sedation; pregnancy.	NR/NR	NR/NR/514	16/10/488
Walsh 2004 Multicenter 5	HSCT	Patients were excluded if they were scheduled to receive TBI as part of their conditioning regimen or any radiation therapy within 24 h of study initiation or during the study period. Other exclusion criteria included (1) nausea or vomiting within 24 h prior to initiation of therapy, (2) receipt of any medication with antiemetic activity with 24 h of study initiation or during the study period such as metoclopramide or dronabinol, and (3) known hypersensitivity to any 5-HT3 receptor antagonist or other study medication. Pregnancy in female patients was also reason for exclusion.	No/NR	NR/NR/110	14/0/96
Yalcn 1999 Single Center 3	women	Pts with vomiting or who had used antiemetic drugs within 24 h before chemotherapy; with verified or suspected central nervous system metastasis; with severe hepatic, renal, or cardiac disease; with signs of bowel obstruction; or who used corticosteroids or benzodiazepines.	No/NR	NR/NR/54	0/0/54
Zeidman 1998 Single Center 3, 4, 5	none	NR	none/none	NR/NR/60	2/0/58

Evidence Table 2. Quality assessments of chemotherapy head-to-head trials

Author Year Setting Type of Chemo	Randomization	Allocation	Groups similar at baseline	Eligibility criteria specified	Care provider masked	Patients masked	Attrition Crossover Adherence Contamination	Loss to follow up	Intention-to-treat analysis
Stewart, A. 1995 Multicenter 4	NR	NR	Yes	Yes	Yes	Yes	Yes No No No	No LTFU	No
Walsh 2004 Multicenter 5	Yes	NR	NR - excluded 12.7%	Yes	Yes	Yes	Yes No No No	None	No
Yalcn 1999 Single Center 3	NR	NR	Yes	Yes	Yes	Yes	No No No No	NR	Yes
Zeidman 1998 Single Center 3, 4, 5	NR	NR	Text specifies that groups were similar for "most"	Yes	NR	NR	Yes No No No	None	No

Evidence Table 2. Quality assessments of chemotherapy head-to-head trials

Author Year Setting Type of Chemo	Postramdomization exclusions	Quality rating	Controlled group standard of care	Funding	Relevance
Stewart, A. 1995 Multicenter 4	No	Fair	Yes	4 (of 13) authors employed by Glaxo	Yes
Walsh 2004 Multicenter 5	No	Fair for acute Poor for delayed	Yes	Study supported in part by unrestricted educational grant from SmithKline Beecham Pharmaceuticals.	Yes
Yalcn 1999 Single Center 3	No	Fair	Yes	NR	Yes
Zeidman 1998 Single Center 3, 4, 5	No	Fair	Yes	NR	Yes

Evidence Table 2. Quality assessments of chemotherapy head-to-head trials

Author Year Setting Type of Chemo	Subpopulation	Exclusion criteria	Run-in/Wash out	Screened/ Eligible/ Enrolled	Withdrawn/ Lost to fu/ Analyzed
Dolasetron vs Ondansetron					
Fauser 1996 Multicenter 3, 4	women, prior chemo	Pts. were excluded from the study for any of the following reasons: history of congestive heart failure; the presence of significant hepatic, neurological or psychiatric disease excluding alcoholism; vomiting or nausea (Southwest Oncology Group [SWOG] grade 2-4) during the 24h prior to receiving chemo; vomiting resulting from any organic etiology; cerebral metastases that impaired communication or induced emesis; or, treatment with radiotherapy within 7days, treatment with other anti-emetic drugs (e.g., other 5-HT3 antagonists, trimethobenzamide, tricyclic antidepressants, droperidol, diphenhydramine, glucocorticoids) within 24h, treatment with anti-cancer drugs within 21 days of the scheduled chemo. Additionally, any pt who received concomitant medications (for reasons other than control of nausea and emesis) that possessed any anti-emetic activity within 24h before or after chemo (e.g., phenothiazines, corticosteroids) was excluded from efficacy analyses, but not from safety analyses.	NR/NR	NR/399/399	1/0/398
Hesketh 1996 Multicenter 5	prior chemo	Patients with any of the following were excluded from participation: history of significant neurologic or psychiatric illness except alcoholism; history of congestive heart failure, cardiomyopathy, greater than first degree heart block, preexisting complete bundle branch block or requirement for antiarrhythmic medication; clinically significant liver disease; significant electrolyte abnormalities; history of emesis following any previous chemotherapy; pregnant women and women of childbearing age not using an accepted method of birth control; history of vomiting or significant nausea in the 24 hrs before chemotherapy; use of any drugs with potential antiemetic action within 24 hrs of chemotherapy or during the study period.	No/NR	NR/NR/609	51/NR/558
Lofters, Pater (2 papers on 1 trial) 1997 Multicenter 3	corticosteroids	Patients who were pregnant, who were taking anti-convulsants, who had major renal or hepatic dysfunction, who had significant cardiac disease and ECG evidence of conduction abnormality at the time of the study.	NR/NR	NR/NR/407	//

Evidence Table 2. Quality assessments of chemotherapy head-to-head trials

Author Year Setting Type of Chemo	Randomization	Allocation	Groups similar at baseline	Eligibility criteria specified	Care provider masked	Patients masked	Attrition Crossover Adherence Contamination	Loss to follow up	Intention-to-treat analysis
Dolasetron vs Ondansetron									
Fauser 1996 Multicenter 3, 4	Yes	NR	Yes	Yes	Yes	Yes	Yes No No No	No	Yes
Hesketh 1996 Multicenter 5	Yes	NR	Some differences (NS)	Yes	Yes, but not described	Yes, but not described	Yes No No No	No	Yes
Lofters, Pater (2 papers on 1 trial) 1997 Multicenter 3	NR	NR	Yes	Yes	Yes	Yes	Yes No No No	Unable to determine	No

Evidence Table 2. Quality assessments of chemotherapy head-to-head trials

Author Year Setting Type of Chemo	Postramdomization exclusions	Quality rating	Controlled group standard of care	Funding	Relevance
Dolasetron vs Ondansetron					
Fauser 1996 Multicenter 3, 4	No	Good	Yes	Hoescht Marion Roussel, Inc.	Yes
Hesketh 1996 Multicenter 5	No	Good	Yes	Supported by a grant from Hoescht Marion Roussel	Yes
Lofters, Pater (2 papers on 1 trial) 1997 Multicenter 3	Yes	Fair	Yes	Supported by the National Institute of Canada and Hoescht Marion Roussel.	Yes

Evidence Table 2. Quality assessments of chemotherapy head-to-head trials

Author Year Setting Type of Chemo	Subpopulation	Exclusion criteria	Run-in/Wash out	Screened/ Eligible/ Enrolled	Withdrawn/ Lost to fu/ Analyzed
Dolasetron vs Granisetron					
Audhuy 1996 Multicenter 5	women, prior chemo	Patients who had a history of significant neurological or psychiatric illness (except alcoholism), a history of congestive heart failure, arrhythmias requiring medication, heart block greater than first degree, cardiotoxicity due to cumulative doses of anthracyclines or anthracenediones, abnormal serum potassium or calcium concentrations, or evidence of clinically significant liver disease were excluded from the study. Also excluded were pts who had received investigational drugs within 21 days of the trial, chemo in the 72h prior to cisplatin, and treatments that could interfere with interpretation of the study results. Pts who, within 24h preceding chemo, had experienced vomiting or nausea with a severity of 2-4 according to the Southwest Oncology Group scale were also disqualified, as were patients who had experienced vomiting from any organic etiology. Pregnant women and women with uninhibited childbearing potential and pts with body weight > 83 kg (because of problems in using the double-dummy infusion) were also prohibited from entering the study.	NR/NR	NR/NR/476	2/0/474
Tan 2002 Single Center 4, 5	none	Pts receiving chemo with a low to moderate emetogenic potential.	NA/NA	NR/NR/26	0/0/26

Evidence Table 2. Quality assessments of chemotherapy head-to-head trials

Author Year Setting Type of Chemo	Randomization	Allocation	Groups similar at baseline	Eligibility criteria specified	Care provider masked	Patients masked	Attrition Crossover Adherence Contamination	Loss to follow up	Intention-to-treat analysis
Dolasetron vs Granisetron									
Audhuy 1996 Multicenter 5	Yes	NR	Yes	Yes	Yes	Yes	Yes No No No	No	Yes, but 2 excluded because no drug received
Tan 2002 Single Center 4, 5	Not randomized	Not randomized	Inadequate Information	Yes	NR	NR	No No No No	No	Yes

Evidence Table 2. Quality assessments of chemotherapy head-to-head trials

Author Year Setting Type of Chemo	Postramdomization exclusions	Quality rating	Controlled group standard of care	Funding	Relevance
Dolasetron vs Granisetron					
Audhuy 1996 Multicenter 5	No	Good	Yes	Supported by a grant from Hoescht Marion Roussel, Inc.	Yes
Tan 2002 Single Center 4, 5	Unable to determine	Poor	Yes	Roche Laboratories	Yes

Evidence Table 2. Quality assessments of chemotherapy head-to-head trials

Author Year Setting Type of Chemo	Subpopulation	Exclusion criteria	Run-in/Wash out	Screened/ Eligible/ Enrolled	Withdrawn/ Lost to fu/ Analyzed
Palonsetron					
Gralla 2003 Multicenter 4	none	Pts who could not understand or cooperate with study procedures, who were taking any drug with antiemetic activity within 24h prior to treatment until day 5 (including corticosteroids); with evidence of seizure disorder requiring anticonvulsants (unless clinically stable with no seizure activity); vomiting, retching, or National cancer Institute (NCI) Common Toxicity Criteria grade 2 or 3 nausea in the 24h preceding chemotherapy; or were scheduled for radiation of upper abdomen or cranium on days 2-6.	None/NA	NR/NR/570	12/0/563
Eisenberg 2003 Multicenter 3	none	These included receipt of an investigational drug ≤ 30 days before study entry; receipt of (within 24 h of treatment initiation) or scheduled receipt of (up to day 5) any drug with potential antiemetic properties; seizure disorder requiring anticonvulsants unless clinically stable and free of seizure activity; emesis, retching, or NCI Common Toxicity Criteria Grade 2 or 3 nausea ≤24 h before chemo; ongoing emesis due to any organic etiology; moderate or severe nausea and vomiting after any previous chemo; scheduled receipt of highly emetogenic chemo (i.e., any dose of nitrogen mustard, dacarbazine, or streptozotocin; or lomustine >60mg/m2, carmustine ≥ 250mg/m2, or any other chemo with an emetogenicity level of 5); scheduled receipt of any chemotherapeutic agent with an emetogenicity level ≥3 during study Days 2-6; contraindication to 5-HT3 receptor antagonists; enrollment in a previous study with palonosetron; receipt of radiotherapy of the upper abdomen or cranium on study Days 2-6; baseline QTc >500 ms.	NR/NR	NR/NR/592	23/0/569
Granisetron iv vs Granisetron po					
Abang 2000 Multicenter 4	BMT, PBPCT, women	Patients were ineligible if they were unable to tolerate oral therapy, experienced nausea or vomiting 24 h prior to receiving the study medications, were hypersensitive to 5-HT3 receptor antagonists or phenothiazines, or were concurrently receiving butyrophenones, hydroxyzine, benzodiazepines, cannabinoids or metoclopramide.	nr/nr	NR/NR/60	9/0/51

Evidence Table 2. Quality assessments of chemotherapy head-to-head trials

Author Year Setting Type of Chemo	Randomization	Allocation	Groups similar at baseline	Eligibility criteria specified	Care provider masked	Patients masked	Attrition Crossover Adherence Contamination	Loss to follow up	Intention-to-treat analysis
Palonsetron									
Gralla 2003 Multicenter 4	Yes	Yes	Unknown; excluded 7	Yes	Unclear	Unclear	Yes No No No	None	No
Eisenberg 2003 Multicenter 3	Yes	Yes	Unknown, because only reported B/L for PPP	Yes	Yes	Yes	Yes No No No	None	No
Granisetron iv vs Granisetron po									
Abang 2000 Multicenter 4	Yes	NR	Yes	Yes	Yes	Yes	Yes No No No	None	No, only excluded 1

Evidence Table 2. Quality assessments of chemotherapy head-to-head trials

Author Year Setting Type of Chemo	Postramdomization exclusions	Quality rating	Controlled group standard of care	Funding	Relevance
Palonsetron					
Gralla 2003 Multicenter 4	No	Fair	Yes	Helsinn Healthcare	Yes
Eisenberg 2003 Multicenter 3	No	Fair	Yes	Helsinn Healthcare SA	Yes
Granisetron iv vs Granisetron po					
Abang 2000 Multicenter 4	No	Fair	Yes	Supported by a research grant from SmithKline Beecham Pharmaceuticals	Yes

Evidence Table 3. Chemotherapy: placebo-controlled trials

Author Year Country Chemo Level	Study Design Setting	Interventions (drug Regiment, duration)	Eligibility criteria	Age Gender Ethnicity
Aprepitant				
Navari 1999 USA Hesketh chemo level 5	Multicenter DB parallel	A: Day 1: Apr 400 mg po Days 2-5: Apr 300 mg po B: Day 1: Apr 400 mg po Days 2-5: placebo C: 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 gonadatropin in serum.	Mean: 61.7 yrs Range: NR % Male: 62.9% Ethnicity: NR

NCI: National Cancer Institute; ULN: Upper limit of normal

Evidence Table 3. Chemotherapy: placebo-controlled trials

Author Year Country Chemo Level	Other population characteristics	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/analyzed	Allowed other medications/ interventions
Aprepitant				
Navari 1999 USA Hesketh chemo level 5	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		Day 1: Gran 10 mcg/kg+Dex 20 mg po; Days 2-5: not allowed except as rescue

NCI: National Cancer Institute; ULN: Upper limit of normal

Evidence Table 3. Chemotherapy: placebo-controlled trials

Author Year Country Chemo Level	Definition of Outcomes	Method of Outcome Assessment and Timing of Assessment
Aprepitant		
Navari 1999 USA Hesketh chemo level 5	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"	

NCI: National Cancer Institute; ULN: Upper limit of normal

Evidence Table 3. Chemotherapy: placebo-controlled trials

Author Year Country Chemo Level	Results	Method of adverse effects assessment
Aprepitant		
Navari 1999 USA Hesketh chemo level 5	***All comparisons: Group A vs. B vs. C*** ***Acute results (day 1)*** : No vomiting: 93% vs 94% vs 67% (p<0.001 for Groups A&B combined vs C) No emesis and no rescue therapy: 77% vs 83 % vs 57% (p=0.004 for Groups A&B combined vs C) Median nausea VAS scores: 0mm vs 0mm vs 1mm ***Delayed results (days 2-5):*** No vomiting: 82% vs 78% vs 33% (p<0.001 for Groups A&B combined vs C) No emesis and no rescue therapy: 52% vs 43% vs 16% (p<0.001 for A vs C; p=0.003 for B vs C) Pts with 0-2 emetic episodes: 98% vs 93% vs 59% (p<0.001 for Groups A& B combined vs C) No or minimal nausea: 51% vs 48% vs 24% (p=0.007 for A vs C; p=0.01 for B vs C) Median nausea VAS scores: 1mm vs 3mm vs 10mm Overall results (Days 1-5): No or minimal nausea: 49% vs 48% vs 25% (p=0.02 for A vs C; p=0.03 for B vs C) Global satisfaction median rating: 100 vs 98 vs 82 (p=0.001 for A vs C; p=0.03 for B vs C) Median nausea VAS scores: 1mm vs 2mm vs 5mm	

NCI: National Cancer Institute; ULN: Upper limit of normal

Evidence Table 3. Chemotherapy: placebo-controlled trials

Author Year Country Chemo Level	Adverse Effects Reported	Total withdrawals; withdrawals due to adverse events	Comments
Aprepitant			
Navari 1999 USA Hesketh chemo level 5	*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%		

NCI: National Cancer Institute; ULN: Upper limit of normal

Evidence Table 3. Chemotherapy: placebo-controlled trials

Author Year Country Chemo Level	Study Design Setting	Interventions (drug Regiment, duration)	Eligibility criteria	Age Gender Ethnicity
Chawla 2002 International Hesketh chemo level 5	Multicenter DB parallel	A: Day 1: Apr 40 mg po Days 2-5: Apr 25 mg po B: Day 1: Apr 125 mg po Days 2-5: Apr 80 mg po C: Day 1: placebo Days 2-5: placebo D: (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 gonadatropin test result.	Mean: 56.0 yrs Range: NR % Male: 56.4% % White: 58.3% % Black: 6.3% % Other: 35.4%

NCI: National Cancer Institute; ULN: Upper limit of normal

Evidence Table 3. Chemotherapy: placebo-controlled trials

Author Year Country Chemo Level	Other population characteristics	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/analyzed	Allowed other medications/ interventions
Chawla 2002 International Hesketh chemo level 5	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		A: Day 1: Ond 32 mg iv + Dex 20 mg po Day 2-5: Dex 8 mg po B: Day 1: Ond 32 mg iv + Dex 20 mg po Day 2-5: Dex 8 mg po C: Day 1: Ond 32 mg iv + Dex 20 mg po Day 2-5: Dex 8 mg po D: Day 1: Ond 32 mg iv + Dex 20 mg po Day 2-5: Dex 8 mg po

NCI: National Cancer Institute; ULN: Upper limit of normal

Evidence Table 3. Chemotherapy: placebo-controlled trials

Author Year Country Chemo Level	Definition of Outcomes	Method of Outcome Assessment and Timing of Assessment
Chawla 2002 International Hesketh chemo level 5	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 betweem days 19-29 postcisplatin for FU and lab lests.

NCI: National Cancer Institute; ULN: Upper limit of normal

Evidence Table 3. Chemotherapy: placebo-controlled trials

Author Year Country Chemo Level	Results	Method of adverse effects assessment
Chawla 2002 International Hesketh chemo level 5	*Comparisons are for groups A (Apr 40/25) vs. B (Apr 125/80) vs. C(placebo)* ***Acute (Day 1):*** CR: 75.6% vs 83.2% vs 71.4% (p=NR for A vs C; p=0.014 for B vs C) TC: 63.0% vs 67.9% vs. 58.7% (p=NR for both comparisons) CP: 72.3% vs 79.4% VS 66.7% (P<0.05 for A vs C; p=NR for B vs C) No emesis: 80.7% vs 87.0% vs 73.0% (p=NR for A vs C;p<0.01 for B vs C) No rescue: 87.4% vs 93.9% vs 93.7% (p=NR for both comparisons) No nausea:70.6% vs 71.8% vs 66.7% (p=NR for both comparisons) No significant nausea: 86.6% vs 90.8% vs 87.3% (p=NR for both comparisons) ***Delayed (Days 2-5):*** CR: 63.9% vs 72.7% vs 45.2% (p=0.002 for A vs C; p<0.001 for B vs C) TC: 51.3% vs 51.5% vs 32.5% (p<0.01 for A vs C and B vs C) CP: 58.0% vs 67.4% vs 41.3% (p<0.01 for A vs C and B vs C) No emesis: 69.7% vs 77.3% vs 50.0% (p<0.01 for A vs C and B vs C) No rescue: 75.6% vs 85.6% vs 63.5% (p<0.05 for A vs C; p<0.01 for B vs C) No nausea: 52.9% vs 58.3% vs 36.5% (p<0.01 for A vs C and B vs C) No significant nausea: 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):*** CR: 58.8% vs 71.0% vs 43.7% (p<0.05 for A vs C; p<0.01 for B vs C) TC: 44.5% vs 47.3% vs 31.0% (p<0.05 for A vs C; p<0.01 for B vs C) CP: 44.5 % vs 47.3% vs 31.0% (p<0.05 for A vs C; p<0.01 for B vs C) No emesis: 76.3% vs 65.5% vs 48.4% (p<0.01 for A vs C and B vs C) No rescue: 73.1% vs 83.2% vs 63.5% (p=NS for A vs C; p<0.01 for B vs C) No nausea: 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: 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 phsycial exams, including vital signs and weight measurements, lab studies, and electrocardiograms.

NCI: National Cancer Institute; ULN: Upper limit of normal

Evidence Table 3. Chemotherapy: placebo-controlled trials

Author Year Country Chemo Level	Adverse Effects Reported	Total withdrawals; withdrawals due to adverse events	Comments
Chawla 2002 International Hesketh chemo level 5	*Comparisons: Groups A (40/25) vs B (125/80) vs C (placebo) vs D (375/250)* % with ≥ 1 adverse event (AEs)*: 71% vs 76% vs 72% vs 85%* % with drug-related AEs*: 27% vs 27% vs 26% vs 15%* % with serious AEs*: 17% vs 22% vs 12% vs 21%* % discontinued due to AEs*: 1% vs 2% vs 1% vs 9%* % with ≥ 1 laboratory AE*: 22% vs 23% vs 22% vs 27%* % with drug-related laboratory AE*: 6% vs 8% vs 9% vs 0%* With 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%* % with 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%

NCI: National Cancer Institute; ULN: Upper limit of normal

Evidence Table 3. Chemotherapy: placebo-controlled trials

Author Year Country Chemo Level	Study Design Setting	Interventions (drug Regiment, duration)	Eligibility criteria	Age Gender Ethnicity
de Wit 2003 International Hesketh chemo level 5 (this study population seems to be the pre-dose adjustment cadre from the Chawla paper) This study looked at 6 cycles of chemo; data for Cycles 1 & 2 only are abstracted here	Multicenter DB parallel	A: Day 1: Apr 375 mg Days 2-5: Apr 250 mg B: Day 1: Apr 125 mg Days 2-5: Apr 80 mg C: 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)	Mean: 57.7 yrs Range: 20-82 yrs % Male: 63.9% % White: 73.8% % Black: 4.4% % Other: 21.8%

NCI: National Cancer Institute; ULN: Upper limit of normal

Evidence Table 3. Chemotherapy: placebo-controlled trials

Author Year Country Chemo Level	Other population characteristics	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/analyzed	Allowed other medications/ interventions
de Wit 2003 International Hesketh chemo level 5 (this study population seems to be the pre-dose adjustment cadre from the Chawla paper) This study looked at 6 cycles of chemo; data for Cycles 1 & 2 only are abstracted here	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 72h of day 1 of cycle 1

NCI: National Cancer Institute; ULN: Upper limit of normal

Evidence Table 3. Chemotherapy: placebo-controlled trials

Author Year Country Chemo Level	Definition of Outcomes	Method of Outcome Assessment and Timing of Assessment
de Wit 2003 International Hesketh chemo level 5 (this study population seems to be the pre-dose adjustment cadre from the Chawla paper) This study looked at 6 cycles of chemo; data for Cycles 1 & 2 only are abstracted here	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 or rescue therapy	

NCI: National Cancer Institute; ULN: Upper limit of normal

Evidence Table 3. Chemotherapy: placebo-controlled trials

Author Year Country Chemo Level	Results	Method of adverse effects assessment
de Wit 2003 International Hesketh chemo level 5 (this study population seems to be the pre-dose adjustment cadre from the Chawla paper) This study looked at 6 cycles of chemo; data for Cycles 1 & 2 only are abstracted here	<u>Cycle 1 data: (Group B (n=80) vs. C(n=84))</u> % 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 <u>Cycle 2 data: (Group B (n=46) vs. C(n=38))</u> % Complete response: 80% vs 71%, p=NR % Partial response: 10.9% vs15.8%, p=NR % Failures: 8.7% vs 13.1%, p=NR	

NCI: National Cancer Institute; ULN: Upper limit of normal

Evidence Table 3. Chemotherapy: placebo-controlled trials

Author Year Country Chemo Level	Adverse Effects Reported	Total withdrawals; withdrawals due to adverse events	Comments
de Wit 2003 International Hesketh chemo level 5 (this study population seems to be the pre-dose adjustment cadre from the Chawla paper) This study looked at 6 cycles of chemo; data for Cycles 1 & 2 only are abstracted here	*Comparisons: Groups A (375/250, n=23) vs B (125/80, n=62) vs C (placebo, n=60)* **For AEs in cycles 2-6** % with ≥ 1 adverse event (AEs): 74 vs 76 vs 73 % with drug-related AEs: 26 vs 34 vs 25 % with serious AEs: 9 vs 26 vs 15 % discontinued due to AEs: 13 vs 10 vs 10 % with ≥1 laboratory AE: 22 vs 26 vs 27 % with drug-related laboratory AE: 0 vs 7 vs 5 With 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		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)

NCI: National Cancer Institute; ULN: Upper limit of normal

Evidence Table 3. Chemotherapy: placebo-controlled trials

Author Year Country Chemo Level	Study Design Setting	Interventions (drug Regiment, duration)	Eligibility criteria	Age Gender Ethnicity
Hesketh 2003 International Hesketh chemo level 5	Multicenter DB parallel	A: Day 1: Apr 125 mg po Days 2-3: Apr 80 mg po Day 4: placebo B: Day 1: placebo Days 2-4: placebo 1 hour before cisplatin on Day 1, pts recevied 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.	Mean: 58.5 yrs Range: 18-84 yrs % Male: 62.5% % White: 3.0% % Black: 90.6% % Other: 6.4%

NCI: National Cancer Institute; ULN: Upper limit of normal

Evidence Table 3. Chemotherapy: placebo-controlled trials

Author Year Country Chemo Level	Other population characteristics	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/analyzed	Allowed other medications/ interventions
Hesketh 2003 International Hesketh chemo level 5	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	/ /521	A: Day 1: Ond 32 mg iv + Dex 12 mg po Day 2-4: Dex 8 mg po once/day 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

NCI: National Cancer Institute; ULN: Upper limit of normal

Evidence Table 3. Chemotherapy: placebo-controlled trials

Author Year Country Chemo Level	Definition of Outcomes	Method of Outcome Assessment and Timing of Assessment
Hesketh 2003 International Hesketh chemo level 5	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)

NCI: National Cancer Institute; ULN: Upper limit of normal

Evidence Table 3. Chemotherapy: placebo-controlled trials

Author Year Country Chemo Level	Results	Method of adverse effects assessment
Hesketh 2003 International Hesketh chemo level 5	*Comparisons are for groups A(Apr 125/80) vs. B(placebo)* **Acute (Day 1):** CR: 89.2% vs 78.1%; p<0.001 TC: 70.7% vs 64.2%, p=NR CP: 84.8% vs 74.6%, p<0.01 No emesis: 90.0% vs 79.3%, p<0.01 No rescue: 94.2% vs 88.8%, p<0.05 No nausea: 72.3% vs 69.1%, p=NR No significant nausea: 90.6% vs 86.5%, p=NR D**elayed (Days 2-5):** CR: 75.4% vs 55.8%; p<0.001 TC: 49.0% vs 42.7%, p=NR CP: 66.4% vs 51.5%, p<0.01 No emesis: 80.8% vs 58.8%, p<0.01 No rescue: 81.2% vs 73.5%, p<0.05 No nausea: 51.0% vs 47.7%, p=NR No significant nausea: 75.3% vs 68.5%, p=NR **Overall (Days 1-5):** CR: 72.7% vs 52.3%, p<0.001 TC: 45.5% vs 40.0%, p=NR CP: 63.4% vs 49.2%, p<0.01 No emesis: 77.7% vs 55.0%, p<0.01 No rescue: 80.8% vs 70.8%, p<0.01 No nausea: 47.5% vs 44.2%, p=NR No significant nausea: 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

NCI: National Cancer Institute; ULN: Upper limit of normal

Evidence Table 3. Chemotherapy: placebo-controlled trials

Author Year Country Chemo Level	Adverse Effects Reported	Total withdrawals; withdrawals due to adverse events	Comments
Hesketh 2003 International Hesketh chemo level 5	***Comparisons made between Groups A (n=261) and B (n=264)*** % with ≥ 1 clinical adverse event (AE): 65.1% vs 61.4% % with drug-related clinical AEs: 14.6% vs 11.0% % with serious clinical AEs: 16.1% vs 17.0% % with ≥ 1 laboratory AE: 14.0% vs 13.5% % with drug-related laboratory AE: 2.3% vs 1.2% With 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 of the 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 hypnoatremia		

NCI: National Cancer Institute; ULN: Upper limit of normal

Evidence Table 3. Chemotherapy: placebo-controlled trials

Author Year Country Chemo Level	Study Design Setting	Interventions (drug Regiment, duration)	Eligibility criteria	Age Gender Ethnicity
Poli-Bigelli 2003 Latin America Hesketh chemo level 5	Multicenter DB parallel	A: Day 1: Apr 125 mg po Days 2 & 3: Apr 80 mg po Day 4: no Apr given B: 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 wo 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 gonadatropin test result.	Mean: 53.5 yrs Range: 18-82 yrs % Male: 51.5% Black: 5.4% White: 29.5% Other: 65.0%

NCI: National Cancer Institute; ULN: Upper limit of normal

Evidence Table 3. Chemotherapy: placebo-controlled trials

Author Year Country Chemo Level	Other population characteristics	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/analyzed	Allowed other medications/ interventions
Poli-Bigelli 2003 Latin America Hesketh chemo level 5	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		A: Day 1: Ond 32 mg iv Days 2-4: Dex 8 mg po B: Day 1: Ond 32 mg iv Days 2-4: Dex 8 mg po

NCI: National Cancer Institute; ULN: Upper limit of normal

Evidence Table 3. Chemotherapy: placebo-controlled trials

Author Year Country Chemo Level	Definition of Outcomes	Method of Outcome Assessment and Timing of Assessment
Poli-Bigelli 2003 Latin America Hesketh chemo level 5	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

NCI: National Cancer Institute; ULN: Upper limit of normal

Evidence Table 3. Chemotherapy: placebo-controlled trials

Author Year Country Chemo Level	Results	Method of adverse effects assessment
Poli-Bigelli 2003 Latin America Hesketh chemo level 5	*for all results, comparisons are for Group A vs. Group B* ***Acute results (day 1):*** CR: 82.8% vs 68.4% (p<0.001) CP: 80.0% vs 64.6% (p<0.01) TC: 64% vs 57% (p=NS) No emesis: 84% vs 69% (p<0.01) No rescue: 96% vs 90% (p<0.01) ***Delayed results (Days 2-5):*** CR: 67.7% vs 46.8% (p<0.001) CP: 60.9% vs 44.1% (p<0.01) TC: 50% vs 34% (p<0.01) No emesis: 72% vs 48% (p<0.01) No rescue: 83% vs 74% (p<0.05) ***Overall results (Days 1-5):*** CR: 62.7% vs 43.3% (p<0.001) CP: 55.6% vs 40.7% (p<0.01) TC: 44% vs 32 % (p<0.01) No emesis: 66% vs 44% (p<0.01) No rescue: 82% vs 73% (p<0.01) *FLIE: minimal or no impact on daily life: 74.7% vs 63.5% (p=<0.05)*	

NCI: National Cancer Institute; ULN: Upper limit of normal

Evidence Table 3. Chemotherapy: placebo-controlled trials

Author Year Country Chemo Level	Adverse Effects Reported	Total withdrawals; withdrawals due to adverse events	Comments
Poli-Bigelli 2003 Latin America Hesketh chemo level 5	*Comparisons made between Aprepitant (n=282) and Placebo (n=285)* % with ≥ 1 clinical adverse event (AE): 72.7% vs 72.6% % with drug-related clinical AEs: 19.5% vs 14.4% % with serious clinical AEs: 11.0% vs 9.8% % discontinued due to a clinical AE: 7.1% vs 5.3% % with ≥ 1 laboratory AE: 29.6% vs 25.2% % with drug-related laboratory AE: 5.7% vs 3.9% With 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		

NCI: National Cancer Institute; ULN: Upper limit of normal

Evidence Table 3. Chemotherapy: placebo-controlled trials

Author Year Country Chemo Level	Study Design Setting	Interventions (drug Regiment, duration)	Eligibility criteria	Age Gender Ethnicity
Warr 2005 International (95 centers) Hesketh chemo level 4	Multicenter DB parallel	A: (N=438) Day 1: Apr 125 mg po 1 hr before chemo Day 2-3: Apr 80 mg po B: (N=428) Day 1: placebo po Day 2-3: placebo po	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: 52.6 yrs Female: 99.8% White: 78.6%

NCI: National Cancer Institute; ULN: Upper limit of normal

Evidence Table 3. Chemotherapy: placebo-controlled trials

Author Year Country Chemo Level	Other population characteristics	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/analyzed	Allowed other medications/ interventions
Warr 2005 International (95 centers) Hesketh chemo level 4	Motion sickness: 18.9% History of vomiting during pregnancy: 30.5%	910 / unclear / 866	122 / NR / 857	Antiemetic treatments were not allowed within 48 hour before treatment, except for single daily doses of lorazepam. 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 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: 8 mg po bid

NCI: National Cancer Institute; ULN: Upper limit of normal

Evidence Table 3. Chemotherapy: placebo-controlled trials

Author Year Country Chemo Level	Definition of Outcomes	Method of Outcome Assessment and Timing of Assessment
Warr 2005 International (95 centers) Hesketh chemo level 4	Complete response: no vomiting and no recuse 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 questionnare (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.

