

Supplementary Table I: Guideline Search Strategy

MEDLINE: The search strategy for OvidSP MEDLINE (1946 to March Week 2 2015)

Set	History
1	exp neoplasms/ or exp Antineoplastic Agents/ or organ transplantation/ or exp tissue transplantation/ or transplantation, autologous/ or transplantation, heterologous/ or transplantation, heterotopic/ or exp transplantation, homologous/ or (neoplasm* or neoplas* or cancer* or oncolog* or tumor* or tumour* or transplant*).mp. or radiation dosage/ or dose-response relationship, radiation/ or Radiometry/ or Radiotherapy Dosage/ or ((gray or sievert) adj2 unit*) or (radiation adj2 (dosage* or dose or dosing)) or "gy radiation" or "radiation dose-response").mp. or chemoradiotherapy/ or chemoradiotherapy, adjuvant/ or Radiotherapy, Adjuvant/ or rt.fs. or radiotherapy/ or ((adjuvant adj2 chemotherap*) or chemoradiotherap* or radiochemotherap* or cancer* or oncol* or tumour* or tumor* or malignan* or neoplas* or sarcom* or blastoma* or neuroblastoma* or leukem* or leukaem* or carcinoma* or lymphoma* or adenocarcinoma* or hodgkin* or chemotherap* or radiation*).mp.
2	(consensus development conference or consensus development conference, nih or guideline or practice guideline).pt. or practice guideline/ or guideline/ or guidelines as topic/ or practice guidelines as topic/ or consensus development conferences as topic/ or consensus development conferences, nih as topic/ or clinical protocols/ or antineoplastic protocols/ or antineoplastic combined chemotherapy protocols/ or Critical Pathways/ or (guideline* or "evidence-based recommend*" or "evidence based recommend*").ti,ab.
3	1 and 2
4	limit 3 to "all child (0 to 18 years)"
5	(infan* or neonat* or child* or adolescen* or teen* or girl* or boy* or youth* or tot or tots or toddler* or paediatric* or pediatric*).mp
6	4 or (3 and 5)
7	limit 3 to ("all adult (19 plus years)" or "all aged (65 and over)" or "aged (80 and over)")
8	6 not 7
9	limit 9 to (english language and yr="2012 -Current")

EMBASE: The search strategy for OvidSP Embase Classic+Embase (1947 to 2015 Week 10)

Set	History
1	exp neoplasm/ or exp Antineoplastic Agent/ or organ transplantation/ or stem cell transplantation/ or exp allogeneic stem cell transplantation/ or autologous stem cell transplantation/ or exp hematopoietic stem cell transplantation/ or mesenchymal stem cell transplantation/ or bone marrow transplantation/ or tissue transplantation/ or allogenic bone marrow transplantation/ or autologous bone marrow transplantation/ or bone marrow purging/ or bone marrow rescue/ or radiotherapy/ or blood radiation/ or chemoradiotherapy/ or adjuvant chemoradiotherapy/ or radiotherapy/ or blood radiation/ or exp chemoradiotherapy/ or exp cobalt therapy/ or image guided radiotherapy/ or intensity modulated radiation therapy/ or intraoperative radiotherapy/ or megavoltage radiotherapy/ or radiation depth dose/ or radiation dose/ or radiation dose escalation/ or radiation dose fractionation/ or radiation dose reduction/ or radiation response/ or radioimmunotherapy/ or radiation measurement/ or dosimetry/ or radiometry/ or ((gray or sievert) adj2 unit*) or (radiation adj2 (dosage* or dose or dosing)) or "gy radiation" or "radiation dose-response").mp. or rt.fs. or ((adjuvant adj2 chemotherap*) or chemoradiotherap* or radiochemotherap* or cancer* or oncol* or tumour* or tumor* or malignan* or neoplas* or sarcom* or blastoma* or neuroblastoma* or leukem* or leukaem* or carcinoma* or lymphoma* or adenocarcinoma* or hodgkin* or chemotherap* or radiation*).mp.
2	practice guideline/ or clinical pathway/ or clinical protocol/ or consensus development/ or good clinical practice/ or nursing care plan/ or nursing protocol/ or ((standard adj2 care) or consensus).mp. or (guideline* or "evidence-based recommend*" or "evidence based recommend*").ti,ab.
3	1 and 2
4	limit 3 to (infant <to one year> or child <unspecified age> or preschool child <1 to 6 years> or school child <7 to 12 years> or adolescent <13 to 17 years>)
5	(infan* or neonat* or child* or adolescen* or teen* or girl* or boy* or youth* or tot or tots or toddler* or paediatric* or pediatric*).mp.
6	4 or (3 and 5)

7	limit 4 to (adult <18 to 64 years> or aged <65+ years>)
8	6 not 7
9	limit 8 to (english language and yr="2012 -Current")

Supplementary Table II: Search Strategies for Systematic Reviews of primary CINV Studies

MEDLINE: The search strategy for OvidSP MEDLINE (1946 to March Week 2 2015)

Set	History
1	exp neoplasms/ or exp Antineoplastic Agents/ or (Chemotherap* adj2 induc*).mp. or CINV.mp. or ci.fs. or chemotherap*.mp.
2	nausea/ or vomiting/ or (emesis or vomit* or retch* or nauseous or nausea*).mp.
3	((failure* or failing or subsequent* or rescue* or refractory or breakthrough* or "break-through" or (break adj2 through*)) adj15 (nause* or vomit* or retch* or antiemetic* or "anti-emetic*" or emesis or emetic* or emetogenic*).mp.
4	1 and 2 and 3

EMBASE: The search strategy for OvidSP Embase Classic+Embase (1947 to 2015 Week 10)

Set	History
1	exp *neoplasm/ or exp *Antineoplastic Agent/ or *cancer chemotherapy/ or *cancer combination chemotherapy/
2	*"nausea and vomiting"/ or *nausea/ or *retching/ or *vomiting/ or (emesis or vomit* or retch* or nauseous or nausea*).mp.
3	((failure* or failing or subsequent* or rescue* or refractory or breakthrough* or "break-through" or (break adj2 through*)) adj15 (nause* or vomit* or retch* or antiemetic* or "anti-emetic*" or emesis or emetic* or emetogenic*).mp.
4	1 and 2 and 3
5	"chemotherapy induced nausea and vomiting"/ or chemotherapy induced emesis/
6	(failure* or failing or subsequent* or rescue* or refractory or breakthrough* or "break-through" or (break adj2 through*).mp.
7	5 and 6
8	4 or 7

EBM Reviews - Cochrane Central Register of Controlled Trials: OvidSP EBM Reviews - Cochrane Central Register of Controlled Trials < February 2015>

Set	History
1	exp neoplasms/ or exp Antineoplastic Agents/ or (Chemotherap* adj2 induc*).mp. or CINV.mp. or ci.fs. or chemotherap*.mp. or exp *Neoplasms/ or exp *Antineoplastic Agent/ or *cancer chemotherapy/ or *cancer combination chemotherapy/
2	nausea/ or vomiting/ or (emesis or vomit* or retch* or nauseous or nausea*).mp. or *"nausea and vomiting"/ or *nausea/ or *retching/ or *vomiting/ or (emesis or vomit* or retch* or nauseous or nausea*).mp.
3	((failure* or failing or subsequent* or rescue* or refractory or breakthrough* or "break-through" or (break adj2 through*)) adj15 (nause* or vomit* or retch* or antiemetic* or "anti-emetic*" or emesis or emetic* or emetogenic*).mp.
4	1 and 2 and 3
5	"chemotherapy induced nausea and vomiting"/ or chemotherapy induced emesis/
6	(failure* or failing or subsequent* or rescue* or refractory or breakthrough* or "break-through" or (break adj2 through*).mp.
7	5 and 6
8	4 or 7

Supplementary Table III: Search Strategies for Systematic Reviews of Pediatric Methotrimeprazine (Levomepromazine) Studies

MEDLINE: The search strategy for OvidSP MEDLINE (1946 to March Week 1 2015)

Set	History
1	Methotrimeprazine/ or ("apo-methoprazine" or "bayer 1213" or "cl 36467" or "cl 39743" or cl36467 or cl39743 or hirnamin or methoxyphenothiazine or "l mepromazine" or levium or "levo mepromazine " or "levo promazine" or levomeprazine or levomepromazine or levopromazin or levopromazine or levoprome or levozin or mepromazine or methotrimeprazine or methotrimperazine or methozane or milezin or minozinan or neozine or neuractil or neurocil or nirvan or nozinan or "rp 7044" or rp7044 or sinogan or "skf 5116" or skf5116 or tiscerin or tiscercin or veractil).mp.
2	limit 1 to "all child (0 to 18 years)"
3	(infan* or neonat* or child* or adolescen* or teen* or girl* or boy* or youth* or tot or tots or toddler* or paediatric* or pediatric*).mp.
4	1 and 3
5	2 or 4

EMBASE: The search strategy for OvidSP Embase Classic+Embase (1947 to 2015 Week 10)

Set	History
1	levomepromazine/ or ("apo-methoprazine" or "bayer 1213" or "cl 36467" or "cl 39743" or cl36467 or cl39743 or hirnamin or methoxyphenothiazine or "l mepromazine" or levium or "levo mepromazine " or "levo promazine" or levomeprazine or levomepromazine or levopromazin or levopromazine or levoprome or levozin or mepromazine or methotrimeprazine or methotrimperazine or methozane or milezin or minozinan or neozine or neuractil or neurocil or nirvan or nozinan or "rp 7044" or rp7044 or sinogan or "skf 5116" or skf5116 or tiscerin or tiscercin or veractil).mp.
2	limit 1 to (infant <to one year> or child <unspecified age> or preschool child <1 to 6 years> or school child <7 to 12 years> or adolescent <13 to 17 years>)
3	(infan* or neonat* or child* or adolescen* or teen* or girl* or boy* or youth* or tot or tots or toddler* or paediatric* or pediatric*).mp.
4	1 and 3
5	2 or 4