NCI: National Cancer Institute; ULN: Upper limit of normal

Evidence Table 3. Chemotherapy: placebo-controlled trials

Author Year Country Chemo Level	Results	Method of adverse effects assessment
Warr 2005 International (95 centers) Hesketh chemo level 4	Aprepitant vs placebo Complete response for 0-120 hours: 51% vs 42%, p=0.015 Complete response for acute (0-24 h) phase: 76% vs 69%, p=0.34 Complete response for delayed (24-120h) phase: 55% vs 49%, p=0.64 % of patients reporiting no vomiting: 76% vs 59%, p<0.001 No significant difference between groups in use of rescue therapy FLIE: Patients reporting 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 statistcal review of AEs, vital signs, and laboratory values.

NCI: National Cancer Institute; ULN: Upper limit of normal

Evidence Table 3. Chemotherapy: placebo-controlled trials

Author Year Country Chemo Level	Adverse Effects Reported	Total withdrawals; withdrawals due to adverse events	Comments
Warr 2005 International (95 centers) Hesketh chemo level 4	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 Total withdrawals due to AEs: 1.4% (12/866 patients) By drug: apr 1.6% vs placebo 2.1%	

NCI: National Cancer Institute; ULN: Upper limit of normal

Evidence Table 3. Chemotherapy: placebo-controlled trials

Author Year Country Chemo Level	Study Design Setting	Interventions (drug Regiment, duration)	Eligibility criteria	Age Gender Ethnicity
Other outcomes				
Barrenetxea 1996 Spain	Single-center DB parallel	A: Day 1: Ond 8 mg iv Day 2-4: Ond 8 mg po X3 B: Day 1: Ong 8 mg iv Days 2-4: metoclopramide 10 mg po X3 C: Day 1: Ond 8 mg iv Days 2-4: placebo X3	Breast cancer pts who were eligible if they had received no previous chemo, were ≥ 18 yrs, and had a Karnofsky status of ≥ 60%. Pts were receiving either a regimen of CMF [cyclophosphamide 500 mg day 1, methotrexate 50 mg on days 1 & 8, and 5-fluouracil 600 mg days 1 & 8] every 28 days or of FEC [cyclophosphamide 500 mg day 1, epirubicin 75 mg day 1, and 5-fluorouracil on day 1] every 21days. All pts selected were available for follow-up.	Age: NR Gender: NR Ethnicity: NR

NCI: National Cancer Institute; ULN: Upper limit of normal

Evidence Table 3. Chemotherapy: placebo-controlled trials

Author Year Country Chemo Level	Other population characteristics	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/analyzed	Allowed other medications/ interventions
Other outcomes				
Barrenetxea 1996 Spain	Cancer: 100% breast cancer	NR/NR/NR	NR/NR/NR	No

NCI: National Cancer Institute; ULN: Upper limit of normal

Evidence Table 3. Chemotherapy: placebo-controlled trials

Author Year Country Chemo Level	Definition of Outcomes	Method of Outcome Assessment and Timing of Assessment
Other outcomes		
Barrenetxea 1996 Spain	Primary efficacy measure: Number of emetic episodes: Complete response: no emetic episode Major response: 1-2 emetic episodes Minor response: 3-5 emetic episodes Faliure: >5 emetic episodes C+M response = Complete + major responses Failure rate = Minor + failure responses Quality of Life: Functional Living Index (FLIC): 7 pts scale, with 7=good and 1=poor	FLIC questionnaire complete during a 5 day period following chemo; the degree of nausea and disability were recorded each day on a 7-point scale.

NCI: National Cancer Institute; ULN: Upper limit of normal

Evidence Table 3. Chemotherapy: placebo-controlled trials

Author Year Country Chemo Level	Results	Method of adverse effects assessment
Other outcomes		
Barrenetxea 1996 Spain	*(Data given for number of emetic episodes, but not reported here)* *FLIC scores are approximates because they are read from a graph* **CMF Pts FLIC scores by day, A vs B vs C:** Day 1: 5.1 vs 5 vs 1; p<0.0001 for A & B vs C Day 2: 5 vs 5 vs 2.7; p<0.0001 for A & B vs C Day 3: 5 vs. 5.1 vs 3.5; p<0.0001 for A & B vs C Day 4: 5.2 vs 5.6 vs 3.9; p<0.0001 for A & B vs C Day 5: 5.5 vs 6 vs 4.8; p<0.0001 for A & B vs C **FEC pts FLIC scores by day, A vs B vs C:** Day 1: 4.6 vs 3.7 vs 0.7; p<0.0001 for C vs A; p=0.0440 for C vs B Day 2: 3.9 vs 3.3 vs 2.2; p=NS Day 3: 4.6 vs 4.1 vs 2.2; p=0.032 *(note: p-value given but comparison to which it belongs is not stated)* Day 4: 5.3 vs 5.2 vs 3.3; p=NS Day 5: 5.7 vs 6.1 vs 3.7; p=NS	NR

NCI: National Cancer Institute; ULN: Upper limit of normal

Evidence Table 3. Chemotherapy: placebo-controlled trials

Author Year Country Chemo Level	Adverse Effects Reported	Total withdrawals; withdrawals due to adverse events	Comments
Other outcomes			
Barrenetxea 1996 Spain	"No severe or unexpected event was reported by the pts. Constipation and hot flushes tended to be more frequent among pts receiving Ond for 3 days (group A) than in pts assinged to Groups B or C. However, there was no significant differences between the groups (p=0.1421 and p=0.1001 for constipation and hot flushes respectively.)"	NR; NR	

NCI: National Cancer Institute; ULN: Upper limit of normal

Evidence Table 4. Quality assessments of the chemotherapy placebo-controlled trials

	Internal Validity						
Author Year Country Chemo Level	**Randomization adequate?**	**Allocation concealment adequate?**	**Groups similar at baseline?**	**Eligibility criteria specified?**	**Outcome assessors masked?**	**Care provider masked?**	**Patient masked?**
Aprepitant							
Navari 1999 USA Hesketh chemo level 5	Yes	NR	Yes	Yes	NR	Yes	Yes
Chawla 2002 International Hesketh chemo level 5	Yes	NR	Yes	Yes	NR	Yes	Yes
de Wit 2003 International Hesketh chemo level 5 (study looked at 6 cycles of chemo; data for Cycle 1 only is abstracted here) Study is discontinued arm of **Chawla 2002 trial**	NR	NR	Yes	Yes	NR	NR	NR

Evidence Table 4. Quality assessments of the chemotherapy placebo-controlled trials

	Internal Validity				
Author Year Country Chemo Level	**Reporting of attrition, crossovers, adherence, and contamination**	**Loss to follow-up: differential/high**	**Intention-to-treat (ITT) analysis**	**Post-randomization exclusions**	**Quality Rating**
Aprepitant					
Navari 1999 USA Hesketh chemo level 5	Yes, No, No, No	None	No, but only excluded 2 (1.2%)	No	Fair
Chawla 2002 International Hesketh chemo level 5	Yes, No, No, No	None	No, but only excluded 5 (1.3%)	No	Fair
de Wit 2003 International Hesketh chemo level 5 (study looked at 6 cycles of chemo; data for Cycle 1 only is abstracted here) Study is discontinued arm of **Chawla 2002 trial**	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

Evidence Table 4. Quality assessments of the chemotherapy placebo-controlled trials

	External Validity	
Author Year Country Chemo Level	**Number screened/ eligible/ enrolled**	**Exclusion criteria**
Aprepitant		
Navari 1999 USA Hesketh chemo level 5	NR/159/159	Primary exclusion criteria included a Karnofsky score<60; allergy to or intolerance of metoclopramide, dexamethosone, or granisetron; therapy with another antiemetic drug (serotonin antagonists, phenothiazines, butyrophenones, cannabinoids, metoclopramide, or glucocorticoids) within 72h before day 1; an episode of vomiting or retching within 24h before the start of the cisplatin infusion; treatment for or history of a seizure within previous two years; severe concurrent illness other than cancer; gastrointestinal obstruction or active peptic ulcer; radiation therapy to the abdomen or pelvis within 1 week before or after day 1; or any of the following laboratory levels: hemoglobin < 8.5 g/dL, white-cell count <3500/mm3, platelet count <100,000/mm3, serum aspartate aminotransferase level ≥2X upper limit of normal (ULN), serum alanine aminotransferase ≥2X ULN, serum bilirubin ≥2X ULN, serum alkaline phosphatase ≥2X ULN, serum albumin <3 g/dL, and serum creatinine level >2 mg/dL (180 micro-mol/L). Five pts scheduled to receive paclitaxel plus cisplatin were permitted to receive additional glucocoricoids before day 1.
Chawla 2002 International Hesketh chemo level 5	NR/381/381	Exclusion criteria: concomitant treatment with nonapproved drug within 4 wks of study entry; significantly abnormal lab values (including white blood cell count < 3000/mm3, absolute neutrophil count <1500/mm3, platelet count <100,000/mm3, aspartate aminotransferase >2.5X ULN; alanine aminotransferase >2.5X ULN, bilirubin >1.5X ULN, or creatinine >1.5X ULN); known CNS malignancy, active infection or uncontrolled disease that should exclude the patient for safety reasons; a planned regimen of multiple-day, cisplatin-based chemotherapy in a single cycle; moderately or highly emetogenic chemo on the days prior to and/or after cisplatin; or radiation therapy to the abdomen or pelvis within 1 wk prior to day 1. Aside from study drug, additional antiemetics including benzodiazepines, opiates, or other agents (such as 5-HT3 antagonists, phenothiazines, butyrophenones, benzamides, domperidone, or cannabinoids) were not permitted within 72h of day 1, except as rescue therapy for established nausea or emesis after cisplatin. Corticosteroid therapy equivalent to ≤10 mg of prednisone was permittred provided it was not initiated within 72h of day 1.
de Wit 2003 International Hesketh chemo level 5 (study looked at 6 cycles of chemo; data for Cycle 1 only is abstracted here) Study is discontinued arm of **Chawla 2002 trial**	NR/NR/202	see Chawla 2005

Evidence Table 4. Quality assessments of the chemotherapy placebo-controlled trials

	External Validity				
Author Year Country Chemo Level	**Run-in/ Washout**	**Class naïve patients only**	**Control group standard of care**	**Funding**	**Relevance**
Aprepitant					
Navari 1999 USA Hesketh chemo level 5	No/No	Cisplatin naïve	Yes	NR, but 1st author is with Merck	Yes
Chawla 2002 International Hesketh chemo level 5	No/No	Cisplatin naïve	Yes	Merck	Yes
de Wit 2003 International Hesketh chemo level 5 (study looked at 6 cycles of chemo; data for Cycle 1 only is abstracted here) Study is discontinued arm of **Chawla 2002 trial**	NR/NR	Yes	Yes	Merck; 1st author is consultant for Merck	Yes

Evidence Table 4. Quality assessments of the chemotherapy placebo-controlled trials

	Internal Validity						
Author Year Country Chemo Level	**Randomization adequate?**	**Allocation concealment adequate?**	**Groups similar at baseline?**	**Eligibility criteria specified?**	**Outcome assessors masked?**	**Care provider masked?**	**Patient masked?**
Hesketh 2003 International Hesketh chemo level 5	Yes	Yes	Yes	Yes	NR	Yes	Yes
Poli-Bigelli 2003 Latin America Hesketh chemo level 5	Yes	NR	Several statistically insignificant differences	Yes	NR	Yes	Yes
Warr 2005 International Hesketh chemo level 4	Yes	NR	Yes	Yes	NR	Yes	Yes

Evidence Table 4. Quality assessments of the chemotherapy placebo-controlled trials

	Internal Validity				
Author Year Country Chemo Level	**Reporting of attrition, crossovers, adherence, and contamination**	**Loss to follow-up: differential/high**	**Intention-to-treat (ITT) analysis**	**Post-randomization exclusions**	**Quality Rating**
Hesketh 2003 International Hesketh chemo level 5	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
Poli-Bigelli 2003 Latin America Hesketh chemo level 5	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-
Warr 2005 International Hesketh chemo level 4	Yes, No, No, No	No loss to follow-up	No for efficacy (excluded 1%); yes for safety	No	Fair

Evidence Table 4. Quality assessments of the chemotherapy placebo-controlled trials

External Validity

Author Year Country Chemo Level	Number screened/ eligible/ enrolled	Exclusion criteria
Hesketh 2003 International Hesketh chemo level 5	562/530/530	Primary exclusion criteria included: a current user of illicit drugs or had signs of current alcohol abuse; abnormal laboratory values (including WBC< 3,000/mm3 and absolute neutrophil count< 1,500/mm3, platelet count < 100,000/mm3, AST > 2.5X upper limit of normal [ULN], ALT > 2.5X ULN, bilibrubin >1.5X ULN, or creatinine >1.5X ULN); uncontrolled disease for which, in the opinion of the investigator, the patient should be excluded for safety reasons; multiple-day cisplatin-based chemotherapy in a single cycle; or radiation therapy to the abdomen or pelvis within 1 wk before study day 1 or between days 1- 6. Additional chemotherapeutic agents of high emetogenicity (Hesketh level ≥3) were permitted only on day 1; pts could not have received such agents within 6 days before or after day 1. Pts could not receive additional antiemetics within 2 days before day 1 or between days 1 and 6 of the study, unless such medications were given as rescue therapy for established nausea or vomiting.
Poli-Bigelli 2003 Latin America Hesketh chemo level 5	624/569/569	Primary exclusion criteria included: abnormal lab values (including white blood count < 3000/mm3 and absolute neutrophil count < 1500/mm3, platelet count < 100,000/mm3, aspartate aminotransferase >2.5X ULN, alanine aminotransferase >2.5X ULN, bilirubin > 1.5X ULN, or creatinine >1.5X ULN); active infection or uncotrolled disease that excluded the pt for safety reasons; a planned regimen of multiple-day cisplatin-based chemotherapy in a single cycle; radiation therapy to the abdomen or pelvis within 1 week prior to day 1 of study or between day 1 and day 6; or moderately or hightly emetogenic chemotherapy on the 6 days prior to and/or after the day the cisplatin infusion. Additional chemo agents of high emetogenicity (Hesketh level ≥3) were permitted only on day 1, and additional antiemetics were prohibited within 2 days prior to day 1 or between day 1 and day 6 of study, unless such medicaitons were given as rescue therapy for established nausea and vomiting.
Warr 2005 International Hesketh chemo level 4	910/866/866	Patients were excluded if they had a symptomatic CNS malignancy; received radiation therapy to the abdomen or pelvis in the week before treatment; had vomited in the 24 hours before treatment day 1; had an active infection, an active systemic fungal infection, or any severe concurrent illness except for malignancy; or had abnormal laboratory values (including absolute neutrophil count < 1,500/mm3, WBC count < 3,000/mm3, platelet count < 100,000/mm3, AST > 2.5x the upper limit of normal, ALT > 2.5x the upper limit of normal, bilirubin > 1.5x the upper limit of normal, creatinine > 1.5x the upper limit of normal). Patients taking systemic corticosteroid therapy at any dose were excluded. Antiemetic agents could not be administered within 48 hours before treatment, except for single daily doses of lorazepam.

Evidence Table 4. Quality assessments of the chemotherapy placebo-controlled trials

External Validity

Author Year Country Chemo Level	Run-in/ Washout	Class naïve patients only	Control group standard of care	Funding	Relevance
Hesketh 2003 International Hesketh chemo level 5	No/No	Naïve to cisplatin	Yes	Merck	Yes
Poli-Bigelli 2003 Latin America Hesketh chemo level 5	No/No	Cisplatin naïve	Yes	Merck	Yes
Warr 2005 International Hesketh chemo level 4	No/No	Naïve to emetogenic chemotherapy	Yes	Merck	Yes

Evidence Table 4. Quality assessments of the chemotherapy placebo-controlled trials

Internal Validity

Author Year Country Chemo Level	Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors masked?	Care provider masked?	Patient masked?
Other outcomes							
Barrenetxea 1996 Spain	NR	NR	Unclear; comments (no table) made about "evaluable" PATIENTS; whereas it was CYCLES that were evaluated; unclear how number of patients corresponds to number of cycles	Yes	NR	Yes	Yes

Evidence Table 4. Quality assessments of the chemotherapy placebo-controlled trials

	Internal Validity				
Author Year Country Chemo Level	**Reporting of attrition, crossovers, adherence, and contamination**	**Loss to follow-up: differential/high**	**Intention-to-treat (ITT) analysis**	**Post-randomization exclusions**	**Quality Rating**
Other outcomes					
Barrenetxea 1996 Spain	No, No, No, No	Unclear	Unclear	Unclear	Poor

Evidence Table 4. Quality assessments of the chemotherapy placebo-controlled trials

	External Validity	
Author Year Country Chemo Level	**Number screened/ eligible/ enrolled**	**Exclusion criteria**
Other outcomes		
Barrenetxea 1996 Spain	NR/NR/NR	Pts with severe concurrent illness, had jaundice or showed laboratory evidence of hepatic dysfunction not attributable to metastatic involvement; required rescue medication

Evidence Table 4. Quality assessments of the chemotherapy placebo-controlled trials

	External Validity				
Author Year Country Chemo Level	**Run-in/ Washout**	**Class naïve patients only**	**Control group standard of care**	**Funding**	**Relevance**
Other outcomes					
Barrenetxea 1996 Spain	No/No	Chemotherapy naïve	Yes	NR	Yes

Evidence Table 5. Chemotherapy active-controlled trials

Author Year Setting Chemo Level Type of Test	Design	Subpopulation	Exclusion criteria
Bhatia 2004 Single Center 5 Rotterdam	RCT Observer blind Parallel	NR	Pts excluded if any applied: severe concurrent illness, vomiting due to some other cause, antiemetic therapy administered concurrently or in the 24 preceding chemo, administration of benzodiazepines except when given for night sedation, vomiting in 24h before chemo, pregnant or lactating women, concurrent radiation therapy, impaired renal function (serum creatinine >2.0 mg/dL) jaundice (serum bilirubin >2.0 mg/dL) or an elevated aminotranserase level (SGOT/SGPT> 2X ULN).
Lachaine 1999 Single Center 4 EORTC, QLC-3	Not Randomized Not blinded Parallel	women, breast cancer	NR
Clavel 1995 Multicenter 4 FLIE; FLIC	DB RCT Parallel	women, breast cancer	Pts not eligible if any of the following applied: serious disease other than the cancer being treted, another cause of nausea or vomiting other than the chemo, a clinical hepatic disorder, a persistant chronic alcoholism, emesis or anti-emetic treatment during 24h preceding study entry.

Cyclo = cyclophosphamide; Dox = doxorubicin; Epir = epirubicin; Dex = dexamethasone; Ond = ondansetron; meto = metoclopramide

Evidence Table 5. Chemotherapy active-controlled trials

Author Year Setting Chemo Level Type of Test	Intervention	Allowed other medication	Run-in/Wash out	Age Gender Ethnicity	Screened/ Eligible/ Enrolled	Withdrawn/ Lost to fu/ Analyzed
Bhatia 2004 Single Center 5 Rotterdam	There were 6 groups: I, II, IIIa, IIIb IVa, IVb Ond: 8 mg iv (30 min prior to each cisplatin administration); 8 mg ond po tid for 5 days this Ond regimen given to II, IVa, IVb Meto: 20 mg iv (30 min prior to cisplatin); 20 mg po tid for 5 days this meto regiment given to I, IIIa, IIIb	Dex 8 mg iv given to groups IIIb and IVb along with study meds	No run-in; washout-no antiemetics within 24h of study entry	Mean Age: 45.7y 0% male	NR/NR/80	NR/NR/80
Lachaine 1999 Single Center 4 EORTC, QLC-3	A: Ond 21mg (avg dose for Day 1) B: Metaclopramide 306mg	A: for 91% of these pts, Dex ~19 mg on day 1 and 53% received 1 mg lorazepam;		Mean age: 55.4y 0% male Ethnicity: NR	NR/NR/58	5/NR/52
Clavel 1995 Multicenter 4 FLIE; FLIC	A: Ond po (tablet) 16mg (8 mg bid) B: Alizapride iv 150mg	No	No run-in; washout-no antiemetics within 24h of study entry	Mean Age: 51.5y 0%male NR	NR/259/259	5/NR/254

Cyclo = cyclophosphamide; Dox = doxorubicin; Epir = epirubicin; Dex = dexamethasone; Ond = ondansetron; meto = metoclopramide

Evidence Table 5. Chemotherapy active-controlled trials

Author Year Setting Chemo Level Type of Test	Other population characteristics
Bhatia 2004 Single Center 5 Rotterdam	Malignancy: Head and Neck 54% Cervix 41% Others 5% Tumour surgery: Yes: 14% vs No: 86% Alcohol intake: none 80% <7 units/wk 14% >7 units/wk 6% % smokers: 49% Karnofsky Performance mean score: 96.9 (+/- 4.7) % with history of motion sickness: 0%
Lachaine 1999 Single Center 4 EORTC, QLC-3	Average Body Surface: 1.68 m2 (+/- 8.5 m2) Average dose cyclophosphamide: 990 mg (+/- 157mg) Language: French Speaking: 41%; English Speaking: 50% Chemo types: Cyclo + dox: 57%; CMF: 24%; FAC: 3%; Cyclo + carboplatin: 3%; Cyclo + epir 2%
Clavel 1995 Multicenter 4 FLIE; FLIC	Mean body surface area: 1.66 (+/- 0.01) m2 Alcohol consumption >4 units/day: 0% Histological type: Ductal: 87% Lobular: 7% Colloid: 0% Other: 4% Chemotherapy regimens: FEC: 79%, FAC: 20%

Cyclo = cyclophosphamide; Dox = doxorubicin; Epir = epirubicin; Dex = dexamethasone; Ond = ondansetron; meto = metoclopramide

Evidence Table 5. Chemotherapy active-controlled trials

Author Year Setting Chemo Level Type of Test	Results
Bhatia 2004 Single Center 5 Rotterdam	*Comparisons are for* ***I*** *(M+C-20) vs* ***II*** *(O+C-20) vs* ***IIIa*** *(M+C-60) vs* ***IVa*** *(O+C-60) vs* ***IIIb*** *(M+D+C-60)* Quality of Life scores Psychological subscale (QoL): (0="not at all", 1="a little", 2="somewhat", 3="very much") Day 0 score(Day 5 score): 1.1(1.0) vs 2.1(1.8) vs 2.3(1.6) vs 2.9(2.9) vs 2.7(1.8), NS Physcial subscale (QoL): (0="not at all", 1="a little", 2="somewhat", 3="very much") Day 0 score(Day 5 score): 1.2(1.0) vs 1.2(1.2) vs 1.7(2.2) vs 1.9(2.2) vs 1.9(1.5), NS Functional subscale (QoL): (0="without help", 1="w/o helf with difficulty", 2="only with help", 3="unable") Day 0 score(Day 5 score): 1.5(1.5) vs 2.4(2.4) vs 1.9(1.9) vs 1.0(1.0) vs 2.8(2.8), NS Patient satisfaction mean scores: (0="not at all satisfied" to 100="totally satisfied") 75.7 vs 86 vs 45 vs 65 vs 68; IIIb vs IVb, p<0.02
Lachaine 1999 Single Center 4 EORTC, QLC-3	Mean change in ETORCG scores between baseline and Day 3 Physical: -19 vs. -35, p=NS Role Functioning: -2 vs. -13, p=0.002 Emotional: +8 vs. +5, p=NS Cognitive: -5 vs. -13, p=NS Social: -9 vs. -2, p=NS Global health/QoL: -21 vs. -22, p=0.28 Nausea/vomiting: 13 vs. 11, p=NS
Clavel 1995 Multicenter 4 FLIE; FLIC	*all data given as Ond vs Aliz* Pt nausea grade (0= none, 100= nausea as bad as it could be) : 25.8 vs 44.5 (p<0.0001) Pt satisfaction: pts wished to receive same treatment during next chemo regimen: 83% vs 54%, p<0.001 *For FLIC and FLIE, a lower score means a better QoL for the pt* Mean differences in FLIC scores (change from baseline to post-chemo): -0.55 vs 0-.73, p=NS Mean differences in FLIE scores (change from baseline to post-chemo): -1.45 vs -1.93, p=0.04

Cyclo = cyclophosphamide; Dox = doxorubicin; Epir = epirubicin; Dex = dexamethasone; Ond = ondansetron; meto = metoclopramide

Evidence Table 5. Chemotherapy active-controlled trials

Author Year Setting Chemo Level Type of Test	Adverse events	Comments
Bhatia 2004 Single Center 5 Rotterdam	AEs reported (a total of 39 AEs were reported by 20 pts; incidence =25%) *Results given as all Ond groups (n=40) vs all Met groups (n=40), p = NR* Dystonia/akathisia: 0% vs 0% Constipation: 17.5% vs 2.5% Headache: 15% vs 12.5% Heartburn: 10% vs 5% Weakness: 5% vs 12.5% Epigastric pain: 5% vs 7.5% Nervousness: 2.5% vs 2.5%	Chemo: All pts received a regimen consisting of cisplatin, bleomycin and 5-flurouracil, making the chemo uniform in all the patients. Pts were randomized according to a table of random numbers to receive either low dose cisplatin regimen (I and II) or high dose cisplatin (III and IV). In high dose cisplatin, pts given 60 mg/m2 cisplatin iv as a single dose on 1st day; in low dose cisplatin, cisplatin was split into 3 iv doses of 20 mg/m2 each on 3 consecutive days. Cisplatin was administered as continuous iv infusion over 1h. All pts also received bleomycin 15 mg iv on 1st and 5th day, and 5-fluorouracil 500 mg iv for 5 days.
Lachaine 1999 Single Center 4 EORTC, QLC-3	In meto group, 4 pts had serious AEs which caused them to stop the antiemetic (no other data on these AEs given) 0 pts had serious AEs requiring treatment cessation in Ond group	The most frequent chemotherapies were the combination of cyclophosphamide and doxorubicin (64%), and the combination of cyclophosphamide, methotrexate and 5-fluorouracil (CMF) (27%). Two patients received cyclophosphamide. Doxorubicin and 5-fluorouracil (FAC).; two received cyclophosphamide and carboplatin; and one received cyclophosphamide and epirubicin. The type of chemotherapy was not significantly different between the two groups.
Clavel 1995 Multicenter 4 FLIE; FLIC	AEs were minor in both groups, data only given for headache Headache: ond - 1.6% vs aliz - 2.3% , p = NR	

Cyclo = cyclophosphamide; Dox = doxorubicin; Epir = epirubicin; Dex = dexamethasone; Ond = ondansetron; meto = metoclopramide

Evidence Table 5. Chemotherapy active-controlled trials

Author	Year	Setting	Chemo Level	Type of Test
Bhatia	2004	Single Center	5	Rotterdam
Lachaine	1999	Single Center	4	EORTC, QLC-3
Clavel	1995	Multicenter	4	FLIE; FLIC

Cyclo = cyclophosphamide; Dox = doxorubicin; Epir = epirubicin; Dex = dexamethasone; Ond = ondansetron; meto = metoclopramide

Evidence Table 5. Chemotherapy active-controlled trials

Author	Year	Setting	Chemo Level	Type of Test
Bhatia	2004	Single Center	5	Rotterdam
Lachaine	1999	Single Center	4	EORTC, QLC-3
Clavel	1995	Multicenter	4	FLIE; FLIC

Cyclo = cyclophosphamide; Dox = doxorubicin; Epir = epirubicin; Dex = dexamethasone; Ond = ondansetron; meto = metoclopramide

Evidence Table 5. Chemotherapy active-controlled trials

Author Year Setting Chemo Level Type of Test	Design	Subpopulation	Exclusion criteria
Soukop 1992 Multicenter 4 Rotterdam	DB RCT Parallel	women, breast cancer	Pts excluded if any of the following applied: severe concurrent illness, gastrintestinal obstruction, central nervous system metastases, anti-emetic therapy administered concurrently or in 24 h before chemo, administration of benzodiazepines except when given for night sedation, vomiting in th 24h before chemo, cisplatin-containing regimens, and pregnancy.
Crucitt 1996 Multicenter 4 FLIE	DB RCT Parallel	women, breast cancer	Pts who had received chemo or ond at any time during the past as well as pts who had received any medication with potential antiemetic activity (phenothiazines, buytrophenones, hydroxyzine, lorazepam, cannabinoids, metoclopramide, corticosteroids, or trimethobenzamide) within 24h before the first dose of the study drug or during 3 days after initiation of chemo were excluded.