EBM Reviews - Cochrane Central Register of Controlled Trials: Wiley Cochrane Library Central Register of Controlled Trials < February 2015>

Set	History
1	levomepromazine/ or ("apo-methoprazine" or "bayer 1213" or "cl 36467" or "cl 39743" or cl36467 or cl39743 or hirnamin or methoxyphenothiazine or "l mepromazine" or levium or "levo mepromazine " or "levo promazine" or levomeprazine or levomepromazine or levopromazin or levopromazine or levoprome or levozin or mepromazine or methotrimeprazine or methotrimperazine or methozane or milezin or minozinan or neozine or neuractil or neurocil or nirvan or nozinan or "rp 7044" or rp7044 or sinogan or "skf 5116" or skf5116 or tiscerin or tiscercin or veractil).mp.
2	(infan* or neonat* or child* or adolescen* or teen* or girl* or boy* or youth* or tot or tots or toddler* or paediatric* or pediatric*).mp.
3	1 and 2

PsycINFO: Search strategy for OvidSP PsycINFO <1806 to March Week 1 2015>

Set	History
1	Methotrimeprazine/ or ("apo-methoprazine" or "bayer 1213" or "cl 36467" or "cl 39743" or cl36467 or cl39743 or hirnamin or methoxyphenothiazine or "l mepromazine" or levium or "levo mepromazine " or "levo promazine" or levomeprazine or levomepromazine or levopromazin or levopromazine or levoprome or levozin or mepromazine or methotrimeprazine or methotrimperazine or methozane or milezin or minozinan or neozine or neuractil or neurocil or nirvan or nozinan or "rp 7044" or rp7044 or sinogan or "skf 5116" or skf5116 or tiscerin or tiscercin or veractil).mp.
2	limit 1 to (100 childhood <birth to age 12 yrs> or 120 neonatal <birth to age 1 mo> or 140 infancy <2 to 23 mo> or 160 preschool age <age 2 to 5 yrs> or 180 school age <age 6 to 12 yrs> or 200 adolescence <age 13 to 17 yrs>)
3	(infan* or neonat* or child* or adolescen* or teen* or girl* or boy* or youth* or tot or tots or toddler* or paediatric* or pediatric*).mp.
4	1 and 3
5	2 or 4

Supplementary Table IV: Treatment of Breakthrough CINV – Summary of Included Studies

First Author (Year)	Study Design, Objective and Population	Definition of Breakthrough CINV	Antiemetic Prophylaxis and Interventions	Proportion with Complete Control of Breakthrough Nausea and/or Vomiting
Pediatric Studies				
No studies identified				
Adult Studies				
5HT-3 Antagonist - Granisetron				
Jones (2011) [1]	<ul style="list-style-type: none"> Prospective observational trial Aim: Describe the response to antiemetic therapy taken for breakthrough CINV N = 27 Adults with cancer receiving chemotherapy Median age: 57 yrs; range: 30-72 yrs CINV assessment: patient report Emetogenicity classification: moderately or highly emetogenic 	Nausea and/or vomiting requiring antiemetic rescue medication occurring any time during the first 3 days post-chemotherapy	<p>Prophylactic regimen: Dexamethasone: 25/27 (93%) Granisetron: 20/27 (74%) Palonosetron: 7/27 (26%) Aprepitant: 1/27 (4%)</p> <p>*Guideline consistent antiemetic prophylaxis: unable to determine (authors report prophylactic regimens were based on antiemetic guidelines)</p> <p>Breakthrough intervention: G1: Prochlorperazine 10mg PO (n=24) G2: 5-HT antagonist (granisetron 1mg PO (n=1), ondansetron 8mg IV (n=1), ondansetron 8mg sublingually (n=1))</p>	<p>Proportion with complete control of breakthrough vomiting: G1: 23/24 (96%) G2: 3/3 (100%)</p> <p>Proportion with complete control of breakthrough nausea: G1: 2/24 (8.3%) G2: 1/3 (33.3%)</p> <p>Proportion with complete control of breakthrough CINV: not reported</p> <p>Time of occurrence of breakthrough CINV: acute and delayed phases (over 3 days)</p> <p>Timeframe of assessments: Acute phase (baseline (when breakthrough treatment initiated) then every half hour x 4hrs)</p>
Marty (1990)[2]	<ul style="list-style-type: none"> Prospective trial Aim: Compare the efficacy and safety of granisetron vs chlorpromazine + dexamethasone for CINV, evaluation of rescue with a second dose of granisetron was evaluated secondarily in the granisetron arm N = 23 Adults with cancer receiving chemotherapy Median age: Not reported for breakthrough cohort CINV assessment: patient and clinician report Emetogenicity classification: moderately or highly emetogenic 	Moderate or severe nausea	<p>Prophylactic regimen: Granisetron 40mcg/kg IV (5 min pre-chemo)</p> <p>*Guideline consistent antiemetic prophylaxis: no</p> <p>Breakthrough intervention: Additional Granisetron doses of 40mcg/kg IV up to a maximum of 120mcg/kg</p>	<p>Proportion with complete control of breakthrough CINV after 1 additional granisetron dose: 11/23 (47.8%)</p> <p>Proportion with complete control of breakthrough CINV after 2 additional granisetron doses: 4/8 (50%)</p> <p>Time of occurrence of breakthrough CINV: acute phase</p> <p>Timeframe of assessments: acute phase (30min after administration of additional granisetron doses)</p>

First Author (Year)	Study Design, Objective and Population	Definition of Breakthrough CINV	Antiemetic Prophylaxis and Interventions	Proportion with Complete Control of Breakthrough Nausea and/or Vomiting
Riviere (1994)[3]	<ul style="list-style-type: none"> Prospective open-label study Aim: Compare the efficacy and safety of 3 different doses of granisetron, evaluation of rescue with a second dose of granisetron was evaluated secondarily N = 64 Adult patients receiving cisplatin-containing chemotherapy Median age: Not reported for breakthrough cohort CINV assessment: patient and clinician report Emetogenicity classification: highly emetogenic 	Moderate or severe nausea (more than mild nausea or vomiting occurred)	<p>Prophylactic regimen for all patients (5 min pre-chemo): G1: Granisetron 2mcg/kg IV G2: Granisetron 10mcg/kg IV G3: Granisetron 40mcg/kg IV</p> <p>*Guideline consistent antiemetic prophylaxis: no</p> <p>Breakthrough intervention: Granisetron 3mg IV up to 2 x's, administered at least 10min apart</p>	<p>Proportion with complete control of breakthrough CINV after 1 additional granisetron dose: G1: 26/30 (86.7%) G2: 12/19 (63.2%) G3: 9/15 (60%)</p> <p>Proportion with complete control of breakthrough CINV after 2 additional granisetron doses: G1: 5/12 (41.7%) G2: 9/11 (81.8%) G3: 2/7 (28.6%)</p> <p>Time of occurrence of breakthrough CINV: not reported</p> <p>Timeframe of assessments: acute phase (baseline, 6hrs, 12hrs, 18hrs, and 24hrs)</p>
Tagigawa (1996)[4]	<ul style="list-style-type: none"> Prospective observational trial Aim: Determine the usefulness of granisetron rescue therapy for CINV N = 20 Adults with urogenital malignant tumors receiving chemotherapy (including cisplatin) Mean age: 61.9 ± 15 yrs; range: 25-76 yrs CINV assessment: Not reported, patients examined by a healthcare professional q6h for 24hrs Emetogenicity classification: highly emetogenic 	No response to antiemetics or emesis	<p>Prophylactic regimen: Not reported</p> <p>*Guideline consistent antiemetic prophylaxis: unable to determine/not reported</p> <p>Breakthrough intervention: Granisetron 3mg IV administered 30min after the onset of nausea or vomiting</p>	<p>Proportion with complete control of breakthrough vomiting: 5/20 (25%)</p> <p>Proportion with complete control of breakthrough nausea: 15/20 (75%)</p> <p>Proportion with complete control of breakthrough CINV: not reported</p> <p>Time of occurrence of breakthrough CINV: not reported</p> <p>Timeframe of assessments: acute phase (q6h x 24hrs)</p>
5HT-3 Antagonist - Ondansetron				
Ariyoshi (1992)[5]	<ul style="list-style-type: none"> Double-blind randomized comparison with placebo Aim: Determine the antiemetic efficacy and safety of ondansetron tablets N = 12 Adults with cancer receiving a single dose of cisplatin 50mg/m² or higher Median Age: Not reported for breakthrough cohort CINV assessment: Not reported, patients examined by a healthcare professional q6h for 24hrs Emetogenicity classification: highly emetogenic 	"Satisfactory" anti-emetic effects not obtained	<p>Prophylactic regimen: Ondansetron 4mg PO once (2hrs pre-chemo)</p> <p>*Guideline consistent antiemetic prophylaxis: no</p> <p>Breakthrough intervention: Ondansetron 4mg IV once</p>	<p>Proportion with complete control of breakthrough vomiting: not reported</p> <p>Proportion with complete control of breakthrough nausea: not reported</p> <p>Proportion with complete control of breakthrough CINV: not reported, 5/12 (41.7%) achieved a "satisfactory response"</p> <p>Timeframe of assessments: acute phase (q6h x 24hrs after administration of cisplatin)</p>