Cyclo = cyclophosphamide; Dox = doxorubicin; Epir = epirubicin; Dex = dexamethasone; Ond = ondansetron; meto = metoclopramide

Evidence Table 5. Chemotherapy active-controlled trials

Author Year Setting Chemo Level Type of Test	Intervention	Allowed other medication	Run-in/Wash out	Age Gender Ethnicity	Screened/ Eligible/ Enrolled	Withdrawn/ Lost to fu/ Analyzed
Soukop 1992 Multicenter 4 Rotterdam	O: Ond 8mg M: metoclopramide 60mg	Dex 16 mg iv one time only	No run-in; washout-no antiemetics within 24h of study entry	Mean Age: 48.58y 0% male	NR / 187/ 187	4/ NR / 183
Crucitt 1996 Multicenter 4 FLIE	O: Ond po 16mg (8 mg bid) for up to 3 days P: Prochlorperazine po 20mg (10 mg bid) for up to 3 days	No	No run-in; washout-no drugs with antiemetic activity within 24h of study entry	Mean Age: 57.8y 10% male White: 87% Black: 9% Other: 4%	NR / NR/ 133	20/ NR/ 113 (133 for safety)

Cyclo = cyclophosphamide; Dox = doxorubicin; Epir = epirubicin; Dex = dexamethasone; Ond = ondansetron; meto = metoclopramide

Evidence Table 5. Chemotherapy active-controlled trials

Author Year Setting Chemo Level Type of Test	Other population characteristics
Soukop 1992 Multicenter 4 Rotterdam	Height mean: 161.0 (+/- 6.71) cm range: 140-181 cm Mean weight: 65.14 (+/- 12.85) kg range: 40.5-135.0 kg Surface area (SA) mean: 1.66(+/- 0.17) m2 SA range: 1.2 - 2.4 m2
Crucitt 1996 Multicenter 4 FLIE	Mean body weight = 72 kg (range: 43-149 kg) Chemotherapy regimen: CYC/DOX :10% CYC/DOX/FU 24:18% CYC/DOX/FU/VCR : 1%; CYC/DOX/VCR: 4% CYC/DOX/VCR/prednisone: 8% CYC/DOX/VP16: 1%; DOX/FU:1% CYC/methotrexate/FU: 58%; Data Not Available:1% Alcohol consumption: < 5 drinks/y 66%; < 7 drinks/wk 30% 1-4 drinks/d 3%; > 5 drinks/d 0% Prior heavy use: > 5 drinks/d: 1%

Cyclo = cyclophosphamide; Dox = doxorubicin; Epir = epirubicin; Dex = dexamethasone; Ond = ondansetron; meto = metoclopramide

Evidence Table 5. Chemotherapy active-controlled trials

Author Year Setting Chemo Level Type of Test	Results
Soukop 1992 Multicenter 4 Rotterdam	Quality of Life: Rotterdam subscales *Differences in scores between baseline and Day 5, O vs M* Psychological: +25% vs +12%, p=0.002 Physical: -24% vs –24%, p=NS Change in functional activity: 0 vs 0
Crucitt 1996 Multicenter 4 FLIE	*Ondansetron vs Prochlorperazine* FLIE scores (100 is highest possible score) decrease in nausea subscore, baseline to final score: -25.3 vs -33.5, p=NS decrease in vomiting subscore, baseline to final score: -7.9 vs -26.3, p=0.01 for O vs P

Cyclo = cyclophosphamide; Dox = doxorubicin; Epir = epirubicin; Dex = dexamethasone; Ond = ondansetron; meto = metoclopramide

Evidence Table 5. Chemotherapy active-controlled trials

Author Year Setting Chemo Level Type of Test	Adverse events	Comments
Soukop 1992 Multicenter 4 Rotterdam	Met: 15% withdrawn due to extrapyramidal symptoms (EPS). 4% reported EPS (restlessness, agitation) of a less severe nature that did not lead to withdrawal Ond: 0% reported EPS Skin rashes : Ond - 4% vs Met - 0% Allergy: Ond - 1% vs Met - 0% (likely caused by methotrexate, not Ond) 1 pts showed elevated liver enzymes in 2nd course but no further abnormalities in courses 3-6 <u>Most common AEs, O vs M</u> EPS: 0% vs 19% Diarrhea: 0% vs 14% Constipation: 19% vs 5% Headache: 13% vs 9%	
Crucitt 1996 Multicenter 4 FLIE	*Data given as O vs P* Headache: 16% vs 3%, p<0.05 No other AE occurred in ≥3% in either group 3 pts were withdrawn from studye due to AEs: 2 pts (1 in O and 1 in P) were withdrawn due to injection site reation (iv infiltration due to cheo; considered not to be related to administration of study drug); 1 P pt had persistent vomiting that required hospitalization (considered unlikely to be related to the study drug)	

Cyclo = cyclophosphamide; Dox = doxorubicin; Epir = epirubicin; Dex = dexamethasone; Ond = ondansetron; meto = metoclopramide

Evidence Table 5. Chemotherapy active-controlled trials

Author	Year	Setting	Chemo Level	Type of Test
Soukop	1992	Multicenter	4	Rotterdam
Crucitt	1996	Multicenter	4	FLIE

Cyclo = cyclophosphamide; Dox = doxorubicin; Epir = epirubicin; Dex = dexamethasone; Ond = ondansetron; meto = metoclopramide

Evidence Table 5. Chemotherapy active-controlled trials

Author	Year	Setting	Chemo Level	Type of Test
Soukop	1992	Multicenter	4	Rotterdam
Crucitt	1996	Multicenter	4	FLIE

Cyclo = cyclophosphamide; Dox = doxorubicin; Epir = epirubicin; Dex = dexamethasone; Ond = ondansetron; meto = metoclopramide

Evidence Table 6. Quality assessment for chemotherapy active-controlled trials

Author Year Setting Chemo Level	Subpopulation	Exclusion criteria	Run-in/ Washout	Screened/ Eligible/ Enrolled
Bhatia 2004 Single Center 5	NR	Patients were excluded if any of the following applied: severe concurrent illness, vomiting due to some other cause, antiemetic therapy administered concurrently or in the 24 preceding chemotherapy, administration of benzodiazepines except when given for night sedation, vomiting the the 24 h before chemotherapy, pregnant or lactating woemn, concurrent radiation therapy, impaired renal function (serum creatinine > 2.0 mg/dl), jaundice (serum bilirubin > 2.0 mg/dl) or an elevated aminotransferase level (SGOT/SGPT > twice the upper normal limit).	No/No	NR/NR/NR
Lachaine 1999 Single Center 3-4	women, breast cancer	NR	No/No	NR/NR/58
Clavel 1995 Multicenter 4 FLIE; FLIC	women, breast cancer	Patients not eligible if any of the following applied: serious disease other than the cancer being treted, another cause of nausea or vomiting other than the chemo, a clinical hepatic disorder, a persistant chronic alcoholism, emesis or anti-emetic treatment during 24h preceding study entry.	No/No	NR/NR/259
Soukop 1992 Multicenter 4 Rotterdam	women, breast cancer	Patients were excluded if any of the following applied: severe concurrent illness, gastrintestinal obstruction, central nervous system metastases, anti-emetic therapy administered concurrently or in the 24 h before chemotherapy, administration of benzodia	No/No	NR/NR/187
Crucitt 1996 Multicenter 4	women, breast cancer	Patients who had received chemotherapy or ondansetron at any time during the past as well as patients who had received any medication with potential antiemetic activity (phenothiazines, buytrophenones, hydroxyzine, lorazepam, cannabinoids, metoclopramide, corticosteroids, or trimethobenzamide) within 24 hours before the first dose of the study drug or during the 3 days after initiation of chemotherapy were excluded.	No/No	NR/NR/133

Evidence Table 6. Quality assessment for chemotherapy active-controlled trials

Author Year Setting Chemo Level	Withdrawn/ Lost to fu/ Analyzed	Randomization	Allocation	Groups similar at baseline	Eligibility criteria specified	Care provider masked	Patients masked	Attrition Crossover Adherence Contamination
Bhatia 2004 Single Center 5	NR/NR/80	NR	NR	Yes	Yes	No	No	No, No, No, No
Lachaine 1999 Single Center 3-4	6/0/52	NR	NR	No, more patients in O group were English-speakers (70% vs 36%)	Yes	Yes	Yes	Yes, No, No, No
Clavel 1995 Multicenter 4 FLIE; FLIC	5/0/254	NR	NR	Yes	Yes	Yes	Yes	Yes, No, No, No
Soukop 1992 Multicenter 4 Rotterdam	4 didn't return diaries/NR/187	NR	NR	Yes	Yes	Yes	Yes	Yes, No, No, No
Crucitt 1996 Multicenter 4	20/0/113 (57 for QOL)	NR	NR	Yes	Yes	Yes	Yes	Yes, No, No, No

Evidence Table 6. Quality assessment for chemotherapy active-controlled trials

Author Year Setting Chemo Level	Loss to follow up	Intention-to-treat analysis	Post-randomization exclusions	Quality rating	Controlled group standard of care	Funding	Relevance
Bhatia 2004 Single Center 5	Unclear	Unclear	Unclear	**Fair**	Yes	NR	Yes
Lachaine 1999 Single Center 3-4	None	No	No	**Fair**	Yes	NR	Yes
Clavel 1995 Multicenter 4 FLIE; FLIC	None	No	No	**Fair**	Yes	NR	Yes
Soukop 1992 Multicenter 4 Rotterdam	None	Yes	Unclear	**Fair**	Yes	NR	Yes
Crucitt 1996 Multicenter 4	None	No	No	**Fair**	Yes	Glaxo Research Institute funded this study	Yes

Evidence Table 7. Radiation: controlled-clinical trials

Author, Year	Design	Inclusion criteria	Type of radiation
Direct comparison trials			
Spitzer 2000 Multicenter	RCT, DB Parallel	Pts with a diagnosis of either malignant disease or aplastic anemia and who were hospitalized to receive 11 fractions of 120 cGy over 4 days prior to BMT and initiation of any conditioning chemo. Females of childbearing potential were required to have a negative serum or urine hCG pregnancy test and had to continue using adequate contraception during the study. Males had to be either surgically sterilized or practising adequate contraception throughout the study.	11 fractions each of 120cGy of radiation over 4 days for a total radiation expose of 1320 cGy prior to BMT and chemo. on day 0 to 1, the chest wall was blocked during radiation to protect the lungs. The block was removed for fractions given on days 2 and 3 to allow for radiation of the ribs and soft tissue underlying the lungs.

RT = radiotherapy; ODT = orally disintegrating tablets; BMT = bone marrow transplantation; TBI = total body irradiation

Evidence Table 7. Radiation: controlled-clinical trials

Author, Year	Exclusion criteria	Intervention
Direct comparison trials		
Spitzer 2000 Multicenter	Excluded were pts with a Karnofsky Performance Status score <60, those who had received an investigational new drug within 30 days or 5 half lives of the medication, received conditioning or intrathecal chemo within 24h of first dose of TBI, received emetogenic systemic or intrathecal chemo during the study, or who had an unstable medical disorder or primary or secondary brain neoplasm with increased intracranial pressure. Other reasons for exclusion included known hypersensitivity to any 5HT3 receptor antagonist, unwillingness or inability to comply with the study protocol, or any medication with antiemetic activity taken within 24h of receiving study medication on Day 0. Those who experienced nausea within 1 hr or any emesis (vomiting or retching) within 24h of receiving study mediations on Day 0 were excluded from the protocol defined population but were included in the intent to treat population.	G: Granisetron 2mg O: Ondansetron 24mg

RT = radiotherapy; ODT = orally disintegrating tablets; BMT = bone marrow transplantation; TBI = total body irradiation

Evidence Table 7. Radiation: controlled-clinical trials

Author, Year	Allowed other medication	Run-in/Wash out	Age Gender Ethnicity	Other population characteristics
Direct comparison trials				
Spitzer 2000 Multicenter	No	No/ NR	41.3 32% female White = 31 (91.2%) African American = 2 (5.9%) Other = 1 (2.9%)	Mean weight = 178.4 pounds Range of weights = 117.5 to 323.0 pounds Mean height = 67.7 inches Range of heights = 60.0-75.0 in

RT = radiotherapy; ODT = orally disintegrating tablets; BMT = bone marrow transplantation; TBI = total body irradiation

Evidence Table 7. Radiation: controlled-clinical trials

Author, Year	Screened/ Eligible/ Enrolled	Withdrawn/ Lost to fu/ Analyzed	Results
Direct comparison trials			
Spitzer 2000 Multicenter	36/ 34/ 34	2/ 0/ 34	*Data given as Gran po 2 vs Ond po 8* Complete emetic control: no emetic episodes and no rescue antiemetic medication use overall: 27.8% vs 26.7% Day 0: 61.1% vs 46.7% Day 1: 50% vs 54.5% Day 2: 87.5% vs 87.5% Day 3: 62.5% vs 66.7% Complete nausea control: no nausea and no rescue medications by day overall: 11.1 % vs 13.3% Day 0: 44.4% vs 26.7% Day 1: 20% vs 36.4% Day 2: 28.6% vs 50% Day 3: 37.5% vs 66.7% Emetic episodes on day 0 and overall (over 4 days) 0 episodes: Day 0: 61.1% vs 46.7% overall : 33.3% vs 26.7% 1-2 Episodes: overall: 22.2% vs 20% Day 0: 5.6% vs 26.7% 3-5 Episodes: overall: 44.4% vs 33.3% Day 0: 33.3% vs 26.7% >5 Episodes (failure): overall: 0% vs 20% Day 0: 0% vs 0% Median time to first emesis: 36 h vs 15.8 h

RT = radiotherapy; ODT = orally disintegrating tablets; BMT = bone marrow transplantation; TBI = total body irradiation

Evidence Table 7. Radiation: controlled-clinical trials

Author, Year	Adverse events	Comments
Direct comparison trials		
Spitzer 2000 Multicenter	*Data given as Gran po 2 vs Ond po 8* All adverse events Rash: 0% vs 12.5% Back pain: 0% vs 12.5% Peripheral edema: 5.6% vs 12.5% Insomnia: 5.6% vs 12.5% Asthenia: 11.1% vs 0% Diarrhea: 22.2% vs 6.3% Headache: 27.8% vs18.8% Serious AEs (Ond only) Nonfatal irregular pulse: 6%	

RT = radiotherapy; ODT = orally disintegrating tablets; BMT = bone marrow transplantation; TBI = total body irradiation

Evidence Table 7. Radiation: controlled-clinical trials

Author, Year	Design	Inclusion criteria	Type of radiation
Placebo-controlled trials			
Bey 1996	RCT, DB multicenter parallel	Cancer pts ≥ 18 y of either gender undergoing radiotherapy to the upper abdominal field, incl. the epigatrium, in single, high-dose exposure; pts had riven malignant disease and had a Karnofsky performance score of ≥50%. Pts did not have to be chemo-naive.	Single fraction radiotherapy of ≥6 Gy over fields of either 80-100 cm2 centered between T10 and L2 inclusive or fields of 100-150 cm2 centered between T8 and L3 inclusive.
Lanciano 2001	RCT, DB multicenter parallel	Cancer pts ≥ 18 y of either gender undergoing radiotherapy; males were surgically sterilized or agreed to practise adequate contraception during the study. Females were of nonchildbearing potential or were of childbearing potential, had negative pregnancy tests, and agreed to practise adequate contraception during the study.	Abdominal radiotherapy to fields encompassing T11-L3 with a field size ≥ 100 cm2; pts had to receive between 10 and 30 fractions of radiotherapy with a a radiation dose of ≥ 1.8 Gy/fraction (9.0Gy weekly for ≥ 2 weeks) at the midplane of the treated volume, not to exceed 3.0 Gy/fraction. Seminoma pts could receive a lower dose of <1.5 Gy/fraction and pts undergoing total abdomical irradiation could receive <1.8 Gy/fraction.

RT = radiotherapy; ODT = orally disintegrating tablets; BMT = bone marrow transplantation; TBI = total body irradiation

Evidence Table 7. Radiation: controlled-clinical trials

Author, Year	Exclusion criteria	Intervention
Placebo-controlled trials		
Bey 1996	If pts had chemo within 2 weeiks of the study; also excluded wer pts who had radiotherpay <7 days before study entry, had a history of significant neurological, cardiac, or psychiatric illness (except alcoholism), showed abnormal prestudy serum potassium and/or sodium, were receiving antiarrhythmic therapy, or showed evidence of clinical significant liver disease (ie, serum aspartate aminotransferase / alanine aminotransferase ≥ 2 the upper limit of normal (ULN), serum bilirubin ≥2.0 IU/dL or known liver metastases). Also excluded were pts who were pregnant or female of childbearing potential not using contraception measures, had been administered any drug with antiemetic efficacy within 24h of study initiation, had received previous therapy with Dol, had vomitied as a result of any organic etiology or had vomited in the 24h preceding radiotherapy, had experienced SWOG grade 2-4 nausea in the 24h preceding radiotherapy, or had used any investigational drug within 21 days of the study.	D1: Dolasetron (Dol) 0.3 mg/kg iv D2: Dol 0.6 mg/kg iv D3: Dol 1.2 mg/kg iv Pl: placebo 30 min before radiation start
Lanciano 2001	Pts were not eligible if they had participated in any drug trial using an investigational drug within 30 d or 5-half lives (whichever was longer) prior to screening, had an unstable medical disorder, or a Karnofsky performance status score of <60. They could not receive chronic (≥1 month) or concurrent (day 0 and through end of assessment treatment with agents known to have significant effect on emesis, including ondansetron, sedating antihistamines, antipsychotics, cannabinoids, corticosteroids, metoclopramide, narcotic analgesics and benzodiazepines. Pts could not have primary or secondary brain turmors with signs or sumptoms of increased intracranial pressure. Pts were excluded if they had known hypersensitivity to 5-HT3 receptor antagonist or were unwilling/unable to comply with study protocol or experienced nausea within 1 h and/or emesis within 24h before administration of study medication on Day 0. Emetogenic chemo could not be administered within 72h of study medication or during study assessment period. Previous abdominal radiotherapy (T11-L3), wedge-field radiation therapy to the spine, and prophylactic radiotherapy to the CNS were also reasons for exclusion. No radiation therapy could be administered 24h prior to day 0.	G: Gran 2 mg (n=134) po qd Pl: Placebo

RT = radiotherapy; ODT = orally disintegrating tablets; BMT = bone marrow transplantation; TBI = total body irradiation

Evidence Table 7. Radiation: controlled-clinical trials

Author, Year	Allowed other medication	Run-in/Wash out	Age Gender Ethnicity	Other population characteristics
Placebo-controlled trials				
Bey 1996	No	Washout: 2 wks for chemo, 7 d for radiotherapy, 24 h for any drugs with antiemetic properties No run-in	Median age: 63y 34% female Ethnicity: NR	Median dose of radiotherapy: 6.76 Gy Median duration of radiotherapy: 0.17 h % of pts receiving previous chemo or radiotherapy: 66% % experiencing nausea and/or vomiting after prior treatment: 36%
Lanciano 2001	No (only nonemetogenic chemotherapy was allowed concomitantly)	Washout: 30 d for investigational drug, 72 for emetogenic chemotherapy, 24 h for radiation No run-in	Mean age: 55.3y Range: 19-88y 34.8% female White: 78.4% African American: 10.6% Asian: 1.5% Other: 9.5%	Mean weight: 170 lbs (Range: 76.5-348 lbs) Mean height: 68 in (Range: 57-77.2 in) Mean alcohol units/week: 4.45 units/wk Range: 0-79.4 units/week Primary disease sites: Genitourinary system: 45.5% Lymphatic/hematologic system: 19.7% Gastrointestinal system: 22% Mean total dose of radiation: 24.4 Gy Mean daily dose: 1.85 Gy Mean days of treatment: 19.1 days

RT = radiotherapy; ODT = orally disintegrating tablets; BMT = bone marrow transplantation; TBI = total body irradiation

Evidence Table 7. Radiation: controlled-clinical trials

Author, Year	Screened/ Eligible/ Enrolled	Withdrawn/ Lost to fu/ Analyzed	Results
Placebo-controlled trials			
Bey 1996	NR/50/50	NR/ NR 50	*All data are given as D1; D2; D3; Pl (if not noted; p=NS and p given only for each D group vs. placebo and not for D groups vs one another)* % pts having emesis or use of rescue medication per group: 9.1% (p=0.05); 28.6%; 41.7%, 46.1% Time range for first emesis or use of rescue medication: (3.4); (2.0 - 22.5); (3.0 - 15.8); (0.5 - 8.0) % with complete response: 91% (p=0.05 vs Pl); 71%, 58%, 54% Complete + Major response: 100% (p=0.011); 93% (p=0.019); 83%, 54% Pt max nausea VAS score over 24h: 1.3 (p=0.014); 9.9; 13.8; 22.4 % with no nausea (<= 5 mm nausea VAS): 54%; 62;%; 70%; 54% Investigator assessment of no nausea (% of pts): 91%; 86%; 67%; 54% Mean pt satisfaction score (0-100, with 100="completely satisfied"): 98; 100; 78; 93
Lanciano 2001	NR/ 264/ 264	121/ NR/ 260	*All data are G vs Pl* Median time to first emesis: 35 days vs 9 days, p<0.001 Median time to first nausea: 11 days vs 1 day, p<0.001 Emesis-free pts (overall endpoint analysis): 57.7% (77 of 134) vs 42.1% (53 of 126), p=0.0047 % of pts nausea free on all days of study: 31.3% vs 16.7%, p<0.001 *Data below is estimated from graphs:* % pts emesis-free at 24h: 91% vs 61%, p<0.0001 % pts emesis-free at 10 fractions: 85% vs 68%, p=0.0012 % pts emesis-free at 20 fractions: 75% vs 64%, NS (p=0.0636) % of pts with 0 episodes of emesis at 24 h; 10 fractions; and 20 fractions: 98% vs 71%; 86% vs 71%; 76% vs 63%, p = NR % of pts experiencing severe nausea at 24 h: 1.5% vs 15.15, p=NR

RT = radiotherapy; ODT = orally disintegrating tablets; BMT = bone marrow transplantation; TBI = total body irradiation

Evidence Table 7. Radiation: controlled-clinical trials

Author, Year	Adverse events	Comments
Placebo-controlled trials		
Bey 1996	1 serious AE in D2 group (a pt who presented with a suspected colon cancer and was hospitalized for mild melena 48h after sutdy medication administration) was not considered to be related to study medication; 9 events across the four groups (8 events in 6 Dol pts and 1 event in 1 Pl pt) were considered treatment-related. Most commonly reported AEs: *(data given as D1; D2; D3; Pl)* Overall rate: 27.3%; 42.9%; 58.3%; 7.7% Headache: 0%; 7.1%; 0%, 0% Abdominal pain: 0%; 14%; 8.3%; 0% Fever: 18%; 0%; 8.3%; 7.7% Tachycardia: 0%; 0%; 17%; 7.7% Back pain: 0%; 7.1%; 8.3%; 0%	
Lanciano 2001	Pts reporting ≥ 1 AE: 75.8% (G: 82.1% vs Pl: 69.2%) AEs probably unrelated to treatment drug: G: 50.4% vs Pl: 50.4% Commonly-reported AEs, G vs. Pl: Diarrhea: 27.6% vs 33.8% Asthenia: 25.4% vs 19.2% Constipation: 19.4% vs NR Headache: NR vs 11.5% 2 G pts had 3 AEs (constipation, abnormal thinking, and rash) deemed treatment related 3 Pl pts had 3 AEs (abdominal pain, moniliasis, and nausea) deemed treatment related Deaths: G: 4 pts vs Pl 7 pts deemed not related to study medication	PTs withdrawal counted as a pt needing rescue medication.