First Author (Year)	Study Design, Objective and Population	Definition of Breakthrough CINV	Antiemetic Prophylaxis and Interventions	Proportion with Complete Control of Breakthrough Nausea and/or Vomiting
Fabi (2008)[6]	<ul style="list-style-type: none"> Open-label randomized trial Aim: evaluate the efficacy and safety of two different schedules of ondansetron as rescue antiemetic treatment N = 44 Adults with cancer receiving chemotherapy Median age: Not reported for breakthrough cohorts CINV assessment: patient report Emetogenicity classification: moderately emetogenic 	At least 1 episode of nausea and/or vomiting occurring from days 2-6 of cycle 1 of chemotherapy	<p>Prophylactic regimen for all patients: Day 1: Dexamethasone 8mg IV + ondansetron 8mg IV Days 2-5: Dexamethasone 8mg PO once daily</p> <p>*Guideline consistent antiemetic prophylaxis: yes</p> <p>Breakthrough intervention: G1: Ondansetron 8mg IM (n=22) G2: ODT ondansetron 16mg PO (n=22)</p>	<p>Proportion with complete control of breakthrough vomiting: G1: 7/22 (31.8%) G2: 18/22 (81.8%) p=0.001</p> <p>Proportion with complete control of breakthrough nausea: G1: 9/22 (40.9%) G2: 17/22 (77.3%) p=0.01</p> <p>Proportion with complete control of breakthrough CINV: not reported</p> <p>Time of occurrence of breakthrough CINV: delayed phase (days 2-6)</p> <p>Timeframe of assessments: acute and delayed phases (patients followed for 6 days following chemo)</p>
Jones (2011)[1]	<ul style="list-style-type: none"> Prospective observational trial Aim: Describe the response to antiemetic therapy taken for breakthrough CINV N = 27 Adults with cancer receiving chemotherapy Median age: 57 yrs; range: 30-72 yrs CINV assessment: patient report Emetogenicity classification: moderately or highly emetogenic 	Nausea and/or vomiting requiring antiemetic rescue medication occurring any time during the first 3 days post-chemotherapy	<p>Prophylactic regimen: Dexamethasone: 25/27 (93%) Granisetron: 20/27 (74%) Palonosetron: 7/27 (26%) Aprepitant: 1/27 (4%)</p> <p>*Guideline consistent antiemetic prophylaxis: unable to determine (authors report prophylactic regimens were based on antiemetic guidelines)</p> <p>Breakthrough intervention: G1: Prochlorperazine 10mg PO (n=24) G2: 5-HT antagonist (granisetron 1mg PO (n=1), ondansetron 8mg IV (n=1), ondansetron 8mg sublingually (n=1))</p>	<p>Proportion with complete control of breakthrough vomiting: G1: 23/24 (96%) G2: 3/3 (100%)</p> <p>Proportion with complete control of breakthrough nausea: G1: 2/24 (8.3%) G2: 1/3 (33.3%)</p> <p>Proportion with complete control of breakthrough CINV: not reported</p> <p>Time of occurrence of breakthrough CINV: acute and delayed phases (over 3 days)</p> <p>Timeframe of assessments: Acute phase (baseline (when breakthrough treatment initiated) then every half hour x 4hrs)</p>
Ohta (1992)[7]	<ul style="list-style-type: none"> Double-blind randomized comparison with placebo Aim: Determine the antiemetic efficacy and safety of IV ondansetron N = 7 Adults with cancer receiving a single dose of cisplatin 50mg/m² or higher Median age: Not reported for breakthrough cohort CINV assessment: Not reported, patients examined by a healthcare professional q6h for 24hrs Emetogenicity classification: highly emetogenic 	Insufficient anti-emetic effect after initial dose of IV ondansetron	<p>Prophylactic regimen: Ondansetron 4mg IV (15 min pre-chemo)</p> <p>*Guideline consistent antiemetic prophylaxis: no</p> <p>Breakthrough intervention: Ondansetron 4mg IV once</p>	<p>Proportion with complete control of breakthrough vomiting: not reported</p> <p>Proportion with complete control of breakthrough nausea: not reported</p> <p>Proportion with complete control of breakthrough CINV: not reported, 1/7 (14.3%) achieved an "inhibitory effect" from the rescue ondansetron dose</p> <p>Timeframe of assessments: acute phase (q6h for the first 24hrs after administration of cisplatin)</p>

First Author (Year)	Study Design, Objective and Population	Definition of Breakthrough CINV	Antiemetic Prophylaxis and Interventions	Proportion with Complete Control of Breakthrough Nausea and/or Vomiting
5HT-3 Antagonist - Palonosetron				
Musso (2009)[8]	<ul style="list-style-type: none"> ▪ Prospective observational trial ▪ Aim: Evaluate the efficacy of a single dose of palonosetron for CINV control, evaluation of rescue with a second dose of palonosetron was evaluated secondarily ▪ N =27 ▪ Adolescents and adults with haematological malignancies receiving multiple day chemotherapy (2-7 days) ▪ Median age: Not reported for breakthrough cohorts ▪ CINV assessment: patient report ▪ Emetogenicity classification: moderately or highly emetogenic 	Not reported	<p>Prophylactic regimen:</p> <p>G1: Dexamethasone 8mg IV + palonosetron 0.25mg IV on day 1 (15 min pre-chemo) Dexamethasone 4mg IV twice daily was administered every day during the entire chemotherapy period</p> <p>G2: Dexamethasone 8mg IV + ondansetron 8mg IV on day 1 (15 min pre-chemo) Dexamethasone 4mg IV twice daily was administered every day during the entire chemotherapy period</p> <p>Dexamethasone excluded for patients receiving DHAP (dexamethasone + cisplatin + cytarabine)</p> <p>*Guideline consistent antiemetic prophylaxis: yes for MEC, no for HEC</p> <p>Breakthrough intervention:</p> <p>G1: Palonosetron 0.25mg IV 72 hrs after administration of the first dose</p> <p>G2: Metoclopramide 20mg IV q6h or q12h</p>	<p>Proportion with complete control of breakthrough vomiting: not reported</p> <p>Proportion with complete control of breakthrough nausea: not reported</p> <p>Proportion with complete control of breakthrough CINV: G1: 6/9 (67%) G2: 4/18 (22%) p=0.039</p> <p>Time of occurrence of breakthrough CINV: acute and delayed phases (over 5 days)</p> <p>Timeframe of assessments: not reported</p>
Musso (2010)[9]	<ul style="list-style-type: none"> ▪ Prospective open-label trial ▪ Aim: Evaluate the efficacy of a single dose of palonosetron for CINV control, evaluation of rescue with a second dose of palonosetron was evaluated secondarily ▪ N = 51 ▪ Adolescents and adults with haematological malignancies receiving conditioning for autologous stem cell transplant ▪ Median age: Not reported for breakthrough cohorts ▪ CINV assessment: patient reported ▪ Emetogenicity classification: moderately or highly emetogenic 	Not reported	<p>Prophylactic regimen for all patients:</p> <p>Dexamethasone 8mg IV + palonosetron 0.25mg IV on day 1 (30 min pre-chemo) Dexamethasone 4mg IV twice daily was administered every other day for the remainder of the conditioning regimen</p> <p>*Guideline consistent antiemetic prophylaxis: no</p> <p>Breakthrough intervention:</p> <p>Palonosetron 0.25mg IV 48 or 72 hrs after administration of the first dose</p>	<p>Proportion with complete control of breakthrough vomiting when palonosetron administered 72hrs after initial dose: 25/51 (50%)</p> <p>Proportion with complete control of breakthrough vomiting when palonosetron administered 48hrs after initial dose: 9/20 (45%)</p> <p>Proportion with complete control of breakthrough nausea: Not reported</p> <p>Proportion with complete control of breakthrough CINV: not reported</p> <p>Time of occurrence of breakthrough AINV: delayed phase</p> <p>Timeframe of assessments: not reported</p>

First Author (Year)	Study Design, Objective and Population	Definition of Breakthrough CINV	Antiemetic Prophylaxis and Interventions	Proportion with Complete Control of Breakthrough Nausea and/or Vomiting
Methotrimeprazine				
McCabe (2003)[10]	<ul style="list-style-type: none"> ▪ Prospective observational study ▪ Aim: Evaluate the efficacy of levomepromazine for management of breakthrough CINV ▪ N = 32 ▪ Adult patients with high grade delayed chemotherapy-induced emesis requiring hospital admission to control this ▪ Median age: 58 yrs; range: 35-76 yrs ▪ CINV assessment: patient report ▪ Emetogenicity classification: highly emetogenic 	Delayed chemotherapy-induced emesis Grade II and above (graded using the NCI-CTC)	<p>Prophylactic regimen for all patients: various potential regimens described (not reported which regimens actually received by patients included in the analysis)</p> <p>*Guideline consistent antiemetic prophylaxis: unable to determine/not reported</p> <p>Breakthrough intervention: Levomepromazine 25mg SC over 24-48 hrs</p>	<p>Proportion with complete control of breakthrough vomiting in 24 hours: 28/32 (88%)</p> <p>Proportion with complete control of breakthrough vomiting in 48 hours: 30/32 (94%)</p> <p>Proportion with complete control of breakthrough nausea in 24 hours: 24/32 (75%)</p> <p>Proportion with complete control of breakthrough nausea in 48 hours: 30/32 (94%)</p> <p>Time of occurrence of breakthrough CINV: acute and delayed phase (within 24 and 48 hours)</p> <p>Timeframe of assessments: acute and delayed phases (baseline, 24hrs , and 48hrs)</p>
Metoclopramide				
Musso (2009)[8]	<ul style="list-style-type: none"> ▪ Prospective observational trial ▪ Aim: Evaluate the efficacy of a single dose of palonosetron for CINV control, evaluation of rescue with a second dose of palonosetron was evaluated secondarily ▪ N =27 ▪ Adolescents and adults with haematological malignancies receiving multiple day chemotherapy (2-7 days) ▪ Median age: Not reported for breakthrough cohorts ▪ CINV assessment: patient report ▪ Emetogenicity classification: moderately or highly emetogenic 	Not reported	<p>Prophylactic regimen:</p> <p>G1: Dexamethasone 8mg IV + palonosetron 0.25mg IV on day 1 (15 min pre-chemo) Dexamethasone 4mg IV twice daily was administered every day during the entire chemotherapy period</p> <p>G2: Dexamethasone 8mg IV + ondansetron 8mg IV on day 1 (15 min pre-chemo) Dexamethasone 4mg IV twice daily was administered every day during the entire chemotherapy period</p> <p>Dexamethasone excluded for patients receiving DHAP (dexamethasone + cisplatin + cytarabine)</p> <p>*Guideline consistent antiemetic prophylaxis: yes for MEC, no for HEC</p> <p>Breakthrough intervention:</p> <p>G1: Palonosetron 0.25mg IV 72 hrs after administration of the first dose</p> <p>G2: Metoclopramide 20mg IV q6h or q12h</p>	<p>Proportion with complete control of breakthrough vomiting: not reported</p> <p>Proportion with complete control of breakthrough nausea: not reported</p> <p>Proportion with complete control of breakthrough CINV: G1: 6/9 (67%) G2: 4/18 (22%) p=0.039</p> <p>Time of occurrence of breakthrough CINV: acute and delayed phases (over 5 days)</p> <p>Timeframe of assessments: not reported</p>

First Author (Year)	Study Design, Objective and Population	Definition of Breakthrough CINV	Antiemetic Prophylaxis and Interventions	Proportion with Complete Control of Breakthrough Nausea and/or Vomiting
Navari (2013)[11]	<ul style="list-style-type: none"> Double-blinded randomized trial Aim: Compare the use of olanzapine vs metoclopramide for the treatment of breakthrough CINV N = 108 Chemotherapy-naïve adults with cancer receiving chemotherapy (cisplatin $\geq 70\text{mg}/\text{m}^2$ or doxorubicin $\geq 50\text{mg}/\text{m}^2$ + cyclophosphamide $\geq 600\text{mg}/\text{m}^2$) Median age: G1: 61 yrs; range: 38-75 yrs G2: 63 yrs; range: 42-79 yrs CINV assessment: patient report Emetogenicity classification: highly emetogenic 	Any emesis and/or any moderate to severe nausea (>3 on visual analogue scale of 0 to 10)	<p>Prophylactic regimen for all patients (30-60min pre-chemo): Day 1: Dexamethasone 12mg IV + palonosetron 0.25mg IV + fosaprepitant 150mg IV Days 2-4: Dexamethasone 4mg PO twice daily</p> <p>*Guideline consistent antiemetic prophylaxis: yes</p> <p>Breakthrough intervention: G1: Olanzapine 10mg PO once daily x 3 days (n=56) G2: Metoclopramide 10mg PO q8h x 3 days (n=52)</p> <p>Oral dexamethasone discontinued immediately once breakthrough treatment with olanzapine initiated</p>	<p>Proportion with complete control of breakthrough vomiting: G1: 39/56 (70%) G2: 16/52 (31%) p<0.01</p> <p>Proportion with complete control of breakthrough nausea: G1: 38/56 (68%) G2: 12/52 (23%) p<0.01</p> <p>Proportion with complete control of breakthrough CINV: not reported</p> <p>Time of occurrence of breakthrough CINV: acute and delayed phases (over 3 days)</p> <p>Timeframe of assessments: acute and delayed phases (at least once daily x 72hrs)</p>
Olanzapine				
Chanthawong (2014)[12]	<ul style="list-style-type: none"> Phase II open label pilot study Aim: Evaluate the efficacy and safety of olanzapine for breakthrough CINV N = 46 Adults with cancer receiving chemotherapy Median age: 33.5 yrs (males; 18 yrs (females) Emetogenicity classification: highly emetogenic 	Any vomiting episode during days 1 to 4	<p>Prophylactic regimen for all patients: Day 1: Ondansetron 24mg IV BID + dexamethasone 10mg IV BID Days 2-4: Metoclopramide 10mg TID PO + dexamethasone 10mg BID PO</p> <p>*Guideline consistent antiemetic prophylaxis: no</p> <p>Breakthrough intervention: Olanzapine 5 mg PO q12h x 2 doses Lorazepam 0.5 to 2mg/dose PO q4 – 6h PRN added if olanzapine not effective</p>	<p>Proportion with complete control of breakthrough vomiting: 28/46 (60.8%)</p> <p>Proportion with complete control of breakthrough nausea: 23/46 (50.0%)</p> <p>Proportion with complete control of breakthrough CINV: not reported</p> <p>Time of occurrence of breakthrough CINV: not reported</p> <p>Timeframe of assessments: q6h x 24 hrs after receipt of olanzapine</p>
Navari (2013)[11]	<ul style="list-style-type: none"> Double-blinded randomized trial Aim: Compare the use of olanzapine vs metoclopramide for the treatment of breakthrough CINV N = 108 Chemotherapy-naïve adults with cancer receiving chemotherapy (cisplatin $\geq 70\text{mg}/\text{m}^2$ or doxorubicin $\geq 50\text{mg}/\text{m}^2$ + cyclophosphamide $\geq 600\text{mg}/\text{m}^2$) Median age: G1: 61 yrs; range: 38-75 yrs G2: 63 yrs; range: 42-79 yrs CINV assessment: patient report Emetogenicity classification: highly emetogenic 	Any emesis and/or any moderate to severe nausea (>3 on visual analogue scale of 0 to 10)	<p>Prophylactic regimen for all patients (30-60min pre-chemo): Day 1: Dexamethasone 12mg IV + palonosetron 0.25mg IV + fosaprepitant 150mg IV Days 2-4: Dexamethasone 4mg PO twice daily</p> <p>*Guideline consistent antiemetic prophylaxis: yes</p> <p>Breakthrough intervention: G1: Olanzapine 10mg PO once daily x 3 days (n=56) G2: Metoclopramide 10mg PO q8h x 3 days (n=52)</p> <p>Oral dexamethasone discontinued immediately once breakthrough treatment with olanzapine initiated</p>	<p>Proportion with complete control of breakthrough vomiting: G1: 39/56 (70%) G2: 16/52 (31%) p<0.01</p> <p>Proportion with complete control of breakthrough nausea: G1: 38/56 (68%) G2: 12/52 (23%) p<0.01</p> <p>Proportion with complete control of breakthrough CINV: not reported</p> <p>Time of occurrence of breakthrough CINV: acute and delayed phases (over 3 days)</p> <p>Timeframe of assessments: acute and delayed phases (at least once daily x 72hrs)</p>

First Author (Year)	Study Design, Objective and Population	Definition of Breakthrough CINV	Antiemetic Prophylaxis and Interventions	Proportion with Complete Control of Breakthrough Nausea and/or Vomiting
Prochlorperazine				
Jones (2011)[1]	<ul style="list-style-type: none"> Prospective observational trial Aim: Describe the response to antiemetic therapy taken for breakthrough CINV N = 27 Adults with cancer receiving chemotherapy Median age: 57 yrs; range: 30-72 yrs CINV assessment: patient report Emetogenicity classification: moderately or highly emetogenic 	Nausea and/or vomiting requiring antiemetic rescue medication occurring any time during the first 3 days post-chemotherapy	Prophylactic regimen: Dexamethasone: 25/27 (93%) Granisetron: 20/27 (74%) Palonosetron: 7/27 (26%) Aprepitant: 1/27 (4%) *Guideline consistent antiemetic prophylaxis: unable to determine (authors report prophylactic regimens were based on antiemetic guidelines) Breakthrough intervention: G1: Prochlorperazine 10mg PO (n=24) G2: 5-HT antagonist (granisetron 1mg PO (n=1), ondansetron 8mg IV (n=1), ondansetron 8mg sublingually (n=1))	Proportion with complete control of breakthrough vomiting: G1: 23/24 (96%) G2: 3/3 (100%) Proportion with complete control of breakthrough nausea: G1: 2/24 (8.3%) G2: 1/3 (33.3%) Proportion with complete control of breakthrough CINV: not reported Time of occurrence of breakthrough CINV: acute and delayed phases (over 3 days) Timeframe of assessments: Acute phase (baseline (when breakthrough treatment initiated) then every half hour x 4hrs)
Other				
Bleicher (2008)[13]	<ul style="list-style-type: none"> 2 prospective open-label trials Aim: Describe the efficacy of ABH gel in reducing breakthrough CINV N = 33 Adults with cancer receiving chemotherapy Median age: Not reported CINV assessment: patient report Emetogenicity classification: highly emetogenic 	Significant nausea and/or vomiting in the days following chemotherapy	Prophylactic regimen for all patients: not reported *Guideline consistent antiemetic prophylaxis: unable to determine (authors report patients were given standard antiemetic prophylaxis similar to those recommended in established guidelines with ASCO guidelines referenced) Breakthrough intervention: 0.5mL of ABH gel applied topically to the wrists q6h prn ABH 0.5 mL contains: lorazepam 2 mg, diphenhydramine 25 mg, haloperidol 2mg ABH gel ingredients: 120mg lorazepam, 1500mg diphenhydramine, 120mg haloperidol, 12mL lecithin organogel, 5mL ethoxydiglycol, 1mL water, and 60mL pluronic gel 20% qs	Proportion with complete control of breakthrough vomiting: not reported Proportion with complete control of breakthrough nausea: not reported Proportion with complete control of breakthrough CINV: 10/33 (30.3%) Time of occurrence of breakthrough CINV: not reported Timeframe of assessments: variable (within 1 month for 23 patients; at baseline and every half hour x 4hrs in 10 patients)