RT = radiotherapy; ODT = orally disintegrating tablets; BMT = bone marrow transplantation; TBI = total body irradiation

Evidence Table 7. Radiation: controlled-clinical trials

Author, Year	Design	Inclusion criteria	Type of radiation
LeBourgeois 1999	RCT, DB multicenter parallel	Male and female pts ≥ 18 y with a diagnosis of cancer who were to receive a course of ≥5 daily fractions of radiotherapy to sites between the thorax and pelvis.	≥ 5 daily fractions of radiotherapy to sites between the thorax and pelvis median total dose: 8 Gy *% and numbers below are out of total of 416 ITT pts* reason for fractionated RT: radical: 76%; palliative: 24% RT site: thorax - 18% abdomen - 42% pelvis - 23% spine - 4% other - 13%
Tiley and Powles 1992 UK	Consecutive pts ≥18 y underoing conditioning with melphalan (110 mg/m2) and TBI prior to auotlogous or allogeneic BMT	Radiation delivered as a single fraction from opposed 60 Co sources as at rate of 4cGy/min to a total lung dose of 10.5 Gy	

RT = radiotherapy; ODT = orally disintegrating tablets; BMT = bone marrow transplantation; TBI = total body irradiation

Evidence Table 7. Radiation: controlled-clinical trials

Author, Year	Exclusion criteria	Intervention
LeBourgeois 1999	Pts with severe concurrent illness (other than neoplasia) or with other potential causes of emesis and nausea (.eg. gastrointestinal obstruction, raised intracranial pressure, hypercalcaemia, brain metastases); pts who had experienced emesis and/or moderate/severe nausea in the preceding 24h, had received chemo in the preceding 5 days, had in the last 30 days received or were about to receive an investigational drug, or who were receiving conditioning for bone marrow transplantation were excluded. Other exclusion criteria were: concurrent or past medical conditions that might interfere with the study, impaired hepatic function, pregnancy, or lactation.	O1: Ond 8 mg ODT O2: Ond 16 mg ODT Pl: placebo Pts were instructed to take study drug only if emesis or moderate or severe nausea occurred
Tiley and Powles 1992 UK	Pts undergoing autologous transplantation for acute myeloid leukemia were excluded because they are conditioned with melphalan at 140 mg/m2	O: Ond 8 mg iv Pl: placebo iv single dose given at commencement of TBI

RT = radiotherapy; ODT = orally disintegrating tablets; BMT = bone marrow transplantation; TBI = total body irradiation

Evidence Table 7. Radiation: controlled-clinical trials

Author, Year	Allowed other medication	Run-in/Wash out	Age Gender Ethnicity	Other population characteristics
LeBourgeois 1999	No	Washout: 5 d for chemo, 30 d for investigational drugs	Mean age: 48y 46% Female Caucasian: 95% African American: 3% Asian: <1% Other: 2%	Mean weight: 70.6 kg Mean height: 170 cm Previous motion sickness: 15% Previous sickness during pregnancy: 39.6% (76 of 192 women) Current alcohol use: none: 58% <7 units/wk: 26% 7-28 units/week: 13% >28% units/wk: 2%
Tiley and Powles 1992 UK	Yes: metoclopramide 20 mg iv, dexamethasone 4 mg iv, and lorazepam 1-2 mg po given to all pts pts prior to melphalan All pts given phenobarbitone 60 mg/m2 iv and dexamethasone 8 mg iv at 10 pm on day prior to TBI and at 6 am on day of TBI	No, No	Median age: O - 23y; Pl - 32.5y Age range: 19-53 y 30% female Ethnicity: NR	Diagnosis: AML CR1: 40% ALL CR1: 40% CR2: 15% REL1: 5% Mean irradiation time: 316 min Total time to deliver TBI: 369 min % pts anxious at randomization: 75% % pts vomiting at randomization: 5%

RT = radiotherapy; ODT = orally disintegrating tablets; BMT = bone marrow transplantation; TBI = total body irradiation

Evidence Table 7. Radiation: controlled-clinical trials

Author, Year	Screened/ Eligible/ Enrolled	Withdrawn/ Lost to fu/ Analyzed	Results
LeBourgeois 1999	NR/1492/1489	unclear /unclear / 461	*Data given as O1 vs O2 vs Pl* treatment success (ts): 0-1 emetic episodes in 0-2h after study medication; 0 emetic episodes after 2 h until the end of assessment pd; no worse than mild nausea during assessment period; no rescue; no withdrawal Complete control (no emesis, nausea, rescue, or premature withdrawal): 53% vs 58% vs 405 (p = NS for O1 vs O2) % of pts with treatment success (ts) in 12h after administration of study meds: 53% vs 56% vs 41% (p=NS for O1 vs O2) % of pts with ts in 2 h period immediately after administration of study meds: 69% vs 70% vs 52% (p = NS for O1 vs O2)
Tiley and Powles 1992 UK	NR/20/20		*Data given as O vs Pl* Vomiting during TBI: 10 % vs 50%, p=0.07 Nausea or retching during TBI: 10% vs 50%, p = 0.07 Any emetic event during TBI: 10% vs 60%, p= 0.029 Any emetic event 6 h after TBI: 10% vs 50%, p= 0.07 Any emetic event 12 h after TBI: 20% vs 10%, p = NS Time in TBI lost for nausea and vomiting: 0.5 min vs 12.5 min, p=0.01

RT = radiotherapy; ODT = orally disintegrating tablets; BMT = bone marrow transplantation; TBI = total body irradiation

Evidence Table 7. Radiation: controlled-clinical trials

Author, Year	Adverse events	Comments
LeBourgeois 1999	Serious AE in O1 group: 2 pts experienced nausea and vomiting and 1 pt a variety of events related to breathing disorders and bone/skeletal pain *data given as O1 [n=150] vs O2 [n=139] vs Pl [n=127]* Most common AEs during treatment: Any AE: 8% vs 4% vs 3% (total = 5%) Nausea and vomiting: 3% vs 0.8% vs 0% (total: 2%) Headache: 2% vs 0% vs 3% (total: 2%) Diarrhea: 0% vs 2% vs 0% (total: 0.5%) Most common AEs during treatment (*O1 vs O2 vs Pl*): Any AE: 5% vs 6% vs 3% (total: 4%) Diarrhea: 1% vs 0.8% vs 0.7% (total: 1%) Gastrointestinal discomfort and pain: 1% vs 0% vs 0% (total: 0.5%)	1492 was # of pts entering study; but study only evaluated those who had nausea or emesis after radiation treatment, so the number of pts analyzed was 416.
Tiley and Powles 1992 UK	No AEs noted in either pt group nor were any biochemical abnormalities seen	

RT = radiotherapy; ODT = orally disintegrating tablets; BMT = bone marrow transplantation; TBI = total body irradiation

Evidence Table 7. Radiation: controlled-clinical trials

Author, Year	Design	Inclusion criteria	Type of radiation
Active-controlled trials			
Sykes 1997 UK	RCT Single center parallel	>18 pts who were to receive pallative single fraction radiotherapy	60 pts received a single fraction to the lower half- body of 8 Gy; 6 pts received a single fraction of 12.5 Gy to the upper lumbar spine
Priestman 1990 **Priestman** 1989	RCT, DB parallel	Males or females 18-80y who were to be treated with single anterior or single posterior fields to the upper abdomen giving incident doses of 8-10 Gy or those treated with opposed fields to this region giving 8-10 Gy as a mid-point dose. Field sizes of 80-100 cm2 had to be centered between T10-L2 inclusive; fields of >100cm1 were centered between T8-L3 inclusive.	8-10 Gy radiation

RT = radiotherapy; ODT = orally disintegrating tablets; BMT = bone marrow transplantation; TBI = total body irradiation

Evidence Table 7. Radiation: controlled-clinical trials

Author, Year	Exclusion criteria	Intervention
Active-controlled trials		
Sykes 1997 UK	Pts not allowed if any of the following applied: concurrent chemo; concurrent antiemetic therapy, including pednisolone and dexamethasone with the exception of the study drugs; severe concurrent illness; gastrointestinal obstruction; CNS metastases; vomiting in the 24h prior to study entry; adminitration of concurrent benzodiazapines excpet for night sedation	O: Ond 8 mg po 1-2 h before rediotherapy + 8 mg 12 h later. Days 1-3, Ond given 8 mg po bd (n=33) C: Chloropromazine (chlor) 25 mg po +dexamethasone (dex) 6 mg po 1 h before radiotherapy + Chlor 25 mg po 12 h later. Days 1-3, Chlor 24 mg tds (n=33)
Priestman 1990 **Priestman** 1989	Pts excluded if clinically jaundiced, had vomited in the previous 24h, had received antiemetics within the previous 24h or were suffereing severe concurrent illness unrelated to their neoplasia.	Pts fasted for 2 hours and then given drugs 1-2 h prior to radiation O: Ond 8 mg po (Days 1-3 or Days 1-5, 8 mg po tid) (n=46) M: metoclopramide 10 mg po (Days 1-3 or Days 1-5, 10 mg po tid) (n=51)

RT = radiotherapy; ODT = orally disintegrating tablets; BMT = bone marrow transplantation; TBI = total body irradiation

Evidence Table 7. Radiation: controlled-clinical trials

Author, Year	Allowed other medication	Run-in/Wash out	Age Gender Ethnicity	Other population characteristics
Active-controlled trials				
Sykes 1997 UK	No	No, No	NR NR NR	NR
Priestman 1990 **Priestman** 1989	No - 13 of 15 withdrawals (exclusions) were due to pts taking concurrent medication with antiemetic properties	Washout: 24 h for antiemetics No run-in	mean age: 64.0y Range: 18-83y 50.5% Female Ethnicity: NR	Primary tumor sites: Lung: 11.3% Breast: 25.8% Gastointestinal: 28.9% Genitourinary: 17.5% Other: 16.5%

RT = radiotherapy; ODT = orally disintegrating tablets; BMT = bone marrow transplantation; TBI = total body irradiation

Evidence Table 7. Radiation: controlled-clinical trials

Author, Year	Screened/ Eligible/ Enrolled	Withdrawn/ Lost to fu/ Analyzed	Results
Active-controlled trials			
Sykes 1997 UK	NR/66/66	NR	Complete or major control of emesis (0-2 emetic episodes) on day 1, O vs C: 93.9% vs 34.4%, p<0.001 Complete or major control of emesis (0-2 episodes) delayed, O vs C: Day 2: 96.2% vs 42.9%, p<0.001 Day 3: 96.2% vs 39.3%, p<0.001 Day 4: 96% vs 37%, p<0.001 Pts rating of antiemetic effectiveness, O vs C: 90% vs <60% Pts and investigators willing to use antiemetic again, O vs C: 98% vs 75% FLIC: no significant differences for decline in scores post-treatment for O vs C FLIE: declines were greater for Ond-treated pts, p=0.02
Priestman 1990 **Priestman** 1989	NR/97/97 (at time of interim analysis; 160 planned)	15/ NR/ 82	*All data given is for O vs M* % pts with complete, major, minor responses, failure/rescued: Day 1: 97%, 3%, 0%, 0% vs. 45%, 25%, 11%, 18%, p<0.001 Days 1-3 inclusive: 68%, 24%, 0%, 8% vs 39%, 27%, 11%, 23%, p=NR Day 4 Complete or major control: 97% vs 88%, p = NS Day 5 Complete or major control: 96.9% vs 95.2%, p = NS Grading of nausea: None, mild, moderate, severe: Day 1: 73%, 22%, 5%, 0% vs. 41%, 20%, 18%, 20%, p =<0.001

RT = radiotherapy; ODT = orally disintegrating tablets; BMT = bone marrow transplantation; TBI = total body irradiation

Evidence Table 7. Radiation: controlled-clinical trials

Author, Year	Adverse events	Comments
Active-controlled trials		
Sykes 1997 UK	No deaths occurred during study period and no significant difference in levels of AEs between O and C. Less drowsiness for O than C, but p= NS	
Priestman 1990 **Priestman** 1989	*All data given as O vs M* deaths: 6 pts vs 4 pts, p = NR (none thought to be related to antiemetic therapy) severe headache and vertigo: 1 pt vs 0 pt, p = NR Fevers and night sweats: 0 pt vs 1 pt, p = NR No changes in clinical chemistry, renal function of hematological parameteres that were considered treatment related for either drug.	

RT = radiotherapy; ODT = orally disintegrating tablets; BMT = bone marrow transplantation; TBI = total body irradiation

Evidence Table 8. Quality assessments of the radiation controlled-clinical trials

Internal Validity

Author, Year	Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors masked?	Care provider masked?	Patient masked?
Comparative trials							
Spitzer 2000	Yes	NR	Yes	Yes			
Placebo-controlled trials							
Bey 1996	NR	NR	Yes	Yes	Not reported	Yes	Yes
Franzen 1996	Yes	NR	Yes for radiotherapy regimens; unknown for other demographic/ prognostic factors because they were NR	Yes	Not reported	Yes	Yes

Evidence Table 8. Quality assessments of the radiation controlled-clinical trials

	Internal Validity				
Author, Year	**Reporting of attrition, crossovers, adherence, and contamination**	**Loss to follow-up: differential/ high**	**Intention-to-treat (ITT) analysis; If No: % analyzed**	**Post-randomization exclusions**	**Quality Rating**
Comparative trials					
Spitzer 2000	Yes, NR, NR, NR				
Placebo-controlled trials					
Bey 1996	Yes, NR, NR, NR	None	Yes	No	Fair
Franzen 1996	Yes, NR, NR, NR	None	No; 98.2%	No	Fair

Evidence Table 8. Quality assessments of the radiation controlled-clinical trials

	External Validity	
Author, Year	**Number screened/ eligible/ enrolled**	**Exclusion criteria**
Comparative trials		
Spitzer 2000		Excluded were pts with a Karnofsky Performance Status score <60, those who had received an investigational new drug within 30 days or 5 half lives of the medication, received conditioning or intrathecal chemo within 24h of first dose of TBI, received emetogenic systemic or intrathecal chemo during the study, or who had an unstable medical disorder or primary or secondary brain neoplasm with increased intracranial pressure. Other reasons for exclusion included known hypersensitivity to any 5HT3 receptor antagonist, unwillingness or inability to comply with the study protocol, or any medication with antiemetic activity taken within 24h of receiving study medication on Day 0. Those who experienced nausea within 1 hr or any emesis (vomiting or retching) within 24h of receiving study mediations on Day 0 were excluded from the protocol defined population but were included in the intent to treat population.
Placebo-controlled trials		
Bey 1996	NR/50/50	If pts had chemo within 2 weeiks of the study; also excluded wer pts who had radiotherpay <7 days before study entry, had a history of significant neurological, cardiac, or psychiatric illness (except alcoholism), showed abnormal prestudy serum potassium and/or sodium, were receiving antiarrhythmic therapy, or showed evidence of clinical significant liver disease (ie, serum aspartate aminotransferase / alanine aminotransferase ≥ 2 the upper limit of normal (ULN), serum bilirubin ≥2.0 IU/dL or known liver metastases). Also excluded were pts who were pregnant or female of childbearing potential not using contraception measures, had been administered any drug with antiemetic efficacy within 24h of study initiation, had received previous therapy with DoI, had vomitied as a result of any organic etiology or had vomited in the 24h preceding radiotherapy, had experienced SWOG grade 2-4 nausea in the 24h preceding radiotherapy, or had used any investigational drug within 21 days of the study.
Franzen 1996	NR/111/111	

Evidence Table 8. Quality assessments of the radiation controlled-clinical trials

External Validity

Author, Year	Run-in/Washout	Class naïve patients only	Control group standard of care	Funding	Relevance
Comparative trials					
Spitzer 2000					
Placebo-controlled trials					
Bey 1996	Washout: 2 weeks for chemo, 7 days for radiotherapy, 24 hours for any drugs with antiemetic properties No run-in	Yes	Yes	Hoechst Marion Roussel	Yes
Franzen 1996	Washout: 24 hours for antiemetic drugs No run-in	No	Yes	Glaxo Wellcome	Yes

Evidence Table 8. Quality assessments of the radiation controlled-clinical trials

Internal Validity

Author, Year	Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors masked?	Care provider masked?	Patient masked?
Placebo-controlled trials, cont.							
Lanciano 2001	NR	NR	No; various differences in radiation treatment	Yes	Not reported	Yes	Yes
LeBourgeois 1999	Unclear; "block balanced"	NR	Unclear; only provided baseline characteristics for 415 (27.8%) patients that received study medication	Yes	Not reported	Yes	Yes
Spitzer 1994	NR	Yes	Yes	Yes	Not reported	Yes	Yes
Tiley and Powles 1992	NR	Yes	No, placebo group older (32.5 vs 23)	Yes	Not reported	Yes	Yes

Evidence Table 8. Quality assessments of the radiation controlled-clinical trials

	Internal Validity				
Author, Year	**Reporting of attrition, crossovers, adherence, and contamination**	**Loss to follow-up: differential/ high**	**Intention-to-treat (ITT) analysis; If No: % analyzed**	**Post-randomization exclusions**	**Quality Rating**
Placebo-controlled trials, cont.					
Lanciano 2001	Yes, NR, NR, NR	None	No; 97.6%	No	Fair
LeBourgeois 1999	Yes, NR, NR, NR	None	No; 99%	No	Fair
Spitzer 1994	Yes, NR, NR, NR	None	Yes	No	Fair
Tiley and Powles 1992	NR, NR, NR, NR	NR	Yes	NR	Fair

Evidence Table 8. Quality assessments of the radiation controlled-clinical trials

	External Validity	
Author, Year	**Number screened/ eligible/ enrolled**	**Exclusion criteria**
Placebo-controlled trials, cont.		
Lanciano 2001	NR/264/264	Pts were not eligible if they had participated in any drug trial using an investigational drug within 30 d or 5-half lives (whichever was longer) prior to screening, had an unstable medical disorder, or a Karnofsky performance status score of <60. They could not receive chronic (≥1 month) or concurrent (day 0 and through end of assessment treatment with agents known to have significant effect on emesis, including ondansetron, sedating antihistamines, antipsychotics, cannabinoids, corticosteroids, metoclopramide, narcotic analgesics and benzodiazepines. Pts could not have primary or secondary brain turmors with signs or sumptoms of increased intracranial pressure. Pts were excluded if they had known hypersensitivity to 5-HT3 receptor antagonist or were unwilling/unable to comply with study protocol or experienced nausea within 1 h and/or emesis within 24h before administration of study medication on Day 0. Emetogenic chemo could not be administered within 72h of study medication or during study assessment period. Previous abdominal radiotherapy (T11-L3), wedge-field radiation therapy to the spine, and prophylactic radiotherapy to the CNS were also reasons for exclusion. No radiation therapy could be administered 24h prior to day 0.
LeBourgeois 1999	NR/1492/1489	Pts with severe concurrent illness (other than neoplasia) or with other potential causes of emesis and nausea (.eg. gastrointestinal obstruction, raised intracranial pressure, hypercalcaemia, brain metastases); pts who had experienced emesis and/or moderate/severe nausea in the preceding 24h, had received chemo in the preceding 5 days, had in the last 30 days received or were about to receive an investigational drug, or who were receiving conditioning for bone marrow transplantation were excluded. Other exclusion criteria were: concurrent or past medical conditions that might interfere with the study, impaired hepatic function, pregnancy, or lactation.
Spitzer 1994	NR/NR/20	
Tiley and Powles 1992	NR/20/20	Pts undergoing autologous transplantation for acute myeloid leukemia were excluded because they are conditioned with melphalan at 140 mg/m2

Evidence Table 8. Quality assessments of the radiation controlled-clinical trials

External Validity

Author, Year	Run-in/Washout	Class naïve patients only	Control group standard of care	Funding	Relevance
Placebo-controlled trials, cont.					
Lanciano 2001	Washout: 30 days for investigational drug, 72 hours for emetogenic chemotherapy, 24 hours for radiation No run-in	No	Yes	NR, 4th author from SmithKline Beecham	Yes
LeBourgeois 1999	Washout: 5 days for chemo, 30 days for investigational drugs	No	Yes	Glaxo Wellcome	Yes
Spitzer 1994	Washout: 30 days for investigational drug No run-in	No	Yes	Glaxo, Inc.	Yes
Tiley and Powles 1992	No, No	NR	Yes	NR	Yes

Evidence Table 8. Quality assessments of the radiation controlled-clinical trials

Internal Validity

Author, Year	Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors masked?	Care provider masked?	Patient masked?
Active-controlled trials							
Prentice 1995	NR	NR	Yes	Yes	Not reported	Yes	Yes
Sykes 1997	NR	NR	NR; baseline characteristics were not presented or discussed	Yes	Not reported	Yes	Yes
Priestman 1990 Priestman 1989	NR	NR	Yes	Yes	Not reported	Yes	Yes
Priestman 1993	NR	NR	Yes	Yes	Not reported	Yes	Yes

Evidence Table 8. Quality assessments of the radiation controlled-clinical trials

	Internal Validity				
Author, Year	**Reporting of attrition, crossovers, adherence, and contamination**	**Loss to follow-up: differential/ high**	**Intention-to-treat (ITT) analysis; If No: % analyzed**	**Post-randomization exclusions**	**Quality Rating**
Active-controlled trials					
Prentice 1995	NR, NR, NR, NR	NR	Yes	No	Fair
Sykes 1997	NR, NR, NR, NR	NR	Unknown, no information about number of patients analyzed	Unknown	Poor
Priestman 1990 Priestman 1989	Yes, NR, NR, NR	None	No, 84.5%	No	Fair
Priestman 1993	Yes, NR, NR, NR	None	Yes	No	Fair

Evidence Table 8. Quality assessments of the radiation controlled-clinical trials

	External Validity	
Author, Year	**Number screened/ eligible/ enrolled**	**Exclusion criteria**
Active-controlled trials		
Prentice 1995	NR/20/20	
Sykes 1997	NR/66/66	Pts not allowed if any of the following applied: concurrent chemo; concurrent antiemetic therapy, including pednisolone and dexamethasone with the exception of the study drugs; severe concurrent illness; gastrointestinal obstruction; CNS metastases; vomiting in the 24h prior to study entry; adminitration of concurrent benzodiazapines excpet for night sedation
Priestman 1990 Priestman 1989	NR/97/97 (at time of interim analysis; 160 planned)	Pts excluded if clinically jaundiced, had vomited in the previous 24h, had received antiemetics within the previous 24h or were suffereing severe concurrent illness unrelated to their neoplasia.
Priestman 1993	NR/NR/192	

Evidence Table 8. Quality assessments of the radiation controlled-clinical trials

External Validity

Author, Year	Run-in/Washout	Class naïve patients only	Control group standard of care	Funding	Relevance
Active-controlled trials					
Prentice 1995	Washout: 66 hours for high-dose CY, 24 hours for antiemetic treatment	No	Yes	SmithKline Beecham	Yes
Sykes 1997	No, No	No	Yes	Glaxo Laboratories, Inc.	Yes
Priestman 1990 Priestman 1989	Washout: 24 hours for antiemetics No run-in	No	Yes	NR, 5th author from Glaxo Group Research Limited	Yes
Priestman 1993	Washout: 24 hours for antiemetics No run-in	No	Yes	NR, 3rd author from Glaxo Gropu Research Limited	Yes

Evidence Table 9. Prevention of PONV: head-to-head trials

Author Year Setting	Design	Exclusion criteria	Intervention	Allow other medication	Run-in/ Wash out
Adults					
Dolasetron vs. Ondansetron					
Browning 2004 Single Center	DB RCT Parallel	Pts excluded if they were <18, pregnant, received and ASA physical classification of ≥ III, experienced emesis 24 h prior to procedure, or received antiemetic medication or investigational research drug 24 h prior to surgery.	Dolasetron iv 12.5mg Ondansetron iv 4mg	No	NR/NR
Paech 2003 Single Center	DB RCT Parallel	Pts experiencing preoperative nausea, receiving medication with antiemetic activity or with contraindication to nonsteroidal anti-inflammatory medication or epidural anesthesia were excluded from this study. Women in whom an open procedures was not performed or who underwent unplanned bowel surgery were excluded.	Dolasetron iv 12.5mg Ondansetron iv 4mg Tropisetron iv 2mg	All premedicated with 20 mg temazepam 1-2 h before transfer to the theatre.	No/NR

Evidence Table 9. Prevention of PONV: head-to-head trials

Author Year Setting	Age/ Gender/ Ethnicity	Screened/ Eligible/ Enrolled	Withdrawn/ Lost to fu/ Analyzed	Other population characteristics
Adults				
Dolasetron vs. Ondansetron				
Browning 2004 Single Center	NR 0%male NR	NR/NR/212	NR/NR/212	NR
Paech 2003 Single Center	48.8 years 0%male NR	NR/NR/120	2 /0/ 118	Mean weight = 76.2 kg History of PONV 33% History of motion sickness 18% Pts in 0-8 days of menstrual period 21% Gynecological procedures 55% Gynecological oncological procedures 43% Median surgical duration: 92.2 min Median vol. of post-op epidural soln:142.3ml Range of surgical durations: 65-152 minutes

Evidence Table 9. Prevention of PONV: head-to-head trials

Author Year Setting	Results	Adverse Events
Adults		
Dolasetron vs. Ondansetron		
Browning 2004 Single Center	Emetic episodes - no data given, only that difference was NS	headache dizziness dysrhythmia allergic reaction
Paech 2003 Single Center	*Dol iv 12.5 vs Ond iv 4 vs Trop iv 2* Complete response: no vomiting and no rescue drugs required during the study period 20% vs 16.7% vs 23.8%, p: NS Incidence of vomiting: overall and by time period recovery-2h : 17.5% vs 25.0% vs 22.0%, p: NS 2-6h: 17.5% vs 11.1% vs 11.9%, p: NS 6-12h: 15.4% vs 13.9% vs 14.3%, p: NS 12-18h: 27.5% vs 22.2% vs 4.3%, p: NS 18-24h: 35.0% vs 47.2% vs 28.6%, p: NS overall: 60% vs 75% vs 69%, p: NS Median no.of antiemetic treatment doses and % receiving rescue drugs No. of treatment doses: 1 dose vs 1 dose vs 1 dose, p: NS % receiving 1 rescue drug : 30% vs 42% vs 31%, p: NS % receiving 2 rescue drugs : 25% vs 33% vs 24%, p: NS Nausea scores: no nausea (score=0), overall, and worst score by time period: score No nausea: 25% vs 33.3% vs 129.3%; p=NS 2h; 2-6h; 6-12h: 0 vs 0 vs 0, p: NS 12-18h: 0 vs 0 vs 8.5, Trop iv 2 vs. Dol and Ond, p=0.02 18-24h: 18 vs 24.5 vs 10, p: NS Overall nausea score (0-24h): scale of 0-100: 14.5 vs 20 vs 20, p: NS Postoperative characteristics (median time in hours) Time to drink: 12 vs 7.25 vs 5.5; p=NS Time to eat: 64.5 vs 66 vs 48; p=NS Time to ambulation: 20 vs 20 vs 19; p=NS Pt satisfaction score with recovery (scale 0-100): 96.5 vs 100 vs 95; p=NS Patient satisfaction score with PONV control (0= not satisfied to 100=completely satisfied): 99.5 vs 97.5 vs 100; p=NS	NR

Evidence Table 9. Prevention of PONV: head-to-head trials

Author Year Setting	Comments
Adults	
Dolasetron vs. Ondansetron	
Browning 2004 Single Center	PACU nurses allowed to administer rescue antiemetics according to postoperative anesthesia orders, if they determined it was needed, if the pt experienced persistent nausea for ≥15 minutes, had ≥1 emetic episode, or if the pts requested medication. Study results were in narritive form only, with the exception of how many patients were in the study, and how many per group received spinal narcotics. No other numbers were given, though the results were all "not significant statistically". Analyses of emetic episodes both in the PACU or in 24h poststurgery were found not to differ significantly between groups. The same results were found for mean numeric nausea intensity scores at any time, pt satisfaction scores, and side effects. S norris 9/13/05: There was no run in or wash out. Pts who got antiemetic in last 24 h were excluded . No data tables or information on attrition. No data provided on number screened or eligible.
Paech 2003 Single Center	A low thoracic (T9-T12) epidural was inserted prior to induction of anesthesia and 6 to 10 ml of epdiucal ropivacaine 7.5 mg/ml with fentanyl 50 micrograms was administered. Muscle relaxation was reversed with iv neostigmine (2.5 mg) and atropin (1.2 mg). Postoperative pain relief was provided by epidural infusion of ropivacaine 2 mg/ml with fentanyl 4 microgram/ml at 6 to 12 ml/h and rectal diclofenac 100 mg was administered twice daily.

Evidence Table 9. Prevention of PONV: head-to-head trials

Author Year Setting	Design	Exclusion criteria	Intervention	Allow other medication	Run-in/ Wash out
Tang 2003 Single Center	DB RCT Parallel	Exclusion criteria included pregnancy; active menstruation; body weight more that 50% above the ideal body weight; vomiting or retching within 24h before the operation; administration of entiemetic or psychoactive medication within 24h before surgery; a previous history of severe (or unstable) cardiovascular, respiratory, metabolic, endocrine, or neurologic disease; alcohol or drug absue; and impaired renal or hepatic function.	Dolasetron iv 12.5mg Ondansetron iv 4mg Saline iv (placebo) mg	Droperidol 0.625 mg iv, and dexamethasone, 4 mg iv, were administered to all patients after induction of anesthesia.	No/No

Evidence Table 9. Prevention of PONV: head-to-head trials

Author Year Setting	Age/ Gender/ Ethnicity	Screened/ Eligible/ Enrolled	Withdrawn/ Lost to fu/ Analyzed	Other population characteristics
Tang 2003 Single Center	54.7 years 37%male NR	NR/NR/135	0/0/135	NR

Evidence Table 9. Prevention of PONV: head-to-head trials

Author Year Setting	Results	Adverse Events
Tang 2003 Single Center	*Data given as Dol iv 12.5 vs Ond iv 4 vs Placebo* Complete response (no emetic episodes and no rescue medication) to PONV prior to discharge: 98% vs 98% vs 98%, p: NS after discharge: 98% vs 98% vs 98%, p: NS Post-operative nausea score (SD) at 30 min: 5(10) vs 3(9) vs 5(12), p: NS at discharge: 3(4) vs 2(3) vs 3(3), p: NS Nausea, vomiting, and rescue rates Need for rescue medication after discharge: 0% vs 0% vs 0%; p=NS Nausea prior to discharge: 9% vs 4% vs 11%; p=NS Nausea after discharge: 6.7% vs 9% vs 11%; p=NS Vomiting prior to discharge: 0% vs 0% vs 0%; p=NS Vomiting after discharge: 2% vs 2% vs 0%; p=NS Need for rescue medication prior to discharge: 2% vs 2% vs4%; p=NS Overall PONV incidence:11% vs 13% vs 18%; p=NS Patients very satisfied: 96% vs 98% vs 93%; p=NS Patients satisfied: 2pts vs 1pts vs 3pts; p=NS Patiens dissatisfed: 0 vs 0 vs 0; p=NS Recovery times after the end of anesthesia Time until pt tolerates oral fluids: 21min vs 22min vs 23min Time to actual discharge: 51min vs 46min vs 48min Time to eye opening: 4min vs 4min vs 4min, p: NS Time to response to commands: 4min vs 4min vs 4min, p: NS Time to orientation: 5min vs 5min vs 5min, p: NS Time to sitting up: 14min vs 12min vs 14min, p: NS Time to pt ambulates: 16min vs 16min vs 17min Time until pt has "fitness" for discharge: 23min vs 22min vs 24min Time of recovery room stay: 37min vs 32min vs 33min Time to standing up: 16min vs 14min vs 15min; p=NS	Only information given on AEs: "Th

Evidence Table 9. Prevention of PONV: head-to-head trials

Author Year Setting	Comments
Tang 2003 Single Center	Ketorolack, 30mg iv, administered during surgery to minimize postoperative pain. Study medications were prepared by the local pharmacy in identical-appearing 5-ml syringes. The maintenance anesthetics were discontinued at the start of skin closure. On awakening from anesthesia, the patients' ablilites to meet specific fast-track discharge criteria were assessed at 2-min intervals. After applying the surgical dressing, the patients were asked to sit up on the operating room table. After standing up, they were allowed to walk to the recovery area with assistance. Rescue medications for PONV (e.g., 10 mg metoclopramide iv) and pain management (ie, 500 mg acetaminophen with 5 mg hydrocodone) were administered upon pt. request. Snorris 9/13/05: "double blind" but unclear who blinded. Drugs prepared "identical". Telephone interviewer (some outcomes) blinded. No antiemetic during last 24 hours, but no information on whether ever had an antiemetic

Evidence Table 9. Prevention of PONV: head-to-head trials

Author Year Setting	Design	Exclusion criteria	Intervention	Allow other medication	Run-in/ Wash out
Zarate 2000 Single Center	DB RCT Parallel	Patients were excluded if they had received an antiemetic medication within 24h before their operation, were pregnant, had clinically significant cardiovascular , neurologic, renal , hepatic, gastrointestinal, or endocrinological diseases, had a history of drug abuse, or were >100% above their ideal body weight	Dolasetron iv 12.5mg Dolasetron iv 25mg Ondansetron iv 4mg Ondansetron iv 8mg	All received midazolam 0.02 mg/kg IV for premedication.	No/No

Evidence Table 9. Prevention of PONV: head-to-head trials

Author Year Setting	Age/ Gender/ Ethnicity	Screened/ Eligible/ Enrolled	Withdrawn/ Lost to fu/ Analyzed	Other population characteristics
Zarate 2000 Single Center	45 years 56%male NR	NR/NR/200	0/0/200	Mean weight = 80.04 kg Previous motion sickness 18% Previous PONV 31% Palate/tonsil surgery 12% Endolymphatic sac procedures 10% Nastoidectomy/tympanoplasty 32% Nasal septal surgery 24% Endosinus surgery 21% Mean duration of surgery = 73.2 min Mean duration of anesth. admin. = 94.2 min

Evidence Table 9. Prevention of PONV: head-to-head trials

Author Year Setting	Results	Adverse Events
Zarate 2000 Single Center	*data given as Dol iv 12.5 vs Dol iv 25 vs Ond iv 4 vs Ond iv 8* Nausea and vomiting rates experienced Nausea while in-hospital: 26% vs 24% vs 23% vs 30% Nausea post-discharge: 18% vs 12% vs 13% vs 14% Nausea 24h symptoms overall: 38% vs 24% vs 27% vs 28% Vomiting while in-hospital: 8% vs 4% vs 4% vs 0% Vomiting post-discharge: 6% vs 4% vs 2% vs 2% Vomiting at 24h overall: 12% vs 8% vs 6% vs 2% Lack of complete response In-hospital: 26% vs 20% vs 21% vs 30%; p=NS Post-discharge: 20% vs 12% vs 10% vs 14%; p=NS 24h period overall: 26% vs 27% vs 25% vs 30%; p=NS Rescue antiemetics needed promethazine only: 26% vs 23% vs 21% vs 28% promethazine + droperidol: 2% vs 2% vs 2% vs 2% promethazine + droperidol + ondansetron: 2% vs 2% vs 0% vs 0% Pts experiencing frequent (≥ 2) PONV episodes: 6% vs 4% vs 2% vs 2% Maximum nausea VAS in PACU (0=none to 100=maximum) Score: 14mm vs 9mm vs 8mm vs 10mm; p=NS Complete response: no emesis, no nausea, no rescue medication for 24h : 74% vs 73% vs 76% vs 70%; p=NS	NR

Evidence Table 9. Prevention of PONV: head-to-head trials

Author Year Setting	Comments
Zarate 2000 Single Center	Anesthesia induced with propofol 1.5 mg/kg IV and reminfentanil 1 microgram/kg IV. Snorris 9,13,05: "double blind", and assessor blinded. But unclear whether patient or provider blinded. Crossover, adherence, contamination NR explicitly. One group was 51, olne 49, could have been due to cross/over?