Emetogenicity classified according to the MASCC and ASCO guidelines

*Prophylaxis considered "guideline consistent" based on current recommendations provided by MASCC and/or ASCO and/or NCCN

Supplementary Table V: Adverse Effects Reported in Pediatric Studies Evaluating the Use of Methotrimeprazine (Levopromazine) – Summary of Included Studies

Author	Study Aim	Patient Characteristics	Methotrimeprazine Dose	Length of Treatment	Adverse Effects Monitored	Adverse Effects Reported	Comments
Randomized or Non-Randomized Trials							
None							
Retrospective Reviews, Case Series and Case Reports							
Hohl (2013)[14]	Retrospective review of methotrimeprazine use for palliative symptoms in children and infants	N=18 Age: 16 days-17 yrs (age at death) M:F = NR	Range: 0.02 to 0.5 mg/kg/dose q4h (n=6), q6h (n=6), q8h (n=1), q24h (n=4) regularly or PRN: q30min (n=3), q1h (n=4), q4h (n=4), q6h (n=2) IV (n=13), PO/GT (n=6), SC (n=4)	NR	NR	EPS: 0/18 NMS:0/18 Sedation: 6/18	Most patients received concurrent medications which may cause EPS. However EPS not reported as an adverse effect experienced by any patient.
Snoek (2014)[15]	Retrospective review of methotrimeprazine use for difficult sedation in pediatric ICU	N=7 Age: 1 -17 yrs M:F = NR	Range: 0.5 – 1.9 mg/kg/dose given q8h enterally	Varied; Range: 16–149 hrs	NR	EPS: 0/7 Fever: 2/7	All patients received concurrent medications, some of which may cause EPS. Fever developed in 1 child with pneumonia and methotrimeprazine was discontinued. A second child developed fever which resolved despite continuation of methotrimeprazine.
van der Zwann (2012)[16]	Case series of 4 pediatric patients given methotrimeprazine for treatment of refractory agitation	N=4 Age (mean): 8.4 yrs (range): 0.7-15 yrs M:F = 3:1	1 mg TID or QID IV, 10 mg bid enterally, 6.25 mg bid orally	NR	NR	No adverse effects reported	All patients received concurrent medications which may cause EPS. However EPS not reported as an adverse effect experienced by any patient
Eshel (1994)[17]	Case report of methotrimeprazine treatment and respiratory distress in a child	N=1 Age: 11 yrs Male	125 mg PO daily	NR (at least 3 weeks)	NR	dyspnea lethargy, hypothermia, bradycardia and prolonged QTc	No additional concomitant medications were administered. Methotrimeprazine was discontinued, supportive care initiated. ECG at 5 weeks revealed normal sinus rhythm and QTc

ECG: electrocardiogram; EPS: extrapyramidal symptoms; NMS: neuroleptic malignant syndrome; NR: not reported; PRN: as needed; QTc= corrected QT interval

Supplementary Table VI: Prevention of CINV in Patients with Refractory CINV – Summary of Included Studies

First Author (Year)	Study Design, Objective and Population	Definition of Refractory CINV and CINV Prophylaxis Provided During Previous Chemo Blocks	Antiemetic Interventions	Proportion with Complete Control of Refractory Nausea and/or Vomiting
Pediatric Studies				
5HT-3 Antagonist – Tropisetron				
Hachimi-Idrissi (1993)[18]	<ul style="list-style-type: none"> Prospective open-label trial Aim: Determine the efficacy and tolerability of ICS 205-930 (tropisetron) in children with refractory CINV N = 19 (169 chemotherapy courses) Children with cancer receiving chemotherapy over 1-5 days Median age: 9 yrs; range: 2-16yrs CINV assessment: parent report Emetogenicity classification: moderately or highly emetogenic 	<p>Grade 3 emesis (> 4 episodes of vomiting/day)</p> <p>Previous prophylactic regimen: Alizapride 4-6mg/kg/day or metoclopramide 5mg/kg day</p> <p>Guideline consistent antiemetic prophylaxis: no</p>	<p>Tropisetron 0.2mg/kg IV (max 5mg) once daily on each day prior to chemo and then PO for 5 days after chemo if patients received cisplatin</p>	<p>Proportion of courses with complete control of vomiting: 131/169 (77.5%)</p> <p>Proportion with complete control of nausea: not reported</p> <p>Proportion with complete control of CINV: not reported</p> <p>Timeframe of assessments: not reported</p>
Aprepitant				
Bauters (2013)[19]	<ul style="list-style-type: none"> Retrospective, observational study Aim: Determine the efficacy of aprepitant in children and adolescents with refractory CINV N = 20 (104 chemotherapy cycles) Children with cancer receiving chemotherapy Mean age: 14 yrs; range: 8-16yrs CINV assessment: Only vomiting evaluated Emetogenicity classification: moderately or highly emetogenic 	<p>Intolerable and uncontrollable emesis in the preceding chemo cycle</p> <p>Previous prophylactic regimen: Tropisetron 0.2mg/kg IV once daily (max 5mg) or ondansetron 5-8mg/m² bid (max 8mg/dose) or granisetron 0.04mg/kg once daily (max 9mg) + dexamethasone 3mg/m² once-twice daily given at least 30 minutes prior to chemo</p> <p>Guideline consistent antiemetic prophylaxis: yes (no for patients receiving HEC > 12yrs where aprepitant use permitted)</p>	<p>Day 1: Aprepitant 125mg PO once</p> <p>Days 2-3: Aprepitant 80mg po once daily</p> <p>Plus Tropisetron 0.2mg/kg IV once daily (max 5mg) or ondansetron 5-8mg/m² bid (max 8mg/dose) or granisetron 0.04mg/kg once daily (max 9mg) + dexamethasone 1.5mg/m² once-twice daily given at least 30 minutes prior to chemo</p>	<p>Proportion with complete control of vomiting: patients: 10/20 (50%) courses: 89/104 (85.6%)</p> <p>Proportion with complete control of nausea: not reported</p> <p>Proportion with complete control of CINV: not reported</p> <p>Timeframe of assessments: not reported</p>

First Author (Year)	Study Design, Objective and Population	Definition of Refractory CINV and CINV Prophylaxis Provided During Previous Chemo Blocks	Antiemetic Interventions	Proportion with Complete Control of Refractory Nausea and/or Vomiting
Adult Studies				
5HT-3 Antagonists – Granisetron				
Arevalo-Araujo (2013)[20] [abstract]	<ul style="list-style-type: none"> Prospective trial (abstract) Aim: Determine the antiemetic efficacy of APF530 (sustained formulation of granisetron) in refractory patients N = 72 Adults with cancer receiving chemotherapy Median age: not reported CINV assessment: not reported Emetogenicity classification: moderately or highly emetogenic 	<p>Failure to achieve a complete response (no emesis or rescue medication) with palonosetron during cycle 1</p> <p>Previous Prophylactic regimen: Palonosetron 0.25mg IV</p> <p>Guideline consistent antiemetic prophylaxis: no</p>	APF530 (sustained formulation of granisetron) 500mg SC	<p>Proportion with complete control of vomiting: not reported</p> <p>Proportion with complete control of nausea: not reported</p> <p>Proportion with complete CINV response (defined as no emesis or rescue medications): acute phase: MEC: 11/19 (57.9%) HEC: 7/12 (58.3%) delayed phase: MEC: 13/34 (38.2%) HEC: 15/33 (45.5%)</p> <p>Timeframe of assessments: not reported/unable to determine</p>
Carmichael (1998)[21]	<ul style="list-style-type: none"> Prospective open-label trial Aim: evaluate the tolerability and antiemetic efficacy of granisetron in refractory patients N = 456 Adults with cancer receiving chemotherapy Median age: not reported for refractory cohort CINV assessment: patient report and direct observation for a minimum of 2hrs from the onset of chemotherapy administration Emetogenicity classification: unable to determine/not reported 	<p>Failed antiemetic therapy during the previous cycle</p> <p>Previous prophylactic regimens: One or more of the following: metoclopramide, Dexamethasone, alizapride, ondansetron, chlorpromazine, "other"</p> <p>Guideline consistent antiemetic prophylaxis: unable to determine/not reported</p>	Granisetron 3mg IV once 5min prior to chemo + up to 2 additional doses of granisetron 3mg IV with at least 10min between doses	<p>Proportion with complete control of vomiting: not reported</p> <p>Proportion with complete control of nausea: not reported</p> <p>Overall proportion with complete CINV response (defined as no vomiting, mild or absent nausea, and no rescue medications): 237/456 (52%)</p> <p>Timeframe of assessments: acute phase (first 24hrs following chemo)</p>