Evidence Table 9. Prevention of PONV: head-to-head trials

Author Year Setting	Design	Exclusion criteria	Intervention	Allow other medication	Run-in/ Wash out
Korttilla 1997 Multicenter	DB RCT Parallel	Pts scheduled for post-operative gastric suctioning or pts who had ingested any drug with antiemetic efficacy within 24h before surgery. Other exclusion criteria included clinically significant cardiac or liver disease, abnormal prestudy serum potassium levels, obesity (.40% above ideal body weight), nausea and vomiting within 24h prior to surgery, previous treatment with dolasetron mesilate, use of any investigational drug within 30 days of dolasetron administration, or known alcohol abuse.	Dolasetron iv 25mg Dolasetron iv 50mg Ondansetron iv 4mg	Pts may have received a benziodiazepine before general anesthesia.	NR/NR

Evidence Table 9. Prevention of PONV: head-to-head trials

Author Year Setting	Age/ Gender/ Ethnicity	Screened/ Eligible/ Enrolled	Withdrawn/ Lost to fu/ Analyzed	Other population characteristics
Korttilla 1997 Multicenter	42.0 years 5%male Caucasian: 365/389 = 93.8% African American: 9/389 = 2.3% Asian: 9/389 = 2.3% Other: 6/389 = 1.5%	NR/NR/518	1/3/514	Previous surgery: yes: 83% Previous surgery: no: 17% Mean weight, kg: 64.6 kg Mean height, cm: 164.0 cm ASA physical status I: 80% ASA physical status II: 19% ASA physical status III: 1% History of PONV: yes: 29% History of PONV: no: 71% History of motion sickness: yes: 15% History of motion sickness: no: 85% Laproscopic surgery: 50% Non-laproscopic surgery: 50% Gynecological surgery: 77% Non-gynecological surgery: 23%

Evidence Table 9. Prevention of PONV: head-to-head trials

Author Year Setting	Results	Adverse Events
Korttilla 1997 Multicenter	*Dol iv 25 vs Dol iv 50 vs Ond iv 4 (p=NS if not specified)* Complete response: 0 emetic episodes and no rescue medication during 24h study period CR, for all pts: 51% vs 71% vs 64% fentanyl equivalent analgesic requirement: >250 mcg : 48% vs 63% vs 57% ≤250 mcg : 55% vs 76% vs 69% Non-gynecological surgery: 55% vs 66% vs 75% Surgical technique: laproscopy: 42% vs 63% vs 60% Anesthesia duration ≤ 1.66h: 60% vs 78% vs 73% History of motion sickness (yes vs. no) Yes(No): 56%(50%) vs 79%(69%) vs 75%(61%) Gynecological surgery: 50% vs 72% vs 61% History of PONV- yes: 33% vs 65% vs 54% ASA physical status (ASA=I vs. ASA=II & III) ASA=I(ASA=II or III): 52%(48%) vs 74%(57%) vs 61%(78%) Age (≤ 43 years vs.> 43 years) ≤ 43 years(> 43 years): 54 %(47%) vs 81%(58%) vs 69%(59%) Males: 75% vs 86% vs 50% Female: 50% vs 70% vs 64% Anesthesia duration >1.66h : 44% vs 63% vs 55% Surgical technique: non-laproscopy: 62% vs 77% vs 67% Total response: complete response plus no nausea (ie, VAS ≤5 at t=2,4, & 6h post-recovery) All pts: 43% vs 60% vs 54% Dol 50 vs. Dol 25: p=0.005 Failure: receipt of rescue medication: all patients: 29% vs 19% vs 24% % with no nausea (max VAS rating ≤ 5) 57% vs 71% vs 62% , Dol 50 vs. Dol 25: p=0.008 Maximum nausea VAS (0= no nausea to 100= as bad as can be) Mean max VAS score : 19 vs 11 vs 18 Dol 50 vs. Dol 25: p=0.013, Dol 50 vs. Ond; p=0.062 Patient satisfaction VAS (0= not at all satisfied to 100= as satisfied as can be) mean score: 83 vs 89 v D50 vs D25: p=0.016	*Dol 50 vs Dol 100 vs Ond 4* Overall AEs : 27% vs 24% vs 27% Bradycardia: 6% vs 5% vs 7% Headache : 6% vs 5% vs 4% Hypertension: 2% vs 5% vs 3% Hypotension: 2% vs 2% vs 3% AV block first degree: 0% vs 2% vs 2% Drowsiness: 2% vs 0% vs 0% Abnormal hepatic function: 1% vs 2% vs 0% Bronchospasm: 1% vs 0% vs 1% Rash: 0% vs 1% vs 2%

Evidence Table 9. Prevention of PONV: head-to-head trials

Author Year Setting	Comments
Korttilla 1997 Multicenter	The placebo arm (n=128) was not included in this abstraction, which gives a total of 389 pts entering this study. 518 pts were enrolled, and 1 pt withdrew from the study after randomization but before receiving study drug (n= 517); 3 pts were withdrawn from study before cessation of anesthesia: 2 had serious AEs, and 1 pt required nasograstric suctioning during and after surgery). Investigators could administer rescue medication according to institutional practise if they determined alternative therapy was needed, or if the pt experienced ≥ 15 min persistent nausea, had >1 emetic episode, or requested rescue medication. Recovery was defined as the first response to the spoken command, "Open your eyes." Pta may have received a benzodiazepine before general anesthesia.

Evidence Table 9. Prevention of PONV: head-to-head trials

Author Year Setting	Design	Exclusion criteria	Intervention	Allow other medication	Run-in/ Wash out
Granisetron vs. Ondansetron					
Dua 2004 Single Center	DB RCT Parallel	Pts with known stomach disorders, history of heartburn, motion sickness, pervious PONV, lower esophageal sphincter disorders, menstruation, uncontrolled hypertension, poorly controlled diabetes, or pre-operative emesis less that 12h prio to surgery were excluded.	Granisetron 1mg Ondansetron 4mg	Glycopyrrolate	None/No
Naguib 1996 NR	DB RCT Parallel	Patients who were receiving drugs known to have antiemetic effects (such as tricyclic antidepressants, scopolamine, phenothiazines, lorazepam, corticosteroids, and trimethobenzamides. Pts were also excluded if they had experienced nausea or vomiting of it they had taken antiemetic treatment in the 48h before surgery. No premedication was given	Granisetron iv 3mg Ondansetron iv 4mg Tropisetron iv 5mg	No	No/NA

Evidence Table 9. Prevention of PONV: head-to-head trials

Author Year Setting	Age/ Gender/ Ethnicity	Screened/ Eligible/ Enrolled	Withdrawn/ Lost to fu/ Analyzed	Other population characteristics
Granisetron vs. Ondansetron				
Dua 2004 Single Center	48.5 years 0%male NR	NR/NR/60	NR/NR/NR	Mean weight in kg = 60.2 kg mean total intraoperative dose of fentanyl=100.7g ASA status 1: 57% ASA status 2: 42% Mean duration of anesthesia = 114.2 min Preoperative PONV: 2% Post-op anesth.:diclofenac Na 75/150 mg: 10%
Naguib 1996 NR	37.4 years 22%male NR	NR/NR/132	0/0/132	Mean weight = 73.7 kg (range: 40-98kg) Mean duration of anesthesia = 118.5 minutes (range: 60-260 min) Mean micrograms of intraoperative fentanyl =182.0 (range: 100-400 mcg)

Evidence Table 9. Prevention of PONV: head-to-head trials

Author Year Setting	Results	Adverse Events
Granisetron vs. Ondansetron		
Dua 2004 Single Center	Gran iv 1 vs Ond iv 4 Patients PONV scores Complete response: no vomiting and no nausea: 75% vs 60%, p: NR PONV = 3 (vomiting ≥2 within 30m): acute: 20% vs 25%, p: NR PONV = 1 (only nausea, no vomiting): 5% vs 10%, p: NS PONV = 2 (1 episode of vomiting): acute: 0% vs 5%, p: NS Pts needing rescue medication in 24 h :15% vs 20%; p=NR	*Gran iv 1mg vs Ond iv 4mg* Headache: 5% vs 10% Dizziness: 0% vs 5% Drowsiness: 5% vs 0% Anxiety, insomnia: 5% vs 0% Others: 5% vs 5% Total number of AEs: 20% vs 20%
Naguib 1996 NR	Gran iv 3 vs Ond iv 4 vs Trop iv 5 vs vs vs 12 Patients with PONV (treatment failures) Patients with PONV (treatment failures): over 24h: 48% vs 34.5% vs 52%, p: NS PONV-free patients (complete response) Complete response: Pts without any PONV in 24h: 52% vs 65.5% vs 48%, p: NS	NR

Evidence Table 9. Prevention of PONV: head-to-head trials

Author Year Setting	Comments
Granisetron vs. Ondansetron	
Dua 2004 Single Center	Before tracheal extubation, a nasogastric tube was inserted and suction was applied to empty the contents of the stomach. At the cessation of the surgical procedure, nitrous oxide and isoflurane administration were ceased.The trachea was extubated when the patient was awake. All patiens received intramuscular injection of diclofenac sodium 75 mg for postoperative pain relief. Snorris 9/13/05: No run-in for treatment drugs. Patients did receive diazepam evenign prior as part of pre-med. Attrition not reported.
Naguib 1996 NR	No premedication was given and pts fasted from midnight before surgery. After tracheal intubation, all pts had an orogastric tube placed to ensure baseline emptying of the stomach of air and gastric contents. All orogastric tubes were removed at the end of surgery and before tracheal extubation. Retching was not assessed separately from vomiting and nausea. If nausea or vomiting occurred, rescue antiemetic treatment of metoclopramide iv 10 mg was administered. For post-operative analgesia, meperidine im 50 mg was administered if pain score was ≥ 5. Study also included a metoclopramide arm (n=24) and a placebo arm (n=29), but these results are not included in this data abstraction. After intubation the concentrations of the nitrous oxide, oxygen, carbon dioxide, and isoflurane were determined continuously by a multiple-gas anaesthesia monitor .Abdominal insufflation for the laparoscopic procedure was accomplished with carbon dioxide. No major adverse effects were observed per the authors.

Evidence Table 9. Prevention of PONV: head-to-head trials

Author Year Setting	Design	Exclusion criteria	Intervention	Allow other medication	Run-in/ Wash out
Children					
Dolasetron vs. Ondansetron					
Karamanlioglu 2003	DB RCT Parallel	Children who received antiemetics or antihistamines in the 24h before surgery were excluded, as were children with diabetes mellitus or gastro-esophageal reflux. Any child unable to swallow the methylene blue capsule or the study drugs or who vomited them before the induction of anesthesia was excluded from the study.	Dolasetron po 1.8mg/kg Ondansetron po 0.15mg/kg	no	None/NA

Evidence Table 9. Prevention of PONV: head-to-head trials

Author Year Setting	Age/ Gender/ Ethnicity	Screened/ Eligible/ Enrolled	Withdrawn/ Lost to fu/ Analyzed	Other population characteristics
Children				
Dolasetron vs. Ondansetron				
Karamanlioglu 2003	9.85 years 49%male NR	NR/NR/150	0/0/150	ASA I - 78% ASA II - 22% Mean weight = 29.45 kg Strabismus surgery --46% Adenotonsillectomy - 29% Orchiopexy - 13% Middle ear surgery - 12% Mean duration of anesthesia = 79.9 min Mean duration of surgery = 76.25 min No. of pts with methylene blue contamination - 12% Median metoclopramide consumption/pt = 0 (range: 0-4.0) Number of pts taking metoclopramide -20%

Evidence Table 9. Prevention of PONV: head-to-head trials

Author Year Setting	Results	Adverse Events
Children		
Dolasetron vs. Ondansetron		
Karamanlioglu 2003	*data given as Dol po 1.8 vs Ond po 0.15* PONV scores for 0-1h post-surgery, Score = 3 (vomiting): 4% vs 6%, p: NS Score = 0 (complete response: no nausea): 84% vs 80%, p: NS Score = 1 (nausea): 8% vs 10%, p: NS Score = 2 (retching): 4% vs 4%, p: NS PONV scores for 0-24h post-surgery, Score = 0 (complete response: no nausea): 68% vs 52%, p: NS Score = 1 (nausea): 16% vs 26%, p: NS Score = 2 (retching): 8% vs 6%, p: NS Score = 3 (vomiting): 8% vs 16%, p: NS Median VAS scores (scale 1-10) for post-operative pain, median (range) t=4h : 4 vs 4, p: NS t=8h : 3 vs 3.5, p: NS t=1h : 5 vs 5, p: NS t=0h : 7 vs 7, p: NS Median sedation scores (0=awake to 2=asleep) at post-surgery times: t=0h, 1h, 4h, 8h post-surgery : 0 vs 0, p = NS for all 4 times Median acetaminophen consumption/patient: 240 vs 240, p: NS % pts receiving acetaminophen: 64% vs 68%, p: NS	Sedation - see efficacy Pain - see efficacy

Evidence Table 9. Prevention of PONV: head-to-head trials

Author Year Setting	Comments
Children	
Dolasetron vs. Ondansetron	
Karamanlioglu 2003	Study also contained a placebo arm (n=50); giving a total of 150 patients entered into the study; but this arm was not included in this abstraction, giving an N=100. metoclopramide was given to any pt with a score of ≥2, or if the child requested an antiemetic. Postoperative analgesia (acetaminophen 10-25 mg/kg) was given to the older children when they complained of pain and to the younger children when they were restless and crying. Oral intake was not allowed until 4h after recovery from anesthesia. Each child received fentanyl 1 microgram kg-1 i.v. before surgery. Patients breathed spontaneously towards the end of operation. Residual muscular relaxation was not antagonized pharmacologically. During extubation, there was as little stimulation and suction of the airway as possible to avoid disturbing the child and stimulating gagging. Contamination of the mouth and endotracheal tube by methylene blue was assessed. SNorris 9/12/05: For 'class naïve' question, this information is not reported; only that patients hadn't taken drug in last 24 hours.

Evidence Table 9. Prevention of PONV: head-to-head trials

Author Year Setting	Design	Exclusion criteria	Intervention	Allow other medication	Run-in/ Wash out
Olutoye 2003 Single Center	DB RCT Parallel	Pts with ASA physical status of ≥ III, a previous history of gastroesophageal feflux, vomiting from organic causes, obesity (>95th percentile of weight for age), emergency surgery, antiemetic therapy within 24h before surgery or the use of neuraxial anesthesia or drugs known to have antiemetic effects (e.g., steroids, propofol). Children undergoing tonsillectomy and adenoidectomy procedures were excluded because they routinely receive steroids at this institution. A history of POV or motion sickness was noted during the preanaesthetic evaluation but did not preclude enrollment.	Dolasetron iv 45micrograms/kg Dolasetron iv 175micrograms/kg Dolasetron iv 350micrograms/kg Dolasetron iv 700micrograms/kg Ondansetron iv 100micrograms/kg	All subjects received midazolam 0.5 mg/kg per os 15-30 min before anesthesia induction.	No/No
Sukhani 2002 Single Center	DB RCT Parallel	Children who received antiemetics, antihistaminics, or psychoactive drugs within 24h before surgery were excluded. Also excluded were children who had a history of diabetes and those who required an iv induction, i.e., those with gastroesophageal reflux, obese children (>150% of ideal body weight), and children with a known history of allergy to any of the drugs used in the study.	Dolasetron iv 0.5mg/kg Ondansetron iv 0.15mg/kg	All received midazolam 0.5-0.6 mg/kg (maximum 20 mg) po 20-30 min before anticipated induction.. Each received acetaminophen 30 mg/kg suppository, fentanyl 1 microgram/kg iv, and dexamethasone 1 mg/kg (max. 25 mg) iv before the start of surgery.	No/NR

Evidence Table 9. Prevention of PONV: head-to-head trials

Author Year Setting	Age/ Gender/ Ethnicity	Screened/ Eligible/ Enrolled	Withdrawn/ Lost to fu/ Analyzed	Other population characteristics
Olutoye 2003 Single Center	6.0 years 73%male NR	NR/225/216	9/3/204	Mean weight = 22.1 kg Herniorrhaphy 44% Orchidopexy 18% Penile surgery 7% Superficial plastic surgery 11% Umbilical hernia surgery 21% Previous history of motion sickness 18% Previous history of POV 2% Mean anesthesia time = 76.0 min Mean surgical time = 39.5 min End of Surgery (EOS) to PACU arrival = 15.0 min EOS to phase 1 PACU discharge = 62.7 min EOS to phase 2 PACU discharge = 150.2 min
Sukhani 2002 Single Center	5.7 years 47%male NR	NR/NR/150	1/2/147	Weight = 24.8 kg ASA physical status = I: 80% ASA physical status = II: 20% Mean anesthesia duration = 54.0 min Mean surgery duration = 38.1 min

Evidence Table 9. Prevention of PONV: head-to-head trials

Author Year Setting	Results	Adverse Events
Olutoye 2003 Single Center	*data given as Dol 45 vs Dol 175 vs Dol 350 vs Dol 700 vs Ond 100* Freedom from postoperative emetic symptoms; complete response: no emesis, no rescue for 0-6h: 54.3% vs 71.9% vs 87.1% vs 78.4% vs 79.7%, p: NS for 24h: 45.7% vs 62.5% vs 74.2% vs 73.0% vs 78.3%, p: NS Rescue antiemetics needed, 2.9% vs 0% vs 3.2% vs 5.4% vs 4.3% ≥ 2 episodes of POV (failure), 25.7% vs 21.9% vs 3.2% vs 0% vs 8.7% Parental satisfaction scores (score (SD)) 8.1(3.3) vs 9.0(1.8) vs 9.2(2.0) vs 9.4(1.9) vs 9.6(0.9) Dol 175 vs. Dol 45, p<0.05; Dol 350 vs. Dol 45, p<0.05; Dol 700 vs. Dol 45, p<0.05; Ond 100 vs. Dol 45, p<0.05 Complete satisfaction with POV control, 65.7% vs 62.5% vs 74.2% vs 73.0% vs 75.4%	NR
Sukhani 2002 Single Center	Dol 0.5 vs Ond 0.15 Complete response (no emesis and no antiemetics given during 48h post-surgery) : 74% vs 76%, p: NS Need for rescue antiemetics: overall and by time period: overall: 8% vs 4%, p: NS 24-48h post-surgery: 2% vs 0%, p: NS Discharge to 24h post-surgery: 0% vs 0%, p: NS in PACU: 6% vs 4%, p: NS Pts experiencing retching/vomiting: In PACU: 8.2% vs 10.0%, p: NS Discharge to 24h post-surgery: 14% vs 8%, p: NS 24h-48h post-surgery: 6% vs 6%, p: NS Post-recovery oral intake: Good/excellent oral intake (discharge to 24h): 85.7% vs 93.9%, p: NS Good/excellent oral intake (24h to 48h): 85.7% vs 93.9%, p: NS Post-recovery problems: Hospital admission (discharge to 24h): 4% vs 0%, p: NS Hospital admission(24h to 48h): 0% vs 2%, p: NS ER visit for vomiting /hydration: 24h-48h: 0% vs 2%, p: NS discharge to 24h: 4% vs 0%, p: NS	NR

Evidence Table 9. Prevention of PONV: head-to-head trials

Author Year Setting	Comments
Olutoye 2003 Single Center	After a minimal fast of 2 h (for clear liquids), all pts received midazolam 0.5 mg/kg per os 15-30 min before induction. Of 216 pts originally enrolled, 1 subject was excluded from analysis after requiring additional surgery, and 8 were excluded because of protocol violations (caudal epidural analgesia, additional intraoperative opioids, or other antiemetics); and 3 pts were lost to followup; 204 pts analyzed. Stomachs suctioned at surgery end, and the trachea extubated when the pt was awake. In the PACU, pain assessed using Children's Hospital of Eastern Ontario Pain Scale (CHEOPS). Pts with severe pain (CHEOPS > 8) received IV morphine (increments of 0.05 mg/kg), those with moderated pain (CHEOPS 5-8) received oral oxycodone (0.1 mg/kg). Mild pain (CHEOPS 3-5) treated with oral acetaminophen 10-15 mg/kg. Pts with postop emesis while still in hospital received rescue: IV ond 0.05 mg/kg, metoclopramide 0.15-0.2 mg/kg, and droperidol 0.05 mg/kg for first, second, and third episodes, respectively. If IV access no longer available, trimethobenzamide (Tigan), 100-200 mg prescribed for rectal administration. Oral intake permitted but not mandatory before discharge(criteria included a fully awake pt who recognized the parents, with stable vital signs, and who was free from pe Nausea, a subjective feeling of emesis, not assessed in this study due to young age of pts. AEs: "There were no differences in the incidence of nonemetic AEs." Snorris 9/12/05: described as 'double blind", but unclear who refers to. Care provider is described as blinded. Unclear if assessor or patient (parent) blinded. Class naïve: NR Screened n-225, 9 declined therefore 216 enrolled; then lost 8 (protocol violation), 3 attrition, 1 second surgery. Therefore 204 analyzed
Sukhani 2002 Single Center	Solid foods permitted until midnight before the day of surgery, and clear liquids permitted until 3 h before start of the expected surgery. All received oral premedication consisting of midazolam 0.5-0.6 mg/kg (maximum 20 mg), 20-30 min before the anticipated induction. Each patient received an acetaminophen 30 mg/kg suppository, fentanyl 1 microgram/kg IV, and dexamethasone 1 mg/kg (maximum 25 mg) IV before the start of surgery. At the conclusion of surgery, gastric contents were scutioned via an orogastric tube.Because nausea is difficult to assess in children, only retching and vomiting were assessed. This information only includes the H2H portion of this study; the placebo group consisted of 50 patients and their data was not included in this abstraction. SNorris 9/12/05: Class naïve NR; only that couldn't have taken antiemetic in last 24 hours. 1 post randomization exclusion for protocol violation; 2 lost to follow-up after discharge

Evidence Table 10. Quality assessment of the head-to-head trials for the prevention of PONV

Author Year Setting	Exclusion criteria	Run-in/Wash out	Screened/ Eligible/ Enrolled	Withdrawn/ Lost to fu/ Analyzed
Adults				
Dol vs Ond				
Browning 2004 Single Center	Pts excluded if they were <18, pregnant, received and ASA physical classification of ≥ III, experienced emesis 24 h prior to procedure, or received antiemetic medication or investigational research drug 24 h prior to surgery.	NR/NR	NR/NR/212	NR/NR/212
Paech 2003 Single Center	Pts experiencing preoperative nausea, receiving medication with antiemetic activity or with contraindication to nonsteroidal anti-inflammatory medication or epidural anesthesia were excluded from this study. Women in whom an open procedures was not performed or who underwent unplanned bowel surgery were excluded.	No/NR	NR/NR/120	2/0/118
Tang 2003 Single Center	Exclusion criteria included pregnancy; active menstruation; body weight more that 50% above the ideal body weight; vomiting or retching within 24h before the operation; administration of entiemetic or psychoactive medication within 24h before surgery; a previous history of severe (or unstable) cardiovascular, respiratory, metabolic, endocrine, or neurologic disease; alcohol or drug absue; and impaired renal or hepatic function.	No/No	NR/NR/135	0/0/135
Zarate 2000 Single Center	Pts excluded if they had received an antiemetic medication within 24h before their operation, were pregnant, had clinically significant cardiovascular , neurologic, renal, hepatic, gastrointestinal, or endocrinological diseases, had a history of drug abuse, or were >100% above their ideal body weight	No/No	NR/NR/200	0/0/200
Kortilla 1997 Multicenter	Pts scheduled for post-operative gastric suctioning or pts who had ingested any drug with antiemetic efficacy within 24h before surgery. Other exclusion criteria included clinically significant cardiac or liver disease, abnormal prestudy serum potassium levels, obesity (40% above ideal body weight), nausea and vomiting within 24h prior to surgery, previous treatment with dolasetron mesilate, use of any investigational drug within 30 days of dolasetron administration, or known alcohol abuse.	NR/NR	NR/NR/518	1/3/514
Gran vs Ond				
Dua 2004 Single Center	Pts with known stomach disorders, history of heartburn, motion sickness, pervious PONV, lower esophageal sphincter disorders, menstruation, uncontrolled hypertension, poorly controlled diabetes, or pre-operative emesis less that 12h prio to surgery were excluded.	None/No	NR/NR/60	NR/NR/NR
Naguib 1996 NR	Patients who were receiving drugs known to have antiemetic effects (such as tricyclic antidepressants, scopolamine, phenothiazines, lorazepam, corticosteroids, and trimethobenzamides. Pts were also excluded if they had experienced nausea or vomiting of it they had taken antiemetic treatment in the 48h before surgery. No premedication was given	No/NA	NR/NR/132	0/0/132

Evidence Table 10. Quality assessment of the head-to-head trials for the prevention of PONV

Author Year Setting	Randomization	Allocation	Groups similar at baseline	Eligibility criteria specified	Care provider masked	Patients masked	Attrition Crossover Adherence Contamination	Loss to follow up
Adults								
Dol vs Ond								
Browning 2004 Single Center	Yes	Yes	Yes, although no data given	Yes	Yes	Yes	No No No No	Unable to determine
Paech 2003 Single Center	Yes	Yes	Yes	Yes	No	Yes	Yes No No No	No
Tang 2003 Single Center	Yes	NR	Yes	Yes	Yes	NR, but is "double blind"	Yes No No No	No
Zarate 2000 Single Center	Yes	NR	Yes	Yes	NR, "double blind"	NR	Yes No No No	No
Kortilla 1997 Multicenter	NR	NR	Yes but for weight	Yes	NR	NR	Yes No No No	No
Gran vs Ond								
Dua 2004 Single Center	Yes	NR	Yes	Yes	Yes	NR	No No No No	NR
Naguib 1996 NR	NR	NR	Yes	Yes	NR, "double blind"	NR	Yes No No No	No

Evidence Table 10. Quality assessment of the head-to-head trials for the prevention of PONV

Author Year Setting	Intention-to-treat analysis	Postramdomization exclusions	Quality rating	Controlled group standard of care	Funding	Relevance
Adults						
Dol vs Ond						
Browning 2004 Single Center	Unable to determine	Unable to determine	Fair	Yes	NR	Unclear
Paech 2003 Single Center	Yes	Yes, only 2	Fair	Yes	A small proportion of each study drug was supplied free by the respective pharmaceutical companies (Novartis for trop., GlaxoWellcome for ond., and Hoechst Marion Roussel for dol.).	Unclear as don't know how pts selected
Tang 2003 Single Center	Yes	No	Fair	Yes	The clinical research fellowships were supported by departmental resources. This study was also supported by the White Mountain Institute, a not-for-profit private foundation in Los Altos, California (Dr. White is the president).	Yes
Zarate 2000 Single Center	Yes	No	Fair	Yes	NR	Unclear
Kortilla 1997 Multicenter	Yes	Yes, 1 withdrew after random, before drug	Fair	Yes	Supported by a research grant from Hoechst Marion Roussel	Yes
Gran vs Ond						
Dua 2004 Single Center	Unclear	Unable to determine	Fair	No	NR	Unclear
Naguib 1996 NR	Yes	No	Fair	Yes	NR	Unclear

Evidence Table 10. Quality assessment of the head-to-head trials for the prevention of PONV

Author Year Setting	Exclusion criteria	Run-in/Wash out	Screened/ Eligible/ Enrolled	Withdrawn/ Lost to fu/ Analyzed
Children				
Dol vs Ond				
Karamanlioglu 2003	Children who received antiemetics or antihistamines in the 24h before surgery were excluded, as were children with diabetes mellitus or gastro-esophageal reflux. Any child unable to swallow the methylene blue capsule or the study drugs or who vomited them before the induction of anesthesia was excluded from the study.	None/NA	NR/NR/150	0/0/150
Olutoye 2003 Single Center	Pts with ASA physical status of ≥ III, a previous history of gastroesophageal feflux, vomiting from organic causes, obesity (>95th percentile of weight for age), emergency surgery, antiemetic therapy within 24h before surgery or the use of neuraxial anesthesia or drugs known to have antiemetic effects (e.g., steroids, propofol). Children undergoing tonsillectomy and adenoidectomy procedures were excluded because they routinely receive steroids at this institution. A history of POV or motion sickness was noted during the preanaesthetic evaluation but did not preclude enrollment.	No/No	NR/225/216	9/3/204
Sukhani 2002 Single Center	Children who received antiemetics, antihistaminics, or psychoactive drugs within 24h before surgery were excluded. Also excluded were children who had a history of diabetes and those who required an iv induction, i.e., those with gastroesophageal reflux, obese children (>150% of ideal body weight), and children with a known history of allergy to any of the drugs used in the study.	No/NR	NR/NR/150	1/2/147

Evidence Table 10. Quality assessment of the head-to-head trials for the prevention of PONV

Author Year Setting	Randomization	Allocation	Groups similar at baseline	Eligibility criteria specified	Care provider masked	Patients masked	Attrition Crossover Adherence Contamination	Loss to follow up
Children								
Dol vs Ond								
Karamanlioglu 2003	Yes	NR	Yes	Yes	Yes	Yes	Yes No No No	No
Olutoye 2003 Single Center	Yes	NR	Yes	Yes	Yes	NR	Yes No No No	No
Sukhani 2002 Single Center	NR	NR	Yes	Yes	Yes	Yes	Yes No No No	No

Evidence Table 10. Quality assessment of the head-to-head trials for the prevention of PONV

Author Year Setting	Intention-to-treat analysis	Postramdomization exclusions	Quality rating	Controlled group standard of care	Funding	Relevance
Children						
Dol vs Ond						
Karamanlioglu 2003	Yes	No	Fair	Yes	NR	Yes
Olutoye 2003 Single Center	No, lost n=9 for protocol violation, attrition n=3	Yes	Fair	Yes	NR	Yes
Sukhani 2002 Single Center	Yes	Yes	Fair	Yes	NR	Yes

Evidence Table 11. Prevention of PONV: active- and placebo-controlled trials

Author Year Setting	Design	Surgery type	Inclusion criteria	Intervention
Adults: Active-controlled trials				
Dolasetron				
Burmeister 2003 Single Center Germany	RCT, ACT, DB	Elective extracorporeal shock wave lithotripsy (ESWL) Mean duration of ESWL: 27.5 min	ASA I or II pts without obstructive pumonary disease	A: Dol 12.5 mg iv B: placebo Given 10 min before start of procedure
Ondansetron				
Doe 1998 Single center US	RCT, ACT DB	Various strabismus surgeries	ASA I-III non-obsese pts without premedication with antiemetics	A: Ond 4 mg iv B: Droperidol (Drop) 1.25 mg iv
Fortney 1998 Multicenter North America (pooled results from 2 studies)	RCT, ACT DB	Outpatient procedures <2 h Gyn procedures: 61.0% muscoskeletal: 17.7% Anesth. duration: 56.3 min	ASA I or II status non-pregnant pts with a history of motion sickness and PONV undergoing procedures with highly emetogenic potential; pts also had to be addiction free	A:Ond 4 mg iv B: Droperidol (Dro) 0.625 mg iv C: Dro 1.25 mg iv D: placebo
Gan 2004 Single Center US	ACT DB	Major breast surgery (100%) Duration of surgery: 210.9 min	Consecutive non-pregnant pts of ASA I, II, or II status without pacemakers and who were acupuncture-naïve	A: Ond 4 mg iv + sham electro-acupoint stimulation B: active electro-acupoint stimulation C: placebo + sham electro-acupoint stimulation

Evidence Table 11. Prevention of PONV: active- and placebo-controlled trials

Author Year Setting	Allow other medication	Run-in/ Wash out	Age/ Gender/ Ethnicity	Other population characteristics	Screened/ Eligible/ Enrolled
Adults: Active-controlled trials					
Dolasetron					
Burmeister 2003 Single Center Germany	NR	NR/ NR	Mean age: 48y Range: 20-77y 57.7% female Ethnicity: NR	History of PONV: 35% History of motion sickness: 27.5% Smoker: 65% Female pts ≤ 50 y: 22.5%	NR/ NR/ 40
Ondansetron					
Doe 1998 Single center US	Premedication of all pts with midazolam 1-2 mg iv	NR/ No drugs with antiemetic properties nor any opioids allowed prior to surgery	Mean age: 30 y Range: 15-65 y 42% female Ethnicity: NR	NR	NR/ NR/ 45
Fortney 1998 Multicenter North America (pooled results from 2 studies)	During anesthesia after study drug administration, pts allowed to receive fentanyl, alentanil, or midazolam ≤ 2 mg	NR/ no drugs with antiemetic properties allowed 24h before surgery	Mean Age: 35 y Range: 18-65y 88.2% female Ethnicity: NR	History of PONV: 86.0% History of motion sickness: 61.8%	NR/ NR/ 2061
Gan 2004 Single Center US	All pts received fentanyl 100 micrograms iv and midazolam 2 mg iv per-operation	NR/ no drugs with antiemetic properties allowed 24h before surgery	Mean Age: 45.6 y Range: NR 100% female Caucasian: 80% African American: 20%	History of PONV or motion sickness: 38.7%	NR/ NR/ 77

Evidence Table 11. Prevention of PONV: active- and placebo-controlled trials

Author Year Setting	Withdrawn/ Lost to fu/ Analyzed	Results - Satisfaction	Results - Resource utilization
Adults: Active-controlled trials			
Dolasetron			
Burmeister 2003 Single Center Germany	NR/ 0/ 40	Pt rating for anagesic properties, A vs B, p=0.99: Excellent: 85% vs 80% Good: 15% vs 20% Fair and Poor : both 0% vs 0% Pt rating for overall quality of anesthesia, A vs B, p=0.32 Excellent: 70% vs 55% Good: 20% vs 20% Fair: 5% vs 15% Poor: 5% vs 10%	Time to discharge, A vs B: 22 min vs 28 min, p<0.05
Ondansetron			
Doe 1998 Single center US	NR/ NR/ 45	NR	Stay in PACU (min): 53.5 vs 50.2, NS Time from end of surgery to discharge (min): 249.5 vs 266.3, NS
Fortney 1998 Multicenter North America (pooled results from 2 studies)	NR/ NR/ 2061	Overall pt satisfaction wih PONV control *A, B, C, D, results* Very satisfied: 68%, 64%, 70%, 60% Somewhat satisfied: 16%, 17%, 15%, 20% Neither satisfied nor dissatisfied: 4%, 5%, 2%, 6% Somewhat dissatisfied: 6%, 7%, 6%, 7% Very dissatisfied: 5%, 5%, 4%, 4% Questionnaire not returned: <1%, 2%, 3%, 3%	Time to home readiness (min): 186 vs 188 vs 207 vs 210, NS
Gan 2004 Single Center US	2/ 0/ 75	Mean score for Patient Satisfaction (on scale of 0-10, with 10 being most satisfied) A: 10 (range: 8-10) B: 8.5 (6.2-10) C: 5.5 (3-10) p=0.007 for A & B vs. C	NR

Evidence Table 11. Prevention of PONV: active- and placebo-controlled trials

Author Year Setting	Design	Surgery type	Inclusion criteria	Intervention
Jokela 2002 Multicenter Finland	RCT, ACT DB	Thyroid or parathyroid surgery mean surgery duration: 114 min	Female adult ASA 1-3 patiets	A: Ond 16 mg po B: Meto 10 mg po C: Trop 5 mg po All given with midazolam 7.5 mg
Khalil 1999 Single Center US	RCT, ACT DB	Elective middle ear surgery All pts had stomach contents aspirated at end of operation Duration of anesthesia: 204.5min Duration of surgery: 152.7 min	Non-obese and non-mentally retarded adult ASA I and II pts	A: Ond 4mg B: Promethazine (Prom) 25mg C: Ond 2mg + Prom 25mg D: placebo
Reihner 1999 Single Center Sweden	RCT, ACT DB	Breast surgery Mean anesth. duration: 101.7 min	Non-pregnant, non-obese ASA I or II women	A: Ond 8 mg iv B: droperidol (drop) 1.25 mg iv C:placebo
Sandhu 1999 NR	RCT, PCT DB	Elective gynecologic laparoscopy with std anesthesia (w/o gastric suctioning) surgery duration: 25.0 min Anesthesia duration: 33.1 min	ASA I-II women	A: Ond 8 mg iv B: Dimenhydrinate 50 mg iv C: placebo
Steinbrook 1996 Single Center US	RCT, DB semi-crossover (see interventio n)	Laproscopic cholecystectomy Mean surgery time: 77.4 min	pts scheduled for laproscopic cholecystectomy	A: Drop 0.625 mg iv + metoclopramide 10 mg B: Ond 4 mg + saline Moderate or severe nausea or vomiting in PACU was treated with the cross-over drug

Evidence Table 11. Prevention of PONV: active- and placebo-controlled trials

Author Year Setting	Allow other medication	Run-in/ Wash out	Age/ Gender/ Ethnicity	Other population characteristics	Screened/ Eligible/ Enrolled
Jokela 2002 Multicenter Finland	Study medication given with midazolam 7.5 mg	NR/ NR	Mean Age: 49.0 y Range: NR 100 % female Ethnicity: NR	History of PONV: 73.2% History of motion sickness: 37.4% Current daily smokers: 22.9%	NR/ NR/ 200
Khalil 1999 Single Center US	Pre-medication with midazolam 2 mg iv	NR / NR	Mean age: Range: 13- 72 y 47.1% female Ethnicity: NR	History of PONV: 21.8% History of motion sickness: 8.0%	NR/ NR/ 87
Reihner 1999 Single Center Sweden	Premedication of all pts with midazolam 4 mg <60kg and 5 mg >60kg im	NR/ NR	Mean age: 54y Range: 18-80 y 100% female Ethnicity: NR	History of PONV: 43.5% History of motion sickness: 21.7% menstrual group (cycle day 1-8): 7.7%	NR/ NR/ 216
Sandhu 1999 NR	NR	NR/ NR	Mean age: 32.7 y Range: NR 100% female Ethnicity: NR		NR/ NR/ 87
Steinbrook 1996 Single Center US	Premedication of all pts with midazolam 1-2 mg iv	NR	Mean age: 43.5 y Range: NR 86% female Ethnicity: NR		NR/ NR/ 215

Evidence Table 11. Prevention of PONV: active- and placebo-controlled trials

Author Year Setting	Withdrawn/ Lost to fu/ Analyzed	Results - Satisfaction	Results - Resource utilization
Jokela 2002 Multicenter Finland	21/ NR/ 179	Patient satisfaction (score: 0-10 "most satisfied") A: 9 (range: 0-10) B: 9 (range: 0--10) C: 10 (range: 0-10), p =0.001 when C compared with B	NR
Khalil 1999 Single Center US	NR/ NR/ 87	Patient Satisfaction Score (0: "very dissatisfied" to 10: "very satisfied"): 9.1 vs 8.8 vs 9.2 vs 8.7; NS	Duration of PACU stay (min): 94 vs 87 vs 89 vs 95; NS
Reihner 1999 Single Center Sweden	9/ NR/ 207	NR	Stay in PACU (min): 120 vs 120 vs 120, NS
Sandhu 1999 NR	NR/ NR/ 87	Overall satisfaction score (0 - 10 "satisfied"): PACU: 9 vs 9 vs 9; NS Home: 8 vs 8 vs 8, NS	Mean time to discharge (min): 189 vs 199 vs 205, NS
Steinbrook 1996 Single Center US	15/ NR/ 200	NR	Discharge time (min): 293 vs 288, NS

Evidence Table 11. Prevention of PONV: active- and placebo-controlled trials

Author Year Setting	Design	Surgery type	Inclusion criteria	Intervention
Adults: Placebo-controlled trials				
Dolasetron				
Diemunsch 1997 multicenter Europe	RCT, PCT DB	Pts undergoing surgery with general anesth. Gyn. surgery: 63.2% Anesth. duration: 1.73 h	Non-pregnant, Dol naïve ASA I or II pts with no alcohol or drug addiction and normal serum Na and K concetrations before surgery	A: Dol 12.5 po B: Dol 25 po C: Dol 50 po D: Dol 100 po F: placebo
Warriner 1997 Multicenter Canada	RCT, PCT DB	Total abdominal hysterectomy (TAH) (100%) Anesth. duration: 1.5 h	non-pregnant ASA I or II women under gen. anesthesia undergoing TAH	A: Dol 25 po B: Dol 50 po C: Dol 100 po D: Dol 200 po F: placebo
Ondansetron				
Cherian 2001 Single center UK	RCT, PCT DB	Elective Caesarian section under spinal subarachnoid block	Pregnant women without pre-eclampsia	A: Ond 4 mg iv at end of surgery + 8 mg added to PCA morphine syringe B: nothing in surgery + no Ond in PCA morhpine syringe (placebo group)
Han 2004 Single center Korea	RCT, PCT DB	elective surgery under gen. anesth. Mean duration of anesth: 163.5 min	Male smoking pts ≥ 61y without a history of PONV, motion sickness, or migraine	A: Ond 4 mg iv B: placebo 15 min before anesth. ended A: Ond 16 mg placed in PAC pump B: placebo in PAC pump

Evidence Table 11. Prevention of PONV: active- and placebo-controlled trials

Author Year Setting	Allow other medication	Run-in/ Wash out	Age/ Gender/ Ethnicity	Other population characteristics	Screened/ Eligible/ Enrolled
Adults: Placebo-controlled trials					
Dolasetron					
Diemunsch 1997 multicenter Europe	No	NR/ no drugs with antiemetic properties allowed 24h before surgery	Mean Age: 40.4 y Range: 18-65y 94.7% female Ethnicity: NR	History of PONV: 45.8% History of motion sickness: NR	NR/ NR/ 337
Warriner 1997 Multicenter Canada	1 mg lorazepam po or sl the night prior to surgery	NR/ no drugs with antiemetic properties allowed 24h before surgery	Mean Age: 43.4 Range: 18-70 100% female White: 81.9% Black: 4% Asian: 10.4% Other: 3.7%	History of PONV: 46.8% History of motion sickness: 27.5%	NR/ NR/ 374
Ondansetron					
Cherian 2001 Single center UK	NR	NR/ NR	NR	NR	NR/ NR/ 81
Han 2004 Single center Korea	NR	NR/NR	Mean age: 67.6 y Range: ≥ 61 y 0% female Ethnicity: NR	Hip surgery: 49% Knee surgery: 22.8%	NR/ NR/ 374

Evidence Table 11. Prevention of PONV: active- and placebo-controlled trials

Author Year Setting	Withdrawn/ Lost to fu/ Analyzed	Results - Satisfaction	Results - Resource utilization
Adults: Placebo-controlled trials			
Dolasetron			
Diemunsch 1997 multicenter Europe	NR/ 0/ 337	Patient satisfaction (VAS score: 0 = not at all satisfied to 100 = complete satisfication) VAS scores not given; the only thing said was that Dol-treated pts were more satisfied with treatment than placebo pts (p<0.003)	NR
Warriner 1997 Multicenter Canada	1/ 0/ 373	Patient satisfaction (VAS score: 0 = not at all satisfied and 100 = as satisfied as pt could be) A: 91.0 (p<0.05 vs placebo) B: 89.8 C: 91.0 (p<0.05 vs placebo) D: 85.0 E: 79.0	NR
Ondansetron			
Cherian 2001 Single center UK	NR/ NR/ 81	Overall satisfaction with care (% pts): *Good* : A: 85%, B: 87.5% *Moderate* : A: 12%, B: 10% *Poor* : A: 3%, B: 2.5% p = NS between A & B	NR
Han 2004 Single center Korea	24/ NR/ 350	Pt satisfaction for analgesia therapy , A vs. B, p = NS for all: "very satisfied": 39.9% vs 42.9% "satisfied": 38.1% vs 38.4% "neither dissatisfied nor satisfied": 18.5% vs 15.8% "Dissatisfied": 3.5% vs 2.8%	

Evidence Table 11. Prevention of PONV: active- and placebo-controlled trials

Author Year Setting	Design	Surgery type	Inclusion criteria	Intervention
Lekprasert 1996 Single center Thailand	RCT, PCT DB	gastrointestinal surgery (laproscopic cholecystectomy (50%), open cholecystectomy (40.2%), appendectomy (7.3%), etc) with general anesth. 80.5% of pts had surgery lasting <2 hrs; 44% had gastric suctioning	ASA I or II status non-pregnant non-drug abusing pts; if women they ahd to be <100kg and if men <120kg	A: Ond 4 mg iv, prior to induction B: placebo iv
Sadhasivam 1999 Single center India	RCT, PCT DB	Modified radical mastectomy Mean anesth. duration: 152 min	ASA I or II non-obese pts	A: Ond 4 mg iv B: placebo at end of surgery
Scuderi 1999 Single-center US	RCT, PCT DB	Outpatient surgery with general anesthesia	ASA I, II, or III outpatients	A: Ond 4 mg iv B: placebo
Sun 1997	RCT, PCT DB	ambulatory otolaryngologic procedures (sinus surgery (70.7%), and others) anesth. duration: 93.3 min	Non-pregnant, non-obese non-drug using ASA I or II pts	A: Ond 4 mg iv before induction of anest. + placebo at end of procedure B: placebo at induction + Ond 4 mg iv at end C:placebo + placebo
Tang 1998 US	RCT, PCT DB	Outpatient laproscopic procedures Duration of anesth. : 79.2 min	ASA I or II non-pregnant, non-obese female pts	A: Ond 2 mg iv pre-induction + Ond 2 mg at end of operation B: Ond 4 mg iv pre-induction + placebo at end C: placebo pre-induction + Ond 4 mg iv at end D: placebo + placebo

Evidence Table 11. Prevention of PONV: active- and placebo-controlled trials

Author Year Setting	Allow other medication	Run-in/ Wash out	Age/ Gender/ Ethnicity	Other population characteristics	Screened/ Eligible/ Enrolled
Lekprasert 1996 Single center Thailand	Some premedicated with benzodiazepines (excluding lorazepam) prior to surgery or at induction	NR/ no drugs with antiemetic properties allowed 24h before surgery	Mean age: 50.1y Range: 12-75y 74.4% female Ethnicity; NR	Opiod use, A vs B: 51.2% vs 80.4%	NR/ NR/ 82
Sadhasivam 1999 Single center India	All pts received diazepam 0.2 mg/kg po the night before surgery and 2h before induction	NR/ no drugs with antiemetic properties allowed 24h before surgery	Mean age: 45.7 y Range: NR 100% female Ethnicity: NR	History of PONV: 5.6% History of motion sickness: 18.5%	NR/ NR/ 54
Scuderi 1999 Single-center US	Premedication with midazolam: 98.8%	NR/ NR	Mean age: 38.2 y Range: 18-65 y 63.3% female White: 80% African American: 18.9% Other: 0.1%	History of risk factors: 58.4%	NR/ NR/ 575
Sun 1997	Premedication of all pts with midazolam 0.02 mg/kg iv	NR/ no drugs with antiemetic properties allowed 24h before surgery	Mean age: Range: 20-70y 46.7% female Ethnicity: NR	History of PONV: 22.7% History of motion sickness: 26.7%	NR/ NR/ 75
Tang 1998 US	Premedication of all pts with midazolam 2 mg iv	NR/ no drugs with antiemetic properties allowed 24h before surgery	Mean age: 37.7 y Range: 20-70y 100% female Ethnicity: NR	History of PONV: 30.1% History of motion sickness: 35.2% Last menstrual period: 0-8 days previously: 26.3%	NR/ NR/ 164

Evidence Table 11. Prevention of PONV: active- and placebo-controlled trials

Author Year Setting	Withdrawn/ Lost to fu/ Analyzed	Results - Satisfaction	Results - Resource utilization
Lekprasert 1996 Single center Thailand	NR/ NR/ 82	Patient Satisfaction levels (p = NS for all comparisons): most satisfied, A vs B: 4.87% vs 21.95% Satisfied, A vs B: 70.73% vs 58.54% Undecided, A vs B: 19.51% vs 17.07% Unsatistied, A vs. B: 4.87% vs 2.44% Most unsatisfied, A vs B: 0% vs 0%	NR
Sadhasivam 1999 Single center India	NR/ NR/ 54	Pt satisfaction scores: (0 = "not satisfied" to 10 = "fully satisfied") Ond vs Plac: 8.1 vs 6.1, p = 0.0000	
Scuderi 1999 Single-center US		Satisfaction with control of PONV: #yes/#no, A vs B: 230/7 (97%) vs 212/16 (93%), p = 0.04	Time to discharge from PACU to day hospital (min): 59 vs 58, NS, Time to discharge from PACU to home (min): 87 vs 92, NS
Sun 1997	NR/ NR/ 75	NR	PACU recovery times (min): 73 vs 63 vs 66, NS Hospital discharge times (min): 225 vs 188 vs 203, NS
Tang 1998 US	8/ NR/ 156	Highly satisfied (% pts): 38 vs 36 vs 37 vs 37, NS	*=p<0.05 vs placebo Discharge-ready (min): 198 vs 180 vs 168* vs 213 Actual discharge (min): 234 vs 207 vs 198* vs 243* Caretaker needed (days): 0.9 vs 0.3 vs 0.8 vs 0.8, NS Return to work (days): 4.5 vs 4.5 vs 4.4 vs 5.6, NS

Evidence Table 11. Prevention of PONV: active- and placebo-controlled trials

Author Year Setting	Design	Surgery type	Inclusion criteria	Intervention
Thagaard 2003 Single Center Norway	RCT, PCT DB	Elective laproscopy for fundolplication (41%) or cholecystectomy (54%) Mean duration of surgery: 100 min	ASA 1 or II pts	A: Ond 8 mg orally disintegrating tablets bid starting the night after surgery B: placebo

Evidence Table 11. Prevention of PONV: active- and placebo-controlled trials

Author Year Setting	Allow other medication	Run-in/ Wash out	Age/ Gender/ Ethnicity	Other population characteristics	Screened/ Eligible/ Enrolled
Thagaard 2003 Single Center Norway	Pre-medication with midazolam 1-2 mg iv; all pts received droperidol 0.1235mg and Ond 4 mg iv prior to emergence from anesthesia Pain medication after surgery: codeine 60 mg+paracetamol 1000mg up to 4X/day	Ond 4 mg iv prior to end of anesthesia	Mean age: 43.1 y Range: ≥ 18 y 68.7% female Ethnicity: NR	History of PONV: 10.3% History of motion sickness: 40.6%	NR/ NR/ 102

Evidence Table 11. Prevention of PONV: active- and placebo-controlled trials

Author Year Setting	Withdrawn/ Lost to fu/ Analyzed	Results - Satisfaction	Results - Resource utilization
Thagaard 2003 Single Center Norway	6/ NR/ 96	Acute: (4-24h post-op): Overall satisfaction compared with expectation: worse/ similar/ better: 41/ 36/ 23 vs 35/ 42/ 23, p=NS Delayed (24-72 h post op): Overall satisfaction compared with expectation: worse/ similar/ better: 29/ 47/ 24 vs 16/ 51/ 33 , p = NS	Acute: (4-24h post-op): Time to discharge ready (min): 299 vs 277, p=NS Pt rating of general function (1 "all time in bed" to 5 "full normal activity"): 2.4 vs 2.4, p = NS Delayed (24-72 h post op): Pt rating of general function (1 "all time in bed" to 5 "full normal activity"): 3.1 vs 3.2, p = NS

Evidence Table 11. Prevention of PONV: active- and placebo-controlled trials

Author Year Setting	Design	Surgery type	Inclusion criteria	Intervention
Children: Active-controlled trials				
Ondansetron				
Bach-Styles 1997 Single Center US	RCT, ACT DB	Pediatric pts undergoing opthamalic surgery Anesth. duration: NR	Pediatric pts ASA status I, II, or III	A: Ondansetron (Ond) 0.15 mg/kg iv B: Metoclopramide (Met) 0.25 mg/kg iv C: placebo
Davis, A. 1995 Single Center Saudi Arabia	RCT, ACT DB	Elective strabismus repair surgery w/o gastric suctioning Mean surgery time: 87 min	ASA I or II pediatric and adult pts	A: Ond 75 mcg/kg B: Ond 150 mcg/kg C: Droperidol 75 mcg/kg
Davis, P. 1995 Single Center US	RCT DB	Dental surgery (with stomach suctioning at end)	ASA I and II pediatric pts	A: Ond 100 mcg/kg iv B: Droperidol (drop) 75 mcg/kg iv C: placebo
Litman 1995 Multicenter US	RCT, ACT DB	Strabismus repair Mean anesthesia time: 81.6 min	healthy ASA I and II children without a history of gastric motility disorders	A: Ond 0.15 mg/kg iv B: Droperidol 0.075 mg/kg iv
Rose 1994 Single Center US	RCT, ACT DB	Strabismus repair	ASA I and II pediatric/adolescent pts	A: Ond 0.15 mg/kg iv B: Metoclopramide (meto) 0.25 mg/kg iv C: placebo

Evidence Table 11. Prevention of PONV: active- and placebo-controlled trials

Author Year Setting	Allow other medication	Run-in/ Wash out	Age/ Gender/ Ethnicity	Other population characteristics	Screened/ Eligible/ Enrolled
Children: Active-controlled trials					
Ondansetron					
Bach-Styles 1997 Single Center US	NR	NR/ NR	Mean Age: NR Range: 1-17 y 94.7% female Ethnicity: NR	"ANOVA showed no dignificant difference between the 3 study groups with regard to Age, height, weight, ASA status, history of vomiting, no. of muscles repaired, iv fluids, or duration of surgery." No specifics other than this statement were given.	NR/ NR/ 52
Davis, A. 1995 Single Center Saudi Arabia	Premedication: midazolam 0.5 mg/kg po (Max 10 mg) for children and 5-10 mg diazepam po for adults	NR/ NR	Mean age: 12.4 y Range: NR 39.4% female Ethnicity: NR		NR/ NR/ 213
Davis, P. 1995 Single Center US	All pts premedicated with either midazolam intranasally (0.2-0.3 mg/ kg, max = 5 mg) or po (0.5 mg/ kg, max 15 mg)	NR/ NR	Mean age: 42.7 mos Range: 2-8 yrs % female: NR Ethnicity: NR		NR/ NR/ 102
Litman 1995 Multicenter US	If needed, pts premedicated with midazolam 0.5 mg/kg po	NR/ NR	Mean age: 5.75 y Range: 3-14yrs 40.3% female Ethnicity: NR		NR/ NR/ 57
Rose 1994 Single Center US	All received midazolam 0.5 mg/kg po (max 20 mg) but one who got midazolam 0.2 mg/kg intranasally and one who received diazepam 0.1 mg/kg po	NR/ NR	Mean age: 72 mos Range: 2-17 y 48.9% female Ethnicity: NR		NR/ NR/ 90

Evidence Table 11. Prevention of PONV: active- and placebo-controlled trials

Author Year Setting	Withdrawn/ Lost to fu/ Analyzed	Results - Satisfaction	Results - Resource utilization
Children: Active-controlled trials			
Ondansetron			
Bach-Styles 1997 Single Center US	NR/ NR/ 52	Satisfaction (% parents): 94% vs 74% vs 74%, NS	Hospital stay (# min): 132 vs 137 vs 132, NS
Davis, A. 1995 Single Center Saudi Arabia	NR/ NR/ 213	NR	Mean discharge times from recovery (min): 44.4 vs 75.3 vs 41, NS
Davis, P. 1995 Single Center US	7/ NR/ 95	NR	PACU length of stay (min): 28.6 vs 39.9 vs 29, NS Hospital length of stay (min): 74 vs 106 vs 85; O>D, p<0.05
Litman 1995 Multicenter US	NR/ NR/ 57	NR	Duration of PACU stay (min): 46.2 vs 54.6, NS Time to discharge (min): 235 vs 258, NS
Rose 1994 Single Center US	NR/ NR/ 90	NR	Time until discharge (min): 111 vs 124 vs 127, NS

Evidence Table 11. Prevention of PONV: active- and placebo-controlled trials

Author Year Setting	Design	Surgery type	Inclusion criteria	Intervention
Splinter 1998 Single Center Canada	RCT, ACT DB	Elective tonsillectomy or adenotonsillectomy	healthy children with ASA I or II status and no sleep apnea Anesth. duration: 31.5 min	A: Ond 150 mcg/kg (max 8 mg) iv B: Perphenazine (perp) 70 mcg/kg iv (max 5 mg)
Stene 1996 Single center US	RCT, ACT DB	Tonsillectomy (92.5%) or adenotonsillectomy (7.5%)	ASA I and II pediatric pts	A: Ond 0.15 mg/ kg iv B: Metoclopramide 0.25 mg/ kg iv C: placebo

Evidence Table 11. Prevention of PONV: active- and placebo-controlled trials

Author Year Setting	Allow other medication	Run-in/ Wash out	Age/ Gender/ Ethnicity	Other population characteristics	Screened/ Eligible/ Enrolled
Splinter 1998 Single Center Canada	Pts received either midazolam 0.5 mg/kg (max 15 mg) po before induction or Midazolam 50 mcg/kg (max 3 mg) iv during surgery All received codeine 1.5 mg/kg im	NR/ NR	Mean age: 6.9 y Range: 2-12 y 54.6% female Ethnicity: NR		NR/ NR/ 220
Stene 1996 Single center US	No predication besides oral atropine allowed	NR/ NR	Mean age:6.0 yrs Range: 2- 12 y % female: NR Ethnicity: NR		NR/ NR/ 132

Evidence Table 11. Prevention of PONV: active- and placebo-controlled trials

Author Year Setting	Withdrawn/ Lost to fu/ Analyzed	Results - Satisfaction	Results - Resource utilization
Splinter 1998 Single Center Canada	4/ NR/ 216	NR	Mean duration of stay in PAR (min): 46 vs 47, NS Duration of stay in day-case surgical unit (median min): 235 vs 240, p=0.007
Stene 1996 Single center US	12/ NR/ 120	NR	Length of stay (min): 449 vs 485 vs 481, NS n=100 (75.7% of randomized) (study rated poor)