First Author (Year)	Study Design, Objective and Population	Definition of Refractory CINV and CINV Prophylaxis Provided During Previous Chemo Blocks	Antiemetic Interventions	Proportion with Complete Control of Refractory Nausea and/or Vomiting
De Wit (2001)[22]	<ul style="list-style-type: none"> ▪ Randomized, double-blind trial ▪ Aim: evaluate the efficacy of crossing over to granisetron after CINV failure while receiving ondansetron ▪ N = 40 ▪ Adults with cancer receiving cisplatin-or cyclophosphamide-based chemotherapy ▪ Median age: G1: 46yrs; range: 29-71yrs G2: 46yrs; range: 30-73yrs ▪ CINV assessment: patient report ▪ Emetogenicity classification: highly emetogenic 	<p>≥ 2 vomits and/or severe nausea (no significant intake possible) or nausea lasting > 4hrs</p> <p>Previous prophylactic regimen: Day 1: Ondansetron 8mg IV + dexamethasone 10mg IV</p> <p>Guideline consistent antiemetic prophylaxis: no</p>	<p>G1: Granisetron 3mg IV + dexamethasone 10mg IV (n=19)</p> <p>G2: Ondansetron 8mg IV + dexamethasone 10mg IV (n=21)</p>	<p>Proportion with complete control of vomiting: not reported</p> <p>Proportion with complete control of nausea: not reported</p> <p>Proportion with complete CINV protection (defined as no vomiting and no or mild nausea): G1: 9/19 (47.4%) G2: 1/21 (4.8%) p=0.005</p> <p>Timeframe of assessments: acute phase (first 24hrs following chemo)</p>
Sigsgaard (2000)[23]	<ul style="list-style-type: none"> ▪ Prospective open-label trial ▪ Aim: Determine the antiemetic efficacy of granisetron + prednisolone + metopimazine in refractory patients ▪ N = 25 ▪ Adults with breast cancer receiving cyclophosphamide + fluorouracil + either methotrexate or epirubicin ▪ Median age: 45yrs; range: 29-66yrs ▪ CINV assessment: patient report ▪ Emetogenicity classification: moderately emetogenic 	<p>≥ 5 emetic episodes during any of days 1-5 following chemo or patients not satisfied with the antiemetic treatment during a previous chemotherapy cycle</p> <p>Previous prophylactic regimen: Either granisetron 3mg IV once OR prednisolone 25mg PO once a day x 3 days + metopimazine 30mg PO qid x 3 days</p> <p>Guideline consistent antiemetic prophylaxis: no</p>	<p>Granisetron 3mg IV once + prednisolone 25mg PO once a day x 3 days + metopimazine 30mg PO qid x 3 days</p>	<p>Proportion of cycles with complete control of vomiting: acute phase: 100/113 (88.5%) delayed phase: 107/113 (94.7%)</p> <p>Proportion of cycles with complete control of nausea: acute phase: 49/113 (43.4%) delayed phase: 56/113 (49.6%)</p> <p>Proportion of cycles with complete control of CINV (defined as no emetic episodes (including vomits and retches) and no or mild nausea): acute phase: 85/113 (75.2%) delayed phase: 93/113 (82.3%)</p> <p>Timeframe of assessments: acute and delayed phases (q24h x 5 days)</p>

First Author (Year)	Study Design, Objective and Population	Definition of Refractory CINV and CINV Prophylaxis Provided During Previous Chemo Blocks	Antiemetic Interventions	Proportion with Complete Control of Refractory Nausea and/or Vomiting
5HT-3 Antagonists – Ondansetron				
Campora (1991)[24]	<ul style="list-style-type: none"> Prospective open-label trial Aim: Evaluate the efficacy of ondansetron for antiemetic prophylaxis in refractory patients N = 24 Adults with cancer receiving chemotherapy Median age: 53yrs; range: 21-70yrs CINV assessment: patient report Emetogenicity classification: moderately or highly emetogenic 	<p>> 15 emetic episodes within 24hrs of therapy while receiving combination antiemetics</p> <p>Previous prophylactic regimen: Metoclopramide 0.5-1mg/kg IV + methylprednisolone 40-125mg IV prior to chemo and repeated after 2hrs: 24/24 pts Lorazepam 2mg IV prior to chemo: 7/24 pts</p> <p>Guideline consistent antiemetic prophylaxis: no</p>	Ondansetron 8mg PO prior to chemo and repeated after 6 and 12hrs on day 1, then 8mg PO tid on days 2-5	<p>Proportion with complete control of vomiting: acute phase (day 1): 10/24 (41.7%) day 2: 20/24 (83.3%) delayed phase (days 3-5): 24/24 (100%)</p> <p>Proportion with complete control of nausea: not reported</p> <p>Proportion with complete control of CINV: not reported</p> <p>Timeframe of assessments: acute and delayed phases (q24h x 5 days)</p>
De Wit (2001) [22]	<ul style="list-style-type: none"> Randomized, double-blind trial Aim: evaluate the efficacy of crossing over to granisetron after CINV failure while receiving ondansetron N = 40 Adults with cancer receiving cisplatin-or cyclophosphamide-based chemotherapy Median age: G1: 46yrs; range: 29-71yrs G2: 46yrs; range: 30-73yrs CINV assessment: patient report Emetogenicity classification: highly emetogenic 	<p>≥ 2 vomits and/or severe nausea (no significant intake possible) or nausea lasting > 4hrs</p> <p>Previous prophylactic regimen: Day 1: Ondansetron 8mg IV + dexamethasone 10mg IV</p> <p>Guideline consistent antiemetic prophylaxis: no</p>	<p>G1: Granisetron 3mg IV + dexamethasone 10mg IV (n=19)</p> <p>G2: Ondansetron 8mg IV + dexamethasone 10mg IV (n=21)</p>	<p>Proportion with complete control of vomiting: not reported</p> <p>Proportion with complete control of nausea: not reported</p> <p>Proportion with complete CINV protection (defined as no vomiting and no or mild nausea): G1: 9/19 (47.4%) G2: 1/21 (4.8%) p=0.005</p> <p>Timeframe of assessments: acute phase (first 24hrs following chemo)</p>
Du Bois (1990)[25]	<ul style="list-style-type: none"> Prospective open-label trial Aim: Determine the antiemetic efficacy of ondansetron N = 17 (34 chemotherapy cycles) Adults with cancer receiving platinum based chemotherapy Median age: 63.5yrs; range 41-75yrs CINV assessment: Patient report Emetogenicity classification: highly emetogenic 	<p>Severe emesis refractory to standard antiemetic regimen</p> <p>Previous prophylactic regimen: Metoclopramide (2-3mg/kg) ± additional antiemetics</p> <p>Guideline consistent antiemetic prophylaxis: no</p>	<p>Day 1: Ondansetron 8mg IV 30 min prior to chemo, then 1mg/hr as a continuous infusion over 8-24hrs</p> <p>Day 2-5: Ondansetron 8mg PO TID 1hr before food</p>	<p>Proportion of cycles with complete control of vomiting: 7/34 (20.6%)</p> <p>Proportion with complete control of nausea: not reported</p> <p>Proportion with complete control of CINV: not reported</p> <p>Timeframe of assessments: acute and delayed phases (q24h x 8 days)</p>

First Author (Year)	Study Design, Objective and Population	Definition of Refractory CINV and CINV Prophylaxis Provided During Previous Chemo Blocks	Antiemetic Interventions	Proportion with Complete Control of Refractory Nausea and/or Vomiting
Harvey (1991)[26]	<ul style="list-style-type: none"> Prospective open-label trial Aim: Report on experience with ondansetron for antiemetic prophylaxis in refractory patients N = 25 Adults with ovarian cancer or testicular germ cell tumors receiving carboplatin + etoposide Median age: 52yrs; range: 24-68yrs CINV assessment: patient report Emetogenicity classification: highly emetogenic 	<p>Multiple episodes of vomiting (≥ 3) during the first 24hrs of the previous course of chemo</p> <p>Previous prophylactic regimens: Metoclopramide 2mg/kg q2h x 3-5 doses: 22 pts Metoclopramide 0.5mg-1/kg IV q2h x 4 doses: 3 pts Lorazepam 1-2mg PO pre-chemo: 16 pts Dexamethasone 8mg IV q6h x 2 doses: 13 pts Haloperidol 2.5mg IV q4h prn: 8 pts Scopaderm patch: 15 pts</p> <p>Guideline consistent antiemetic prophylaxis: no</p>	<p>Ondansetron 4mg IV and 4mg PO prior to chemo, then 8mg PO 6 and 12hrs later, and 8mg PO tid for an additional 4 days</p>	<p>Proportion with complete control of vomiting: acute phase: 17/25 (68%) delayed phase: 14/25 (56%)</p> <p>Proportion with complete control of nausea acute phase: 14/25 (56%) delayed phase: 12/25 (48%)</p> <p>Proportion with complete control of CINV: not reported</p> <p>Timeframe of assessments: acute and delayed phases (q24h x 5 days)</p>
Mitchell (1992)[27]	<ul style="list-style-type: none"> Prospective open-label trial Aim: Report on experience with ondansetron in refractory patients N = 91 Adults with cancer receiving chemotherapy Median age: G1 (non-cisplatin chemotherapy): 47 yrs; range: 19-72yrs G2 (cisplatin-based chemotherapy): 33yrs; range: 18-44yrs CINV assessment: patient report (daily) and nurse report (first 24hrs) Emetogenicity classification: minimal, low, moderate and highly emetogenic agents 	<p>At least 3 (non-cisplatin chemo) or 5 (cisplatin-based chemo) episodes of vomiting in the first 24hrs following previous chemo</p> <p>Previous prophylactic regimen: G1: Metoclopramide $<0.5\text{mg/kg}$ IV/PO x 1-6 doses: 35 pts Metoclopramide 0.5mg-2/kg IV x 1-5 doses: 30 pts Lorazepam 1-5mg PO: proportion of pts not reported Dexamethasone 8mg IV q6h x 2-4 doses: proportion of pts not reported Hyoscine transdermal patch: proportion of pts not reported G2: Metoclopramide 1-2mg/kg IV x 3-5 doses: proportion of pts not reported Lorazepam: proportion of pts not reported Dexamethasone: proportion of pts not reported Haloperidol: proportion of pts not reported</p> <p>Guideline consistent antiemetic prophylaxis: unable to determine/not reported</p>	<p>G1: Ondansetron 4mg IV and 4mg PO prior to chemo, then 8mg PO after 6 and 12hrs, then 8mg PO q8h on days 2-5 (n=75) G2: Ondansetron 8mg IV prior to chemo, then 1mg/hr infusion for 8hrs and 8mg PO at the end of the infusion, then 8mg PO q8h on days 2-6 (n=16)</p>	<p>Proportion with complete control of vomiting: acute phase: G1: 52/75 (69%) G2: 0/16 (0%) delayed phase: G1: 45/75 (60%) G2: 1/16 (6.3%)</p> <p>Proportion with complete control of nausea: acute phase: G1: 38/75 (51%) G2: 2/16 (12.5%) delayed phase: G1: 27/75 (36%) G2: 3/16 (18.8%)</p> <p>Proportion with complete control of CINV: not reported</p> <p>Timeframe of assessments: acute and delayed phases (q24h x 5-6 days)</p>