Evidence Table 11. Prevention of PONV: active- and placebo-controlled trials

Author Year Setting	Design	Surgery type	Inclusion criteria	Intervention
Children: Placebo-controlled trials				
Granisetron				
Carnahan 1997 Single center US	RCT, PCT DB	Tonsillectomy and adenoidectomy (T & A) ; pts had gastric suctioning during surgery	Pediatric pts of ASA I or II undergoing elective outpt T & A	A: Gran 0.01 mg/kg iv B: placebo
Cieslack 1996 Single center US	RCT, PCT DB	Outpatient strabismus correction (42.3%), tonsillo-adenoidectomy (19.6%), or dental surgery (34%) using endotracheal gen. anesth. with end-of-surgery stomach suctioning Mean duration of anesth. = 80.5 min	ASA I and II children who had not recently received an drug with an antiemetic effect	A: Gran 10 mcg/kg iv B: Gran 40 mcg/kg iv C: Placebo
Munro 1999 Single-center US	RCT, PCT DB	Strabismus repair surgery with stomach suctioning at end Anesth. duration: 69.6 min	ASA I-II out-patient pediatric pts	A: Gran 20 mcg/kg suspension B: Gran 40 mcg/kg suspension C: placebo
Patel 1997 multicenter US	RCT, PCT DB	Outpt surgeries with gastric suctioning: stabismus surgery (33.8%), tonsillectomy w/ or w/o andenoidectomy (26.1%), herniorrhaphy (31.9%), or orchidopexy (7.9%) Mean duration of anesth.: 57.2 min	ASA I-III pediatric pts without liver or renal disease or vomiting within 24h before surgery	A: Ond 0.1 mg/kg iv if child ≤ 40kg; 4 mg if child >40kg B:placebo
Ondansetron				
Sennaraj 2002 NR NR	RCT, DB	Strabismus repair under gen. anesthesia Mean anesth. duration: 64.15 min	ASA I or II children who had not received drugs with antiemetic properties within 24h of the study	A: Ond 100 mcg/kg iv at end of procedure + Ond 100 mcg/kg at first signs of PONV (prophylactic) B: placebo at end of procedure + Ond 100 mcg/kg at first signs of PONV (therapeutic)

Evidence Table 11. Prevention of PONV: active- and placebo-controlled trials

Author Year Setting	Allow other medication	Run-in/ Wash out	Age/ Gender/ Ethnicity	Other population characteristics	Screened/ Eligible/ Enrolled
Children: Placebo-controlled trials					
Granisetron					
Carnahan 1997 Single center US	Midazolam 0.5 mg/kg up to 10mg was given 15-30 min before induction	NR/ NR	Mean age: 4.87 y Range: 2-8 y 48.1% female White: 81.5% Black: 11.1% Other: 7.4%	NR	NR/ NR/ 54
Cieslack 1996 Single center US	All pts received midazolam 0.5 mg/kg 15-30 min before induction	NR/ NR	Mean age: 5.2 y Range: 2-16 y 48.4% female Ethnicity: NR		NR/ NR/ 97
Munro 1999 Single-center US	No	NR/ no drugs with antiemetic properties allowed prior to surgery	Mean age: 5.0 y Range: 1-12 y 53.4% female Ethnicity: NR		NR/ NR/ 76
Patel 1997 multicenter US	premedication left up to MD	NR/ no drugs with antiemetic properties allowed within 24h of surgery	Mean age: 5.3y Range: 2-12y 36.8% female Caucasian: 77.8% African American: 13.7% Hispanic: 4.0% Asian: 2.1% Other: 2.3%	Previous history of motion sickness: 8.9% Previous PONV: 6.5%	NR/ NR/ 433
Ondansetron					
Sennaraj 2002 NR NR	No	NR/ no drugs with antiemetic properties allowed 24h before surgery	Mean age: 6.6 y Range: 2-15 y 58.7% female Ethnicity: NR	Prior PONV: 28%	NR/ NR/ 150

Evidence Table 11. Prevention of PONV: active- and placebo-controlled trials

Author Year Setting	Withdrawn/ Lost to fu/ Analyzed	Results - Satisfaction	Results - Resource utilization
Children: Placebo-controlled trials			
Granisetron			
Carnahan 1997 Single center US	NR/ NR/ 54	NR	Pt discharge time: A: 250.0 (+/- 147.27) min (p<0.05) B: 320.8 (+/-118.22) min
Cieslack 1996 Single center US	NR/ NR/ 97	Mean global parental satisfaction score (0= not at all satisfied; 10=fully satisfied), and % of parents giving a score >8: A: 9.3, 93% score>8 B: 9.1, 97% score>8 C: 8.8, 81%, score>8, p=NS for all comparisons	Discharge readiness (min): 129 vs 108 vs 152 G 10 mg>placebo, p<0.05; otherwise NS
Munro 1999 Single-center US	3/ NR/ 73	NR	Time to discharge readiness (min): 104.8, vs 104.7 vs 124, p<0.05 for both G groups vs placebo
Patel 1997 multicenter US	4/ NR/ 429	NR	Mean time to reach home-readiness (min): 155.7 vs 183.2, p<0.05 Mean time between responsiveness to spoken command until discharge from facility (min): 175.6 vs 214.8, p<0.05
Ondansetron			
Sennaraj 2002 NR NR	NR/ NR/ 150	Parental satisfaction score (0= not at all satisfied; 10=fully satisfied): 8.2 vs 6.8, p<0.0001	Mean PACU stay (min): 126.5 vs 141.1, p=0.0002

Evidence Table 12. Quality assessment of active- and placebo-controlled trials for prevention of PONV

	Internal Validity						
Author Year	**Randomization adequate?**	**Allocation concealment adequate?**	**Groups similar at baseline?**	**Eligibility criteria specified?**	**Outcome assessors masked?**	**Care provider masked?**	**Patient masked?**
Adults: active controlled trials							
Dolasetron							
Burmeister 2003	Unclear; done by using an MS Excel macro	NR	Yes	Yes	Yes	Yes	Yes
Ondansetron							
Doe 1998	NR	NR	NR	Yes	NR	Yes	Yes
Fortney 1998	NR	NR	Yes	Yes	NR	Yes	Yes
Gan 2004	Yes	Yes	Yes, but analysis excluded 2 patients (2.6%) that did not complete the study	Yes	Yes	Yes	Yes
Jokela 2002	NR	No, sealed envelope technique	Unclear, excluded 21 patients (10.5%)	Yes	NR	Yes	Yes
Khalil 1999	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Reihner 1999	NR	Yes	No, intraoperative blood loss significantly lower in ond. group; also, only reported baseline characteristics for 95.8%	Yes	NR	Yes	Yes
Sandhu 1999	NR	NR	Yes	Yes	Yes	Yes	Yes
Steinbrook 1996	Yes	Yes	Unclear, analysis excluded 15 pts (7.5%) that were converted to open surgery	Yes	Yes	Yes	Yes

Evidence Table 12. Quality assessment of active- and placebo-controlled trials for prevention of PONV

	Internal Validity				
Author Year	**Reporting of attrition, crossovers, adherence, and contamination**	**Loss to follow-up: differential/ high**	**Intention-to-treat (ITT) analysis**	**Post-randomization exclusions**	**Quality Rating**
Adults: active controlled trials					
Dolasetron					
Burmeister 2003	No, No, No, No	NR	NR	NR	Fair
Ondansetron					
Doe 1998	No, No, No, No	NR	Unclear	No	Fair
Fortney 1998	Yes, No, No, No	No, No	Yes for satisfaction; No for primary outcome (complete response)	No	Fair
Gan 2004	Yes, No, No, No	None	No, excluded 2 patients (2.6%)	No	Fair
Jokela 2002	Yes, No, No, No	None	No, excluded 21 patients (10.5%) who didn't complete due to reoperation (n=6) and unspecified protocol violations (n=15)	No	Fair
Khalil 1999	No, No, No, No	NR	Yes	No	Fair
Reihner 1999	Yes, No, No, No	None	No, excluded 9 pts (4.2%) due to protocol violations	No	Fair
Sandhu 1999	No, No, No, No	NR	Unclear	No	Fair
Steinbrook 1996	Yes, No, No, No	None	No, excluded 15 pts (7.5%)	No	Fair

Evidence Table 12. Quality assessment of active- and placebo-controlled trials for prevention of PONV

	External Validity					
Author Year	**Number screened/ eligible/ enrolled**	**Run-in/ Washout**	**Class naïve patients only**	**Control group standard of care**	**Funding**	**Relevance**
Adults: active controlled trials						
Dolasetron						
Burmeister 2003	NR/NR/40	No run-in/washout	NR	Yes	Aventis	Yes
Ondansetron						
Doe 1998	NR/NR/45	No run-in/washout	NR	Yes		
Fortney 1998	NR/NR/2061	No run-in or washout	NR	Yes	Glaxo Wellcome	Yes
Gan 2004	NR/NR/77	No run-in or washout	NR	Yes	NR	Yes
Jokela 2002	NR/NR/200	No run-in or washout	NR	Yes	NR	Yes
Khalil 1999	NR/NR/87	No run-in/washout	NR	yes	NR	Yes
Reihner 1999	NR/NR/216	No run-in/washout	NR	Yes	NR	Yes
Sandhu 1999	NR/NR/87	No run-in/washout	NR	Yes	NR	Yes
Steinbrook 1996	NR/NR/215	No run-in/washout	NR	Yes	NR	Yes

Evidence Table 12. Quality assessment of active- and placebo-controlled trials for prevention of PONV

	Internal Validity						
Author Year	**Randomization adequate?**	**Allocation concealment adequate?**	**Groups similar at baseline?**	**Eligibility criteria specified?**	**Outcome assessors masked?**	**Care provider masked?**	**Patient masked?**
Adults: placebo-controlled trials							
Dolasetron							
Diemunsch 1997	NR	NR	Yes	Yes	NR	Yes	Yes
Warriner 1997	NR	NR	Yes	Yes	NR	Yes	Yes
Ondansetron							
Cherian 2001	Yes	Yes	No, women in ondansetron group "slightly heavier" (significance NR; data NR)	Yes	NR	Yes	Yes
Lekprasert 1996	NR	NR	No, fewer pts taking ondansetron received intraoperative opioids and more pts taking ondansetron received gastric content suction	Yes	NR	Yes	Yes
Scuderi 1999	Yes	NR	Yes	Yes	NR	Yes	Yes
Sun 1997	NR	Yes	No, fewer pts in the group that received ondansetron first had histories of PONV	Yes	Yes	Yes	Yes
Tang 1998	Yes	Yes	Yes, but only gave information about 95.1%	Yes	Yes	Yes	Yes
Thagaard 2003	Yes	NR	No: placebo patients were older and more of them were undergoing fundoplication; more ondansetron patients had histories of travel sickness and more were undergoing cholecystectomy	Yes	NR	Yes	Yes

Evidence Table 12. Quality assessment of active- and placebo-controlled trials for prevention of PONV

	Internal Validity				
Author Year	**Reporting of attrition, crossovers, adherence, and contamination**	**Loss to follow-up: differential/ high**	**Intention-to-treat (ITT) analysis**	**Post-randomization exclusions**	**Quality Rating**
Adults: placebo-controlled trials					
Dolasetron					
Diemunsch 1997	No, No, No, No	NR	Unclear, data NR	No	Fair
Warriner 1997	Yes, No, No, No	None	No, but only excluded 1 patient (0.3%) that didn't undergo surgery	No	Fair
Ondansetron					
Cherian 2001	No, No, No, No	NR	Yes	No	Fair
Lekprasert 1996	No, No, No, No	NR	Yes	No	Fair
Scuderi 1999	No, No, No, No	NR	Yes	No	Fair
Sun 1997	No, No, No, No	NR	Yes	No	Fair
Tang 1998	Yes, No, No, No	None	No, excluded 8 pts (4.8%) with protocol violations	No	Fair
Thagaard 2003	Yes, No, No, No	Unclear, No	Excluded 6 pts (5.9%)	No	Fair

Evidence Table 12. Quality assessment of active- and placebo-controlled trials for prevention of PONV

	External Validity					
Author Year	**Number screened/ eligible/ enrolled**	**Run-in/ Washout**	**Class naïve patients only**	**Control group standard of care**	**Funding**	**Relevance**
Adults: placebo-controlled trials						
Dolasetron						
Diemunsch 1997	NR/NR/337	Washout: 24 h for drugs with antiemetic properties; 21 d for investigational drugs No run-in	Dolasetron naïve	Yes	Hoechst Marion Roussel	Yes
Warriner 1997	NR/NR/374	Washout: 24 hs for drugs with antiemetic properties No run-in	No	Yes	NR; 3 members of study group affiliated with Hoechst Marion Roussel Canada Research Inc.	Yes
Ondansetron						
Cherian 2001	NR/NR/81	No run-in or washout	NR	Yes	Not funded by the pharmaceutical industry	
Lekprasert 1996	NR/NR/82	No run-in or washout	NR	Yes	NR	Yes
Scuderi 1999	NR/NR/575	No run-in/washout	NR	Yes	NR	Yes
Sun 1997	NR/NR/75	No run-in/washout	NR	Yes	NR	Yes
Tang 1998	NR/NR/164	Washout: 24 h for antiemetic or psychoactive medication	NR	Yes	Glaxo Wellcome	Yes
Thagaard 2003	NR/NR/102	Washout: "recent" for antiemetics No run-in	NR	Yes	Glaxo Wellcome	Yes

Evidence Table 12. Quality assessment of active- and placebo-controlled trials for prevention of PONV

	Internal Validity						
Author Year	**Randomization adequate?**	**Allocation concealment adequate?**	**Groups similar at baseline?**	**Eligibility criteria specified?**	**Outcome assessors masked?**	**Care provider masked?**	**Patient masked?**
Children: active-controlled trials							
Ondansetron							
Bach-Styles 1997	NR	NR	Yes	Yes	Yes	Yes	Yes
Davis, A. 1995	NR	NR	Yes	Yes	Yes	Yes	Yes
Davis, P. 1995	Yes	Yes	Yes, but unclear if included 7 pts (6.9%) that were excluded for various reasons	Yes	Yes	Yes	Yes
Litman 1995	Yes	NR	Yes	Yes	NR	Yes	Yes
Rose 1994	Yes	NR	Yes	Yes	Yes	Yes	Yes
Splinter 1998	NR	NR	Yes, but excluded 4 pts (1.8%) with major protocol violations	Yes	NR	Yes	Yes
Stene 1996	Yes	Yes	Yes, but excluded 12 pts (9%) with breaches in study protocol	Yes	NR	Yes	Yes

Evidence Table 12. Quality assessment of active- and placebo-controlled trials for prevention of PONV

	Internal Validity				
Author Year	**Reporting of attrition, crossovers, adherence, and contamination**	**Loss to follow-up: differential/ high**	**Intention-to-treat (ITT) analysis**	**Post-randomization exclusions**	**Quality Rating**
Children: active-controlled trials					
Ondansetron					
Bach-Styles 1997	No, No, No, No	Unclear, attrition NR	Yes	No	Fair
Davis, A. 1995	No, No, No, No	NR	Yes	No	Fair
Davis, P. 1995	Yes, No, No, No	None	Unclear if included 7 pts (6.9%) that were excluded for various reasons	No	Fair
Litman 1995	No, No, No, No	NR	Unclear	No	Fair
Rose 1994	No, No, No, No	NR	Yes	No	Fair
Splinter 1998	Yes, No, No, No	None	No, excluded 4 pts (1.8%) with major protocol violations	No	Fair
Stene 1996	Yes, No, No, No	None	No, excluded 41 pts (31%); 12 for protocol breaches, 29 for overnight admission due to airway concerns	Yes, overnight admission due to airway concerns	Poor

Evidence Table 12. Quality assessment of active- and placebo-controlled trials for prevention of PONV

	External Validity					
Author Year	**Number screened/ eligible/ enrolled**	**Run-in/ Washout**	**Class naïve patients only**	**Control group standard of care**	**Funding**	**Relevance**
Children: active-controlled trials						
Ondansetron						
Bach-Styles 1997	NR/NR/101	No run-in/washout	NR	Yes		
Davis, A. 1995	NR/NR/213	No run-in/washout	NR	Yes	Glaxo provided ondansetron	Yes
Davis, P. 1995	NR/NR/102	No run-in/washout	NR	Yes	NR	Yes
Litman 1995	NR/NR/57	No run-in/washout	NR	Yes	NR	Yes
Rose 1994	NR/NR/90	No run-in/washout	NR	Yes	NR	Yes
Splinter 1998	NR/NR/220	No run-in/washout	NR	Yes	NR	Yes
Stene 1996	NR/NR/132	No run-in/washout	NR	Yes	NR	Yes

Evidence Table 12. Quality assessment of active- and placebo-controlled trials for prevention of PONV

	Internal Validity						
Author Year	**Randomization adequate?**	**Allocation concealment adequate?**	**Groups similar at baseline?**	**Eligibility criteria specified?**	**Outcome assessors masked?**	**Care provider masked?**	**Patient masked?**
Children: placebo-controlled trials							
Ondansetron							
Carnahan 1997	NR	NR	Yes	Yes	Yes	Yes	Yes
Cieslack 1996	Yes	Yes	Yes	Yes	NR	Yes	Yes
Munro 1999	Yes	NR	Yes, but excluded 3 (3.9%) that refused medication	Yes	Yes	Yes	Yes
Patel 1997	NR	NR	Yes, excluded 4 pts (0.9%) who never took study medication	Yes	NR	Yes	Yes
Granisetron							
Sennaraj 2002	Yes	Yes	Yes	Yes	Yes	Yes	Yes

Evidence Table 12. Quality assessment of active- and placebo-controlled trials for prevention of PONV

	Internal Validity				
Author Year	**Reporting of attrition, crossovers, adherence, and contamination**	**Loss to follow-up: differential/ high**	**Intention-to-treat (ITT) analysis**	**Post-randomization exclusions**	**Quality Rating**
Children: placebo-controlled trials					
Ondansetron					
Carnahan 1997	No, No, No, No	Unclear	Yes	No	Fair
Cieslack 1996	No, No, No, No	NR	Yes	No	Fair
Munro 1999	Yes, No, No, No	None	Yes, if the 3 that didn't take study meds are disregarded	No	Fair
Patel 1997	Yes, No, No, No	None	No, excluded 14 (3.3%) with protocol violations	No	Fair
Granisetron					
Sennaraj 2002	No, No, No, No	NR	Yes	No	Fair

Evidence Table 12. Quality assessment of active- and placebo-controlled trials for prevention of PONV

	External Validity					
Author Year	**Number screened/ eligible/ enrolled**	**Run-in/ Washout**	**Class naïve patients only**	**Control group standard of care**	**Funding**	**Relevance**
Children: placebo-controlled trials						
Ondansetron						
Carnahan 1997	NR/NR/54	No run-in/washout	No	Yes	NR	Yes
Cieslack 1996	NR/NR/97	Washout: "recently" for antiemetics No run-in	NR	Yes	NR	Yes
Munro 1999	NR/NR/76	No run-in/washout	NR	Yes	SmithKlein Beecham	Yes
Patel 1997	NR/NR/433	Washout: 24 hours for antiemetic medications No run-in	NR	Yes	Glaxo Wellcome	Yes
Granisetron						
Sennaraj 2002	NR/NR/150	Washout: 24 hours for antiemetic drugs No run-in	NR	Yes	NR	Yes

Evidence Table 13. Treatment of established PONV: systematic reviews

Author Year	Aims	Time period covered	Eligibility criteria	Number of patients	Characteristics of identified articles: study designs
Kazemi-Kjellberg, 2001	To systematically review the literature on valid data on any treatment of established PONV symptoms, to critically appraise the data, to test for dose-responsiveness for each drug, and to estimate relative efficacy and likelihood for harm of the various treatments	(End dates not reported) Medline from 1966; Embase from 1974; Cochrane Controlled Trials Register 2000, issue 4	Full reports of randomized comparisons of any therapeutic antiemetic intervention (experimental intervention) with placebo, no treatment, or another antiemetic (control intervention) in vomiting or nauseated postoperative patients.	519 granisetron >1539 ondansetron (N not reported for one study)	6 active control trials 10 placebo-controlled trials

Evidence Table 13. Treatment of established PONV: systematic reviews

Author Year	Characteristics of identified articles: populations	Characteristics of identified articles: interventions	Main results early efficacy (within 6 hours)
Kazemi-Kjellberg, 2001		Active-control trials: ondansetron 8 mg vs droperidol 1.25 mg (1 trial) ondansetron 0.1 mg/kg vs droperidol 20 mcg/kg (1 trial) ondansetron 4 mg vs metoclopramide 10 mg (1 trial) granisetron 40 mcg/kg vs droperidol 20 mcg/kg vs metoclopramide 0.2 mg/kg (2 trials) ondansetron 8 mg vs droperiddol 1 mg vs alizapride 100 mg (1 trial) Placebo-controlled trials: dolasetron 12.5 mg, 25 mg, 50 mg, or 100 mg (2 trials) granisetron 0.1 mg, 1 mg, or 3 mg (1 trial) 4-10) ondansetron 0.1 mg/kg, 1 mg, 4 mg, 8 mg, or 16 mg (7 trials)	**Relative risk (95% CI); NNT (95% CI)** <u>Prevention of further nausea</u> Granisetron 0.1 mg: 2.41 (1.56 to 3.73); 4.3 (3.0 to 7.9) Granisetron 1 mg: 2.45 (1.59 to 3.79); 4.2 (2.9 to 7.4) Granisetron 3 mg: 2.56 (1.66 to 3.95); 3.9 (2.7 to 6.6) Ondansetron 8 mg: 2.80 (1.28 to 6.14); 2.0 (1.3 to 4.6) <u>Prevention of further vomiting</u> Dolasetron 12.5 mg: 2.03 (1.46 to 2.82); 3.6 (2.5 to 6.1) Dolasetron 25 mg: 1.85 (1.31 to 2.60); 4.3 (2.8 to 9.0) Dolasetron 50 mg: 1.77 (1.26 to 2.50); 4.7 (3.0 to 11) Dolasetron 100 mg: 1.86 (1.33 to 2.61); 4.3 (2.8 to 8.5) Granisetron 0.1 mg: 2.02 (1.45 to 2.80); 3.7 (2.6 to 6.5) Granisetron 1 mg: 2.20 (1.60 to 3.03); 3.2 (2.3 to 4.9) Granisetron 3 mg: 2.28 (1.66 to 3.13); 3.0 (2.2 to 4.5) Ondansetron 0.1 mg: 1.40 (0.50 to 3.95); NS Ondansetron 1 mg: 1.88 (1.39 to 2.55); 3.7 (2.6 to 6.6) Ondansetron 4 mg: 2.10 (1.58 to 2.79); 3.3 (2.5 to 5.1) Ondansetron 8 mg: 1.84 (1.45 to 2.35); 3.7 (2.7 to 5.8) Ondansetron 16 mg: 3.43 (1.43 to 8.23); 2.6 (1.7 to 6.4) Ondansetron 0.1 mg/kg: 2.27 (1.83 to 2.81); 2.3 (1.9 to 2.9)

Evidence Table 13. Treatment of established PONV: systematic reviews

Author Year	Main results late efficacy (within 24 hours)	Subgroups	Adverse events
Kazemi-Kjellberg, 2001	**Relative risk (95% CI); NNT (95% CI)** Prevention of further nausea Granisetron 0.1 mg: 2.08 (1.22 to 3.53); 7.3 (4.3 to 24) Granisetron 1 mg: 2.35 (1.41 to 3.93); 5.8 (3.7 to 13) Granisetron 3 mg: 2.88 (1.75 to 4.75); 4.2 (2.9 to 7.2) Prevention of further vomiting Dolasetron 12.5 mg: 2.88 (1.83 to 4.54); 4.8 (3.5 to 7.8) Dolasetron 25 mg: 2.54 (1.59 to 4.04); 6.0 (4.1 to 11) Dolasetron 50 mg: 2.93 (1.86 to 4.61); 4.8 (3.5 to 7.7) Dolasetron 100 mg: 2.54 (1.60 to 4.04); 5.9 (4.1 to 11) Granisetron 0.1 mg: 1.96 (1.30 to 2.95); 5.3 (3.4 to 13) Granisetron 1 mg: 2.35 (1.59 to 3.47); 3.8 (2.7 to 6.5) Granisetron 3 mg: 2.50 (1.69 to 3.68); 3.4 (2.5 to 5.5) Ondansetron 0.1 mg: 1.00 (0.32 to 3.12); NS Ondansetron 1 mg: 2.04 (1.51 to 2.75); 4.8 (3.5 to 7.9) Ondansetron 4 mg: 2.29 (1.73 to 3.02); 4.0 (3.0 to 5.7) Ondansetron 8 mg: 2.23 (1.66 to 3.00); 4.1 (3.1 to 6.2) Ondansetron 16 mg: 3.20 (1.32 to 7.76); 2.9 (1.8 to 8.3) Ondansetron 0.1 mg/kg: 3.14 (2.21 to 4.48); 2.8 (2.2 to 3.7)	No information	Headache was the most frequently-reported adverse event, but no comparison of different antiemetics was made, and results not reported separately by drug. Event rates and relative risks (95% CI) vs placebo by dose: Low dose (dolasetron 12.5 mg, granisetron 0.1 mg, tropisetron 0.5 mg, ondansetron 1 mg): 7.7% vs 10.4%; RR 0.75 (0.51 to 1.10) Medium dose (dolasetron 25-50 mg, granisetron 1 mg, tropisetron 2 mg, ondansetron 4 mg): 9.3% vs 9.3%; RR 1.09(0.78 to 1.52) High dose (dolasetron 100 mg, granisetron 3 mg, tropisetron 5 mg, ondansetron 8 mg): 13.3% vs 9.9%; RR 1.36 (0.98 to 1.88)

Evidence Table 13. Treatment of established PONV: systematic reviews

Author Year	Aims	Time period covered	Eligibility criteria	Number of patients	Characteristics of identified articles: study designs
Tramer, 1997	To test the evidence for a dose-response with ondansetron for treatment of PONV and establish whether differences in efficacy between doses are of clinical relevance	Medline (1991-January 22, 1996)	Randomized controlled trials that evaluated the effect of ondansetron compared with a control (placebo, no treatment, or another antiemetic) on established PONV and reported the outcome in dichotomous form.	1,252	Seven randomized controlled trials (4 ondansetron vs placebo, 2 ondansetron vs IV droperidol, 1 ondansetron vs metoclopramide)

Evidence Table 13. Treatment of established PONV: systematic reviews

Author Year	Characteristics of identified articles: populations	Characteristics of identified articles: interventions	Main results early efficacy (within 6 hours)
Tramer, 1997	Four trials in 1043 adults (82% female) who complained of nausea or vomited after general anesthesia; one trial in 100 gynecology patients; one trial in 29 vomiting children, one trial in 80 adults undergoing major abdominal surgery.	Four trials of a single iv dose of ondansetron 1 mg, 4 mg, or 8 mg with placebo; One trial of iv ondansetron 8 mg vs iv droperidol 1.25 mg (both antiemetics could be administered up to 3 times in 24 hours); One trial of iv ondansetron 100 mcg/kg vs iv droperidol 20 mcg/kg (children); One trial of iv ondansetron 4 mg vs iv metoclopramide 10 mg	**Odds Ratio (95% CI); NNT (95% CI)** Complete control of further nausea or vomiting, or both *Ondansetron vs Placebo* Ondansetron 1 mg: 3.0 (1.8 to 4.8); 3.8 (2.6 to 6.6) Ondansetron 4 mg: 3.5 (2.1 to 5.8); 3.2 (2.3 to 5.2) Ondansetron 8 mg: 3.8 (2.5 to 5.8); 3.1 (2.4 to 4.5) *Ondansetron vs droperidol:* Ondansetron 8 mg X 3 vs droperidol 1.25 mg X 3: 0.7 (0.3 to 1.6); NS Ondansetron 100 mcg/kg vs droperidol 20 mcg/kg: 0.6 (0.1 to 3.4); NS0.7 (0.3 to 1.4); NS Trials combined: 0.7 (0.3 to 1.4); NS *Ondansetron 4 mg vs metoclopramide 10 mg* 2.3 (0.7 to 6.7); NS

Evidence Table 13. Treatment of established PONV: systematic reviews

Author Year	Main results late efficacy (within 24 hours)	Subgroups	Adverse events
Tramer, 1997	**Odds Ratio (95% CI); NNT (95% CI)** Complete control of further nausea or vomiting, or both *Ondansetron vs Placebo* Ondansetron 1 mg: 2.7 (1.8 to 3.9); 4.8 (3.5 to 7.9) Ondansetron 4 mg: 3.2 (2.2 to 4.7); 3.9 (3.0 to 5.7) Ondansetron 8 mg: 3.1 (2.1 to 4.5); 4.1 (3.1 to 6.2) *Ondansetron 4 mg vs metoclopramide 10 mg* 1.8 (0.8 to 4.3); NS	No information. 82% of patients in included trials were women.	No information

Evidence Table 14. Treatment of established PONV: comparative clinical trials

Author Year Setting	Design Trial type	Type of Surgery	Other population characteristics	Inclusion criteria
Active-controlled trials				
Coloma 2002 Single Center	DB RCT Parallel Active	Laparoscopic cholecystectomy 68 (76%) Gynecologic laparoscopy 22 (24%)	History of PONV 22(24%) History of motion sickness 15(17%) History of dizziness 18(20%)	Healthy outpatients scheduled for laparoscopic surgery with general anesthesia; patients were enrolled if they complained of nausea orvomiting in the postanesthesia care unit or in the step-down (phase II) recovery unit.
Dabbous 2001 Single Center	DB RCT Parallel Active	Laparoscopic cholecystectomy: 55% Laparoscopic herniorrhaphy: 7% Laparoscopic Appendectomy: 10% Diagnostic Laparoscopy 48: 28%	History of PONV 46 (27%) History of motion sickness 9 (5%)	ASA Class I and II patients undergoing laparoscopic surgery who developed PONV.