First Author (Year)	Study Design, Objective and Population	Definition of Refractory CINV and CINV Prophylaxis Provided During Previous Chemo Blocks	Antiemetic Interventions	Proportion with Complete Control of Refractory Nausea and/or Vomiting
Seynaeve (1991)[28]	<ul style="list-style-type: none"> ▪ Prospective open-label trial ▪ Aim: Evaluate the efficacy of 2 dosage regimens of ondansetron for antiemetic prophylaxis in refractory patients ▪ N = 35 ▪ Adults with cancer receiving chemotherapy ▪ Median age: G1: 45yrs; range: 20-66yrs G2: 3yrs; range: 37-72yrs (Note: median age likely publication error based on the range reported by the authors) ▪ CINV assessment: patient report ▪ Emetogenicity classification: moderately or highly emetogenic 	<p>> 5 emetic episodes while receiving previous standard antiemetics</p> <p>Previous prophylactic regimen: Alizapride or metoclopramide 5-6mg/kg/day</p> <p>Guideline consistent antiemetic prophylaxis: no</p>	<p>G1: Ondansetron 4mg IV and 4mg PO prior to chemo, then 4mg PO qid for an additional 4 days (n=19)</p> <p>G2: Ondansetron 8mg IV prior to chemo, then 8mg PO tid for an additional 4 days (n=16)</p>	<p>Proportion with complete control of vomiting: acute phase: G1: 10/19 (62.5%) G2: 7/10 (70%) delayed phase: G1: 12/16 (75%) G2: 6/16 (37.5%)</p> <p>Proportion with complete control of nausea: acute phase: G1: 5/19 (26%) G2: 7/16 (43.75%)</p> <p>Proportion with complete control of CINV: not reported</p> <p>Timeframe of assessments: acute and delayed phases (q24h x 5 days)</p>
Smith (1991)[29]	<ul style="list-style-type: none"> ▪ Prospective open-label trial ▪ Aim: Assess the efficacy of ondansetron for antiemetic prophylaxis in patients receiving carboplatin ▪ N = 16 ▪ Adults with ovarian cancer receiving carboplatin ▪ Median age: 58yrs; range: 23-73yrs ▪ CINV assessment: patient report ▪ Emetogenicity classification: highly emetogenic 	<p>>2 emetic episodes in the 24hrs following carboplatin</p> <p>Previous prophylactic regimen: Days 1: dexamethasone 8mg PO tid + metoclopramide 20mg PO qid beginning prior to chemo</p> <p>Guideline consistent antiemetic prophylaxis: no</p>	<p>Ondansetron 4mg IV and 4mg PO prior to chemo, then 8mg PO tid x 5 days</p>	<p>Proportion with complete control of vomiting: acute phase: 11/16 (69%) acute and delayed phases (days 1-5): 6/16 (46%)</p> <p>Proportion with complete control of nausea: not reported</p> <p>Proportion with complete control of CINV: not reported</p> <p>Timeframe of assessments: acute and delayed phases (q24hr x 5 days)</p>

First Author (Year)	Study Design, Objective and Population	Definition of Refractory CINV and CINV Prophylaxis Provided During Previous Chemo Blocks	Antiemetic Interventions	Proportion with Complete Control of Refractory Nausea and/or Vomiting
5HT-3 Antagonists – Palonosetron				
Hesketh (2012)[30]	<ul style="list-style-type: none"> ▪ Prospective open-label trial ▪ Aim: Determine the efficacy and safety of a single IV dose of palonosetron for prevention of CINV ▪ N = 34 ▪ Adults with cancer receiving chemotherapy who experienced refractory CINV ▪ Mean age: 64.6 ± 13.77yrs ▪ CINV assessment: patient report ▪ Emetogenicity classification: low emetogenicity 	<p>Vomiting and/or at least moderate nausea during cycle 1</p> <p>Previous prophylactic regimen: not reported</p> <p>Guideline consistent antiemetic prophylaxis: unable to determine/not reported</p>	Day 1: Palonosetron 0.25mg IV 30min prior to chemo	<p>Proportion with complete control of vomiting: acute phase: 31/34 (91.2%) delayed phase: 27/34 (79.4%)</p> <p>Proportion with complete control of nausea: acute phase: 25/34 (73.5%) delayed phase: 18/34 (52.9%)</p> <p>Proportion with complete control of CINV (defined as no emetic episodes, no rescue medications and no more than mild nausea): acute phase: 29/34 (85.3%) delayed phase: 22/34 (64.7%)</p> <p>Timeframe of assessments: acute and delayed phases (q24h x 5 days)</p>
Massa (2009)[31]	<ul style="list-style-type: none"> ▪ Prospective open label trial ▪ Aim: Determine if palonosetron is able to prevent CINV in refractory patients ▪ N = 47 ▪ Adults with cancer receiving chemotherapy ▪ Mean age: 60.7 ± 3yrs; range: 32-89yrs ▪ CINV assessment: patient report ▪ Emetogenicity classification: moderately or highly emetogenic 	<p>Grade 3-4 CINV during the first course of chemo that failed to respond to a different 5-HT3 antagonist</p> <p>Previous prophylactic regimen: D1: 5-HT3 antagonist (granisetron 1mg IV or ondansetron 8mg IV) + dexamethasone 8mg or 12mg IV D2-3 or 4: Dexamethasone 8mg PO</p> <p>Guideline consistent antiemetic prophylaxis: yes for MEC, no for HEC</p>	<p>D1: Palonosetron 0.25mg IV + dexamethasone 16mg IV D2-3: Dexamethasone 8mg IV q12h D4: Dexamethasone 4mg IV q12h ± metoclopramide IM prn</p>	<p>Proportion with complete control of vomiting: not reported</p> <p>Proportion with complete control of nausea: not reported</p> <p>Proportion with complete control of CINV (defined as no emetic episodes, no rescue medications and no more than mild nausea): acute phase: 36/47 (76.6%) delayed phase: 38/47 (80.9%)</p> <p>Timeframe of assessments: acute and delayed phases (q24h x 5 days)</p>

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5HT-3 Antagonists – Tropisetron				
Bruntsch (1993)[32]	<ul style="list-style-type: none"> ▪ Prospective, randomized, open-label trial ▪ Aim: Determine the efficacy of tropisetron in refractory patients compared to conventional antiemetic treatment ▪ N = 115 ▪ Adults with cancer receiving chemotherapy ▪ Mean age: 49 yrs ▪ CINV assessment: patient report plus report by an additional individual for the first 24hrs ▪ Emetogenicity classification: low, moderate and highly emetogenic agents 	<p>≥ 3 vomiting episodes within 24hrs during previous chemo cycles</p> <p>Previous prophylactic regimen: individually prescribed for each patient by investigator</p> <p>Guideline consistent antiemetic prophylaxis: unable to determine/not reported</p>	Tropisetron 5mg IV/PO beginning the day before chemo and continuing for at least 5 days (duration dependent on duration of chemo)	<p>Proportion with complete control of vomiting: acute phase: 60/115 (52%)</p> <p>Proportion with complete control of nausea: acute phase: 37/115 (32%)</p> <p>Proportion with complete control of CINV: not reported</p> <p>Timeframe of assessments: acute and delayed phases (q24h x 6 days)</p>
Falkson (1995)[33]	<ul style="list-style-type: none"> ▪ Prospective open-label trial ▪ Aim: Determine the antiemetic efficacy and safety of tropisetron in refractory patients ▪ N = 164 ▪ Adolescents and adults with cancer receiving chemotherapy ▪ Median age: 48yrs; range: 14-88yrs ▪ CINV assessment: patient report ▪ Emetogenicity classification: moderately emetogenic 	<p>≥ 5 nausea and vomiting episodes despite antiemetic treatment during previous courses of chemo</p> <p>Previous prophylactic regimens:</p> <p>G1: Ondansetron: 46 pts G2: Granisetron: 39 pts G3: Metoclopramide: 40 pts G4: Chlorpromazine: 15 pts G5: Prochlorperazine: 13 pts G6: Cyclizine: 6 pts G7: Hydroxyzine: 5 pts</p> <p>Guideline consistent antiemetic prophylaxis: unable to determine/not reported</p>	<p>Day 1: Tropisetron 5mg IV</p> <p>Days 2-5: Tropisetron 5mg PO once daily</p>	<p>Proportion with complete control of vomiting: acute phase: 29/81 (36%) delayed phase: 33/81 (41%)</p> <p>Proportion with complete control of nausea: not reported</p> <p>Proportion with complete control of CINV: acute phase: 69/164 (42%)</p> <p>Timeframe of assessments: acute and delayed phases (q24h x 5 days)</p>