Evidence Table 14. Treatment of established PONV: comparative clinical trials

Author Year Setting	Exclusion criteria	Intervention	Allowed other medication
Active-controlled trials			
Coloma 2002 Single Center	Patients were excluded if they had taken an antiemetic agent within 24 hours prior to the operation, were pregnant, experiencing menstrual symptoms, had previous experience wih acustimulaiton therapy, had a permanent cardiac pacemaker, or experienced vomiting or retching within 24 hours before surgery.	a) ondansetron 4mg b) ReliefBand c) combination ondansetron + ReliefBand 4mg	Prophylactic antiemetic (e.g., 10mg IV metoclopramide or 0.625 mg IV droperidol) administered to all patients after induction of anesthesia. Fentanyl intraoperatively and fentanyl and morphine postoperatively
Dabbous 2001 Single Center	Patients receiving pre- or intraoperative antiemetics; postoperative pain scores >5, patients who received postoperative narcotics, pregnant females, patients with a nasogastric tube remaining postoperatively, and sedation scores >1 (degree of sedation was assessed as 1=awake, 2=drowsy, 3=asleep).	a) ondansetron 4 mg b) droperidol 1.25 mg c) metoclopramide 10 mg	All patients were premedicated with glycopyrrolate 0.2 mg IM and diazepam 5 mg PO 45 minutes prior to induction of anesthesia.

Evidence Table 14. Treatment of established PONV: comparative clinical trials

Author Year Setting	Run-in/Wash out	Mean Age Gender Ethnicity	Screened/ Eligible/ Enrolled	Withdrawn/ Lost to fu/ Analyzed
Active-controlled trials				
Coloma 2002 Single Center	no/no	40 92% women Not reported	268/ 90/ 90	NR/ 7/ 90
Dabbous 2001 Single Center	no/no	44 77% women Not reported	NR/ NR/ 173	NR/ NR/ 173

Evidence Table 14. Treatment of established PONV: comparative clinical trials

Author Year Setting	Results	Adverse events
Active-controlled trials		
Coloma 2002 Single Center	Ondansetron vs Acustimulation vs Combination Complete response at 2 hours Complete response at 2 hours Number (%): 17(57) vs 12 (40) vs 22 (73) Ondansetron vs acustimulation, p: NS Combination vs acustimulation, p: <0.05 Post-treatment retching Post treatment retching Number(%): 10(33) vs 8(27) vs 10(33) ondansetron vs acustimulation, p: NS combination vs acustimulation, p: NS Post-treatment vomiting Post-treatment vomiting Number(%): 10(33) vs 17(57) vs 8(27) ondansetron vs acustimulation, p: NS combination vs acustimulation, p: <0.05 Time from treatment to rescue antiemetic Time from treatment to rescue antiemetic (minutes) Number(SD): 51(43) vs 63(53) vs 58(37) ondansetron vs acustimulation, p: NS combination vs acustimulation, p: NS Admitted for PONV Admitted for PONV Number(%): 0(0) vs 0(0) vs 0(0) ondansetron vs acustimulation, p: NS combination vs acustimulation, p: NS Highest nausea score Highest nausea score (0-10) Score(Range): 5(0-8) vs 5(0-10) vs 6(0-10) ondansetron vs acustimulation, p: NS combination vs acustimulation, p: NS	ondansetron vs acustimulation pruritus: 3% vs 0% (NS) difficulty voiding: 3% vs 3% (NS) headaches: 0 vs 0 (NS) dizziness: 0% vs 3% (NS) patient felt tingling sensation: 30% vs 57% (NS)
Dabbous 2001 Single Center	ondansetron vs droperidol vs metoclopramide % decrease in nausea scores at 10 minutes: 55.4% vs 41.2% vs 20.2% (p<0.05 between all groups) % decrease in nausea scores at 30 minutes: 84.3% vs 80.0% vs 41.2% (p<0.05 for metoclopramide vs other groups) Need for rescue antiemetic: 5 (8.8%) vs 6 (10.5%) vs 25 (42.3%) p<0.05 for metoclopramide vs other groups, no other statistical differences	ondansetron vs droperidol vs metoclopramide sedation: 0% vs 25% vs 0% headache: 14% vs 10% vs 8% dizziness: 12% vs 10% vs 10% malaise: 12% vs 17% vs 10% agitation: 4% vs 5% vs 5% extrapyramidal symptoms: 0% vs 0% vs 0%

Evidence Table 14. Treatment of established PONV: comparative clinical trials

Author Year Setting	Design Trial type	Type of Surgery	Other population characteristics	Inclusion criteria
Fujii 2000 Single center	DB RCT Parallel Active	Abdominal hysterectomy: 76% Vaginal hysterectomy: 5% Salpingooophorectomy: 19%	None had a history of motion sickness or previous PONV.	Women undergoing major gynecological operations, ASA physical status I or II, ages 23 to 63, with nausea lasting >10 minutes with or without emesis (vomiting, retching) within 3 hours after recovery from general anesthesia.
Fujii 2003 Single Center	DB RCT Parallel Active	Partial mastectomy: 12% Partial mastectomy w/axillary dissection: 9% Modified radical mastectomy: 9% Modified Radical mastectomy w/axillary dissection: 69%	History of PONV: 4% History of motion sickness: 9%	Women with ASA physical status I (no organic, physiologic, biochemical, or psychiatric disturbance) who were experiencing nausea and/or emesis after recovery from general anesthhesia for breast surgery.

Evidence Table 14. Treatment of established PONV: comparative clinical trials

Author Year Setting	Exclusion criteria	Intervention	Allowed other medication
Fujii 2000 Single center	Patients with gastrointestinal disease, those who had a history of motion sickness, previous postoperative nausea and vomiting, or both; and those who had taken an antiemetic medication within 24 hours before the operation.	a) granisetron 40mcg/kg b) droperidol 20mcg/kg c) metoclopramide 0.2mg/kg	None reported
Fujii 2003 Single Center	Patients who had gastrointestinal disease, had taken antiemetics within 24 hours before surgery, or who were pregnant, menstruating, or receiving hormonal therapy.	a) granisetron 40mcg/kg b) droperidol 20mcg/kg c) metoclopramide 0.2mg/kg	Patients received no medication before anesthesia. If the patient complained of pain postoperatively, analgesia was provided with indomethacin 50 mg administered rectally.

Evidence Table 14. Treatment of established PONV: comparative clinical trials

Author Year Setting	Run-in/Wash out	Mean Age Gender Ethnicity	Screened/ Eligible/ Enrolled	Withdrawn/ Lost to fu/ Analyzed
Fujii 2000 Single center	no/no	44 100% women NR	NR/ NR/ 120	0/ 0/ 120
Fujii 2003 Single Center	no/no	53 100% women Not reported	80/ 75/ 75	NR/ NR/ 75

Evidence Table 14. Treatment of established PONV: comparative clinical trials

Author Year Setting	Results	Adverse events
Fujii 2000 Single center	granisetron vs droperidol vs metoclopramide Complete control of PONV (no emesis and no rescue medication) for 24 hours 88% vs 55% vs 50% (p=0.002 for granisetron vs droperidol, 0.00? for granisetron vs metoclopramide) No nausea 92% vs 80% vs 75% (p=0.192 for granisetron vs droperidol, 0.06 for granisetron vs metoclopramide) No retching 100% vs 95% vs 90% (p=0.492 for granisetron vs droperidol, 0.11 for granisetron vs metoclopramide) No vomiting 95% vs 77% vs 77% (p=0.047 for granisetron vs droperidol, 0.04 for granisetron vs metoclopramide) Severity of nausea (median and range) 0 (0-4) vs 0 (0-10) vs 0 (0-10) (p=0.011 for granisetron vs droperidol, 0.00? for granisetron vs metoclopramide) Patient satisfaction rating (median and range) 7 (0-10) vs 2.5 (0-10) vs 3 (0-10) (p=0.001 for granisetron vs droperidol, 0.00? for granisetron vs metoclopramide)	Incidence of adverse events (states "such as headache and dizziness): granisetron: 13% droperidol: 13% metoclopramide: 10% (NS) sedation level (median and range): granisetron: 1 (0-5) droperidol: 1 (0-5) metoclopramide: 1 (0-5) p=0.70 No extrapyramidal symptoms observed in any group.
Fujii 2003 Single Center	granisetron vs droperidol vs metoclopramide Emesis free for 24 hours after administration of study drug Number: 88% vs 64% vs 56% droperidol vs granisetron, p: 0.047 metoclopramide vs granisetron, p: 0.013 Severity of nausea (0=no nausea; 10=severe nausea) Median (Range): 4 (4-6) vs 8 (5-10) vs 8 (5-10) droperidol vs granisetron, p: 0.028 metoclopramide vs granisetron, p: 0.025 Nausea in 24 hours after administration of study drug: 12% vs 32% vs 36% droperidol vs granisetron, p: 0.085 metoclopramide vs granisetron, p: 0.047 Retching in 24 hours after administration of study drug Number: 0% vs 4% vs 4% droperidol vs granisetron, p: 0.50 metoclopramide vs granisetron, p: 0.50 Vomiting in 24 hours after administration of study drug Number: 8% vs 16% vs 20% droperidol vs granisetron, p: 0.083 metoclopramide vs granisetron, p: 0.027	Headache was most frequently reported adverse event. Incidence of headache (8%-12%) did not differ between groups. No other clinically significant adverse events were observed in any group.

Evidence Table 14. Treatment of established PONV: comparative clinical trials

Author Year Setting	Design Trial type	Type of Surgery	Other population characteristics	Inclusion criteria
Unlugenc 2003 Single Center	RCT Parallel Active	Abdominal: 88 (73%) Gynecological: 32 (27%)	No patients with a history of motion sickness or previous postoperative vomiting.	Men and women, ASA Class I and II, ages 18 to 65, who were scheduled for elective gynecological or abdominal surgery under general anesthesia. Patients were included if nausea or vomiting occurred during the first 2 hours in the Postanesthesia Recovery Unit.
Winston 2003 Single Center	RCT Parallel Active	Laparoscopic bilateral tubal ligation 40 (40%) Diagnostic laparoscopy 41 (41%) Operative laparoscopy 19 (19%)	No patients with a history of PONV.	Women with ASA physical status I or II, older than 18 years scheduled to undergo diagnostic laparoscopy, operative laparoscopy, or laparoscopic bilateral tubal occlusion.

Evidence Table 14. Treatment of established PONV: comparative clinical trials

Author Year Setting	Exclusion criteria	Intervention	Allowed other medication
Unlugenc 2003 Single Center	A history of motion sickness, previous postoperative vomiting, known major organ disease, ASA>II, body weight >100% over ideal, a history of alcohol or drug abuse, or receipt of an antiemetic agent within 24 hours.	a) ondansetron 4mg b) propofol 15mg c) midazolam 1mg d) midazolam 2mg	IV piroxicam (0.5 mg kg -1) for postoperative pain relief. If no pain relief was obtained, increments of fentanyl (0.5-1 mcg -1) IV were given.
Winston 2003 Single Center	Subjects excluded if they reported sensitivity to isopropyl alcohol or ondansetron, had an impaired ability to breathe through the nose, were pregnant or using the medication disulfiram, reported preexisting nausea, or reported any antiemetic use within 24 hours before surgery. Patients who reported a history of significant PONV, defined as nausea or vomiting resistant to antiemetic therapy, or had a history of alcoholism were excluded.	a) inhaled isopropyl alcohol 70% b) ondansetron 4mg	None reported

Evidence Table 14. Treatment of established PONV: comparative clinical trials

Author Year Setting	Run-in/Wash out	Mean Age Gender Ethnicity	Screened/ Eligible/ Enrolled	Withdrawn/ Lost to fu/ Analyzed
Unlugenc 2003 Single Center	no/no	45 53% women Not reported	453/ NR/ 120	NR/ NR/ 120
Winston 2003 Single Center	no/no	NR 100% women Not reported	NR/ NR/ 100	NR/ NR/ 100

Evidence Table 14. Treatment of established PONV: comparative clinical trials

Author Year Setting	Results	Adverse events
Unlugenc 2003 Single Center	ondansetron vs propofol vs midazolam 1 mg vs midazolam 2 mg % change in mean nausea score (1=none; 2=mild; 3=moderate; 4=severe; 5=worst) 5 minutes after treatment: 54.2% vs 54.2% vs 50.0% vs 56.0% 15 minutes after treatment: 56.5% vs 58.3% vs 57.7% vs 60.0% 30 minutes after treatment: 56.5% vs 58.3% vs 57.7% vs 60.0% 60 minutes after treatment: 56.5% vs 58.3% vs 61.5% vs 60.0% 120 minutes after treatment: 56.5% vs 58.3% vs 61.5% vs 60.0% 360 minutes after treatment 56.5% vs 58.3% vs 61.5% vs 60.0% Need for second dose of antiemetic 3.3% vs 13.3% vs 43.3% vs 16.6%	Two patients in ondansetron group (7%) compained of headache after a single dose. No further adverse effects attributable to medication were observed.
Winston 2003 Single Center	ondansetran vs isopropyl alcohol Median verbal numeric rating scale scores (0=no nausea, 10=worst nausea imaginable) first complaint: 8.00 vs 8.00 (p=0.854) 5 minutes: 8.00 vs 3.00 (p=0.002) 10 minutes: 5.00 vs 3.00 (p=0.015) 15 minutes: 5.00 vs 2.00 (p=0.036) 30 minutes: 0.00 vs 1.50 (p=0.469) 45 minutes: 0.00 vs 0.00 (p=0.522) 60 minutes: 0.00 vs 0.00 (p=0.871) Mean time to 50% relief of PON: 27.7 minutes vs 6.3 minutes (p=0.002) Mean stay time in PACU: 60.3 vs 58.4 minutes (NS) Mean stay time in SDS unit: 124.2 vs 139.2 minutes (NS)	Not reported

Evidence Table 14. Treatment of established PONV: comparative clinical trials

Author Year Setting	Design Trial type	Type of Surgery	Other population characteristics	Inclusion criteria
Placebo-controlled trials				
Fujii 2004a Single Center	DB RCT Parallel Placebo	Abdominal hysterectomy	No patients with a history of motion sickness and/or PONV	Women ages 33 to 66 years who were categorized as ASA physical status I (no organic, physiologic, biochemical, or psychiatric disturbances) and were experiencing nausea lasting >10 minutes and/or retching or vomiting within 3 hours after recovery from anesthesia in the postanesthetic care unti for abdominal hysterectomy with or without salpingo-oophorectomy.

Evidence Table 14. Treatment of established PONV: comparative clinical trials

Author Year Setting	Exclusion criteria	Intervention	Allowed other medication
Placebo-controlled trials			
Fujii 2004a Single Center	Antiemetics given <= 24 hours before surgery, gastrointestinal disease, menstruation, and a history of motion sickness and/or postoperative emetic symptoms.	a) granistron IV 10 mcg/kg b) granistron IV 20 mcg/kg c) granistron IV 40 mcg/kg d) granistron IV 100 mcg/kg e) placebo (saline 5 mL)	None reported

Evidence Table 14. Treatment of established PONV: comparative clinical trials

Author Year Setting	Run-in/Wash out	Mean Age Gender Ethnicity	Screened/ Eligible/ Enrolled	Withdrawn/ Lost to fu/ Analyzed
Placebo-controlled trials				
Fujii 2004a Single Center	no/no	44 100% women NR	105/ 100/ 100	0/ 0/ 100

Evidence Table 14. Treatment of established PONV: comparative clinical trials

Author Year Setting	Results	Adverse events
Placebo-controlled trials		
Fujii 2004a Single Center	Complete control of emetic symptoms over 24 hours (p vs placebo) granisetron 10 mcg/kg: 35% (p=0.500) granisetron 20 mcg/kg: 85% (p=0.001) granisetron 40 mcg/kg: 85% (p=0.001) granisetron 100 mcg/kg: 80% (p=0.002) placebo: 30% No nausea over 24 hours (p vs placebo) granisetron 10 mcg/kg: 65% (p=1.000) granisetron 20 mcg/kg: 90% (p=0.064) granisetron 40 mcg/kg: 90% (p=0.064) granisetron 100 mcg/kg: 90% (p=0.064) placebo: 65% No vomiting over 24 hours (p vs placebo) granisetron 10 mcg/kg: 70% (p=0.500) granisetron 20 mcg/kg: 90% (p=0.064) granisetron 40 mcg/kg: 90% (p=0.064) granisetron 100 mcg/kg: 90% (p=0.064) placebo: 65% Severity of nausea, median (range); 0=none, 10=severe (p vs placebo) granisetron 10 mcg/kg: 8 (6-10) (p=0.430) granisetron 20 mcg/kg: 5 (4-6) (p=0.038) granisetron 40 mcg/kg: 4.5 (4-5) (p=0.038) granisetron 100 mcg/kg: 8 (6-10) (p=0.038) placebo: 65%: 8 (7-10) Rescue medication used (p vs placebo) granisetron 10 mcg/kg: 20% (p=0.500) granisetron 20 mcg/kg: 0% (p=0.024) granisetron 40 mcg/kg: 0% (p=0.024) granisetron 100 mcg/kg: 0% (p=0.024) placebo: 25%	The most frequent adverse event was headache. Incidence (5%-10%) did not differ signficicantly between groups (data not reported).

Evidence Table 14. Treatment of established PONV: comparative clinical trials

Author Year Setting	Design Trial type	Type of Surgery	Other population characteristics	Inclusion criteria
Fujii 2004b Single Center	DB RCT Parallel Placebo	Laparoscopic cholecystectomy Indication for surgery: Symptomatic cholelithiasis: 77% cholecystic polyp: 12% chronic cholecystitis: 11%	No patients with a history of motion sickness and/or PONV	Male and female patients ages 23 to 68 years with ASA physical status I (no organic, physiologic, biochemical, or psychiatric disturbance) who were experiencing nausea lasting >10 minutes or retching or vomiting with 3 hours after recovery from general anesthesia for laparoscopic cholecystectomy.

Evidence Table 14. Treatment of established PONV: comparative clinical trials

Author Year Setting	Exclusion criteria	Intervention	Allowed other medication
Fujii 2004b Single Center	Patients who received antiemetics within 24 hours before surgery, who had gastrointestinal disease, who had a history of motion sickness and/or PONV. Patients who were pregnant, possibly pregnant, breastfeeding, or menstruating.	a) granistron IV 10 mcg/kg b) granistron IV 20 mcg/kg c) granistron IV 40 mcg/kg d) granistron IV 80 mcg/kg e) placebo	Indomethacin 50 mg if the patient experienced pain postoperatively.

Evidence Table 14. Treatment of established PONV: comparative clinical trials

Author Year Setting	Run-in/Wash out	Mean Age Gender Ethnicity	Screened/ Eligible/ Enrolled	Withdrawn/ Lost to fu/ Analyzed
Fujii 2004b Single Center	no/no	47 60% women NR	105/100/100	NR/NR/100

Evidence Table 14. Treatment of established PONV: comparative clinical trials

Author Year Setting	Results	Adverse events
Fujii 2004b Single Center	Emesis free over 24 hours (p vs placebo) granisetron 10 mcg/kg: 55% (NS) granisetron 20 mcg/kg: 85% (p=0.02) granisetron 40 mcg/kg: 90% (p=0.007) granisetron 80 mcg/kg: 90% (p=0.007) placebo: 50% No nausea over 24 hours (p vs placebo) granisetron 10 mcg/kg: 65% (NS) granisetron 20 mcg/kg: 90% (NS) granisetron 40 mcg/kg: 90% (NS) granisetron 80 mcg/kg: 90% (NS) placebo: 70% No vomiting over 24 hours (p vs placebo) granisetron 10 mcg/kg: 75% (NS) granisetron 20 mcg/kg: 95% (NS) granisetron 40 mcg/kg: 95% (NS) granisetron 80 mcg/kg: 95% (NS) placebo: 80% Severity of nausea, median (range); 0=none, 10=severe (p vs placebo) granisetron 10 mcg/kg: 8 (6-10) (NS) granisetron 20 mcg/kg: 5 (4-6) (p=0.043) granisetron 40 mcg/kg: 5 (4-6) (p=0.043) granisetron 80 mcg/kg: 5.5 (4-5) (p=0.043) placebo: 8.5 (7-10)	The most frequent adverse event was headache. Incidence (5%-10%) did not differ signficicantly between groups (data not reported). The next most common adverse events were dizziness (≤5%) and constipation (≤5%). Severity of adverse events was not evaluated.

Evidence Table 15. Quality assessments of the comparative clinical trials of treatment of established PONV

Author Year Setting (subpopulation)	Trial type	Exclusion criteria	Run-in/ Wash out	Screened/ Eligible/ Enrolled
Coloma 2002 Single Center	Active	Patients were excluded if they had taken an antiemetic agent within 24 hours prior to the operation, were pregnant, experiencing menstrual symptoms, had previous experience wih acustimulaiton therapy, had a permanent cardiac pacemaker, or experienced vomiting or retching within 24 hours before surgery.	no/no	268/90/90
Dabbous 2001 Single Center	Active	Patients receiving pre- or intraoperative antiemetics; postoperative pain scores >5, patients who received postoperative narcotics, pregnant females, patients with a nasogastric tube remaining postoperatively, and sedation scores >1 (degree of sedation was assessed as 1=awake, 2=drowsy, 3=asleep).	no/no	NR/NR/173
Fujii 2003 Single Center	Active	Patients who had gastrointestinal disease, had taken antiemetics within 24 hours before surgery, or who were pregnant, menstruating, or receiving hormonal therapy.	no/no	80/75/75
Unlugenc 2003, 2004 Single Center	Active	A history of motion sickness, previous postoperative vomiting, known major organ disease, ASA>II, body weight >100% over ideal, a history of alcohol or drug abuse, or receipt of an antiemetic agent within 24 hours.	no/no	453/NR/120
Winston 2003 Single Center	Active	Subjects excluded if they reported sensitivity to isopropyl alcohol or ondansetron, had an impaired ability to breathe through the nose, were pregnant or using the medication disulfiram, reported preexisting nausea, or reported any antiemetic use within 24 hours before surgery. Patients who reported a history of significant PONV, defined as nausea or vomiting resistant to antiemetic therapy, or had a history of alcoholism were excluded.	no/no	NR/NR/100
Fujii 2004 Single Center	Placebo	Antiemetics given <= 24 hours before surgery, gastrointestinal disease, menstruation, and a history of motion sickness and/or postoperative emetic symptoms.		105/100/100
Tzeng 2003 Single Center	Placebo	Patients with a history of PONV, motion sickness, or gastrointestinal disorders, a major systemic disease (e.g., hypertension, diabetes mellitus, and morbid obesity), contraindications to epidural anesthesia and analgesia, chronic opioid use, or who had received an antiemetic within 48 hours before surgery. Patients who needed rescue analgesics for pain during surgery were also excluded.		NR/NR/70

Evidence Table 15. Quality assessments of the comparative clinical trials of treatment of established PONV

Author Year Setting (subpopulation)	Withdrawn/ Lost to fu/ Analyzed	Randomization	Allocation	Groups similar at baseline	Eligibility criteria specified	Care provider masked	Patients masked	Attrition Crossover Adherence Contamination	Loss to follow up
Coloma **2002** Single Center	NR/7/90	Yes	NR	No	Yes	Yes	Yes	Yes No Yes No	No
Dabbous **2001** Single Center	NR/NR/173	Yes	NR	Yes	Yes	Yes	Yes	No No No No	No
Fujii 2003 Single Center	NR/NR/75	Yes	NR	Yes	Yes	Yes	Yes	No No No No	No
Unlugenc **2003, 2004** Single Center	NR/NR/120	Yes	NR	Yes	Yes	Yes	Yes	No No No No	Not reported
Winston **2003** Single Center	NR/NR/100	NR	NR	Yes	Yes	Yes	Yes	No No No No	No
Fujii **2004** Single Center		Yes	NR	Yes	Yes	Yes	Yes	Yes No No No	No
Tzeng **2003** Single Center		Yes	NR	unable to determine	Yes	Yes	Yes	Yes No No No	No

Evidence Table 15. Quality assessments of the comparative clinical trials of treatment of established PONV

Author Year Setting (subpopulation)	Intention-to-treat analysis	Post randomization exclusions	Quality rating	Controlled group standard of care	Funding	Relevance
Coloma 2002 Single Center	Yes	No	Fair	Yes	GlaxoSmithKline and Woodside Biomedical	Yes
Dabbous 2001 Single Center	Yes (but 24-hour results not reported?)	No	Fair	Yes	Not reported	Yes
Fujii 2003 Single Center	Yes	No	Fair	Yes	Not reported	Women
Unlugenc 2003, 2004 Single Center	Unable to determine	Unable to determine	Fair	Yes	Not supported by external funds	Yes
Winston 2003 Single Center	Yes	No	Fair	Yes	Not reported	Women
Fujii 2004 Single Center	Yes	No	Fair		Not reported	
Tzeng 2003 Single Center	No	Yes	Fair		Not reported	Women

Evidence Table 16. Long-term uncontrolled intervention studies of safety and adverse events

Author Year Country	Exposure duration	5-HT3 Antagonist	Concomitant medication	Ascertainment techniques	Age (mean) Gender -% female Ethnicity
Adults					
Kirchner 1993	Unclear	Dolasetron 10-50 mg iv	NR	Adverse events checklist (unspecified) was completed 24 hours after last dolasetron dose	46.9 years 32.2% female Ethnicity NR
Watanabe 1995	Unclear; 5.9 courses of chemotherapy (mean)	Granisetron 50 mg/kg iv	NR	NR	22.8 years 84.7% Ethnicity NR
Khoo 1993	Up to 6 days	Ondansetron 1 mg/hr iv plus 8 mg po bid-tid	Dexamethasone	At end of assessment period, patients asked if they experienced any side effects	43 years 20% Ethnicity NR
Manso Ribiero 1993	3-5 days	Ondansetron	NR	NR	NR (62.7% < age 60 years) 53% Ethnicity NR
Marty 1989	24 hours	Ondansetron 8 mg iv, then 1 mg/hr	NR	NR	Median=54 years 35.7% female Ethnicity NR

Evidence Table 16. Long-term uncontrolled intervention studies of safety and adverse events

Author Year Country	Hesketh Score Primary malignancy	Screened Eligible Enrolled	Withdrawn Lost to fu Analyzed	Safety Outcomes
Adults				
Kirchner **1993**	5 Lung	NR NR 31	NR NR 31	Thrombocytopenia: 1 patient Septicemia that led to death: 1 patient Both attributed to cytotoxic chemotherapy and/or cancer
Watanabe **1995**	5 Bone and soft-tissue sarcoma	NR NR 72	NR NR Unclear	One patient reported chest pressure
Khoo **1993**	5 NR	NR NR 25	NR NR 25	Encephalopathy: 1 patient
Manso Ribiero **1993**	Unclear NR	NR NR NR	NR NR 145	Major adverse events (considered unrelated by investigators): 5 patients (included death, shock, respiratory failure, central nervous system hemorrhage and fever, vomiting and jaundice
Marty **1989**	5 Cancer site=other	NR NR 28	2 0 26	Thrombocytopenia: 3 (11.5%) Another patient experienced palpitations of moderate severity accompanied by throbbing, sweating, and arterial hypertension None of the events were considered due to ondansetron

Evidence Table 16. Long-term uncontrolled intervention studies of safety and adverse events

Author Year Country	Exposure duration	5-HT3 Antagonist	Concomitant medication	Ascertainment techniques	Age (mean) Gender -% female Ethnicity
Children					
Craft 1995	Single dose	Granisetron 40 mg/kg iv	None		Mean age NR (range=2-16 yrs) 45% female 97.5% caucasian 2.5% asian
Hewitt 1993	3-5 days	Ondansetron iv (dose calculated by surface area; max=8 mg), then 24 mg po (tid)	NR	NR	8.8 years Gender/ethnicity NR
Pinkerton 1990	5 days	Ondansetron 5 mg/m2 iv, then po (dose calculated by surface area; max=24 mg (tid))	NR	NR	9.5 years 50% female Ethnicity NR

Evidence Table 16. Long-term uncontrolled intervention studies of safety and adverse events

Author Year Country	Hesketh Score Primary malignancy	Screened Eligible Enrolled	Withdrawn Lost to fu Analyzed	Safety Outcomes
Children				
Craft **1995**	Unclear (dosages NR) Acute lymphoblastic leukemia	NR NR 40	NR NR NR	Hyponatremia: 1 patient
Hewitt **1993**	Unclear NR	NR NR 200	25 0 200	Withdrawal due to major adverse events: 3 patients Patient 1: moderate headaches Patient 2: transient nystagmus, diplopia and ataxia Patient 3: renal failure
Pinkerton **1990**	Group A: 5 Group B: 4 Group 3: 4 Solid tumors	NR NR 30	NR NR NR	One child developed hepatitis

Evidence Table 17. Quality assessment of long-term uncontrolled intervention studies of safety and adverse events

Author Year	Non-biased selection?	Low overall loss to follow-up?	Adverse events pre-specified and defined?	Ascertainment techniques adequately described?	Non-biased and adequate ascertainment methods?	Statistical analysis of potential confounders?	Overall adverse event assessment quality
Kirchner 1993	Unclear	Unclear	No	No	Unclear	No	Poor
Watanabe 1995	Unclear	Unclear	No	No	Unclear	No	Poor
Khoo 1993	Unclear	None	No	No	Unclear	No	Poor
Manso Ribiero 1993	Unclear	Unclear	No	No	Unclear	No	Poor
Marty 1989	Yes	None	No	No	Unclear	No	Fair
Craft 1995	Yes	Unclear	No	No	Unclear	No	Fair
Hewitt 1993	Yes	None	No	No	Unclear	No	Fair
Pinkerton 1990	Unclear	Unclear	No	No	Unclear	No	Poor