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Fosaprepitant				
Covens [abstract] (2014)[34]	<ul style="list-style-type: none"> Prospective open-label study Aim: Demonstrate that fosaprepitant improves vomiting control N= 106 Adults with breast or gynaecological cancer with refractory CINV in the first cycle Median age: 45 yrs (breast cancer); 55 yrs (gynaecological cancer) CINV assessment: not reported Emetogenicity: moderately or highly emetogenic 	<p>Vomiting or retching during the first 5 days in cycle 1.</p> <p>Previous prophylactic regimen: not reported</p> <p>Guideline consistent antiemetic prophylaxis: unable to determine</p>	Not reported	<p>Proportion with complete control of vomiting and retching: 58%</p> <p>Timeframe of assessments: within first 120 hours after initiation of chemotherapy</p>
Aprepitant				
Abbrederis (2009)[35]	<ul style="list-style-type: none"> Prospective open-label trial Aim: evaluate the incidence of CINV during treatment of gastrointestinal tumors with chemotherapy and assess the effect of aprepitant after failure of first line antiemetic prophylaxis N = 7 Adults with gastrointestinal tumors Median age: not reported for refractory cohort CINV assessment: patient report Emetogenicity classification: moderately or highly emetogenic 	<p>CINV \geq grade 2 (NCI definition) during the first course of chemo</p> <p>Previous prophylactic regimen: Day 1: Granisetron 1.5mg IV + dexamethasone 12mg IV Days 2-3: Dexamethasone 8mg PO once daily</p> <p>Guideline consistent antiemetic prophylaxis: yes for MEC, no for HEC</p>	<p>Day 1: Aprepitant 125mg PO Days 2-3: Aprepitant 80mg PO + previous prophylactic regimen described</p>	<p>Proportion with complete control of vomiting: not reported</p> <p>Proportion with complete control of nausea: not reported</p> <p>Proportion with “complete relief” from CINV (assumed to be complete control): 5/7 (71%) p=0.096</p> <p>Timeframe of assessments: not reported</p>

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Caranana [abstract] (2013) [36]	<ul style="list-style-type: none"> Prospective open-label trial Aim: Evaluate efficacy of aprepitant in addition to standard antiemetic prophylaxis N = 24 Adults with breast cancer receiving docetaxel 75mg/m² + cyclophosphamide 600mg/m² IV with refractory CINV in the first cycle Median age: not reported for refractory cohort CINV assessment: patient diary and Functional Living Index-Emesis questionnaire Emetogenicity classification: moderately emetogenic 	<p>Vomiting or receipt of rescue antiemetic therapy despite prophylaxis with a 5-HT3 antagonist and dexamethasone in cycle 1</p> <p>Previous prophylactic regimen: Day 0: dexamethasone 8mg PO at night Day 1: dexamethasone 8mg TID PO + 5-HT3 antagonist Day 2 and 3: dexamethasone 8mg BID PO</p> <p>Guideline consistent antiemetic prophylaxis: no</p>	<p>Day 1: Aprepitant 125mg PO Days 2-3: Aprepitant 80mg PO once daily + previous prophylactic regimen described</p> <p>Previous dexamethasone dose was reduced by 50%.</p>	<p>Proportion with complete control of vomiting and no use of rescue antiemetic treatment: 14/24 (56%)</p> <p>Proportion with complete control of nausea: not reported</p> <p>Proportion with complete control of CINV: not reported</p> <p>Timeframe of assessments: within first 120 hours after initiation of chemotherapy</p>
Fukazawa (2011)[37]	<ul style="list-style-type: none"> Trial design: Prospective, open-label trial Aim: evaluate the effect of aprepitant on acute and delayed nausea and vomiting N = 13 Adults with colorectal cancer receiving chemotherapy Mean age: 65±11yrs CINV assessment: Patient report (diary) Emetogenicity classification: moderately emetogenic 	<p>Definition: Delayed CINV occurring in the previous chemotherapy block</p> <p>Previous prophylactic regimen: Granisetron 3mg IV + dexamethasone 8mg IV 30-60min pre-chemo</p> <p>Guideline consistent antiemetic prophylaxis: yes</p>	<p>Day 1: Aprepitant 125mg PO + granisetron 3mg IV + dexamethasone 4mg IV 30-60min pre-chemo Days 2-3: Aprepitant 80mg PO 1 hr pre-chemo</p>	<p>Proportion with complete control of vomiting: acute phase: 13/13 (100%) delayed phase: 13/13 (100%)</p> <p>Proportion with complete control of nausea: acute phase: 10/13 (76.9%) delayed phase: 6/13 (46.2%), p<0.05</p> <p>Proportion with complete control of CINV (defined as no emesis, no rescue therapy, and no significant nausea): acute phase: 12/13 (92.3%) delayed phase: 9/13 (69.2%)</p> <p>Timeframe of assessments: acute and delayed phases (q24h x 5 days)</p>

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Hesketh (2009)[38]	<ul style="list-style-type: none"> Prospective open-label trial Aim: Determine the antiemetic activity of aprepitant when used as salvage antiemetic therapy N = 44 Adults with breast cancer receiving anthracycline + cyclophosphamide Median age: not reported for refractory cohort CINV assessment: patient report Emetogenicity classification: moderately emetogenic 	<p>Any vomiting, nausea, or use of rescue antiemetic medications during cycle 1</p> <p>Previous Prophylactic regimen: Day 1: A 5-HT3 antagonist (ondansetron 8mg IV or 24mg PO, dolasetron 100mg IV or PO, or granisetron 1mg IV or 2mg PO) + dexamethasone 8-10mg IV or PO Days 2-3: Dexamethasone 4mg PO bid</p> <p>Guideline consistent antiemetic prophylaxis: yes</p>	<p>Day 1: Aprepitant 125mg PO + a 5-HT3 antagonist + dexamethasone 8-10mg IV or PO</p> <p>Days 2-3: Aprepitant 80mg PO + dexamethasone 4mg PO once daily</p>	<p>Proportion with complete control of vomiting (acute and delayed phases): 36/44 (82%)</p> <p>Proportion with complete control of nausea (acute and delayed phases): 8/44 (18%)</p> <p>Proportion with complete control of CINV (including no use of rescue antiemetics): acute phase: 13/44 (30%) delayed phase: 10/44 (23%)</p> <p>Timeframe of assessments: acute and delayed phases (q24h x 5 days)</p>
Hu (2014) [39]	<ul style="list-style-type: none"> Prospective open-label study Aim: Evaluate effectiveness of aprepitant in addition to standard antiemetic prophylaxis N = 25 Adults with cancer receiving cisplatin 75mg/m2/dose with refractory CIV in the first cycle Median age: 61 yrs (range: 32 to 72 yrs) CINV assessment: patient diary Emetogenicity: highly emetogenic 	<p>Vomiting greater than or equal to NCI-CTCAEv3.0 and receipt of rescue antiemetic therapy despite prophylaxis with granisetron and dexamethasone in cycle 1</p> <p>Previous prophylactic regimen: Day 1: granisetron 3mg IV x 1 dose and dexamethasone 10mg IV x 1 dose Day 1-3: metoclopramide 10mg TID PO and dexamethasone 1.5mg TID PO</p> <p>Guideline consistent antiemetic prophylaxis: no</p>	<p>Day 1: Aprepitant 125mg PO</p> <p>Days 2-3: Aprepitant 80mg PO once daily + previous prophylactic regimen described</p> <p>Dexamethasone dose was not reduced.</p>	<p>Proportion with complete control of vomiting and no use of rescue antiemetic treatment: 16/25 (64%)</p> <p>Proportion with complete control of nausea: acute phase: 6/8 (75%) delayed phase: 7/25 (28%)</p> <p>Proportion with complete control of CINV: 7/25 (28%)</p> <p>Timeframe of assessments: within first 120 hours after initiation of chemotherapy</p>
Oechsle (2006)[40]	<ul style="list-style-type: none"> Prospective open-label trial Aim: evaluate the efficacy of the addition of aprepitant in refractory patients N = 34 Adults with cancer receiving chemotherapy Median age: 51yrs; range: 23-77yrs CINV assessment: patient report Emetogenicity classification: moderately or highly emetogenic 	<p>At least 2 days of nausea and/or emesis considered intolerable by the patient despite the use of guideline-based antiemetic standard prophylaxis</p> <p>Previous prophylactic regimen: Acute: Granisetron 1-3mg IV once daily + dexamethasone 4-8mg IV at least twice daily or 20mg IV once daily on the days of chemo Delayed: Dexamethasone 4mg IV/PO bid + metoclopramide 10mg PO tid x 3 days after completion of chemo</p> <p>Guideline consistent antiemetic prophylaxis: yes For MEC, no for HEC</p>	<p>Day 1: Aprepitant 125mg PO + granisetron 1-3mg IV + dexamethasone 4-8mg IV/PO x 2 doses</p> <p>All further days of chemo: Aprepitant 80mg PO + granisetron 1-3mg IV + dexamethasone 4-8mg IV/PO bid</p> <p>Days 2-3 after chemo: Aprepitant 80mg PO + dexamethasone 4mg PO bid + metoclopramide 20mg PO tid</p>	<p>Proportion with complete control of vomiting (acute and delayed phases): 26/34 (76.5%)</p> <p>Proportion with complete control of nausea: not reported</p> <p>Proportion with complete control of CINV: not reported</p> <p>Timeframe of assessments: acute and delayed phases (q24h x 5 days after the last dose of chemo)</p>

First Author (Year)	Study Design, Objective and Population	Definition of Refractory CINV and CINV Prophylaxis Provided During Previous Chemo Blocks	Antiemetic Interventions	Proportion with Complete Control of Refractory Nausea and/or Vomiting
Wu (2012)[41]	<ul style="list-style-type: none"> Prospective open-label trial Aim: Evaluate aprepitant as secondary antiemetic prophylaxis N = 40 Adults with cancer receiving cisplatin + 5-fluorouracil ± other chemotherapy with refractory CINV Median age: not reported for refractory cohort CINV assessment: investigator (physicians and nurses) and patient report Emetogenicity classification: highly emetogenic 	<p>Failure to achieve complete protection from vomiting with a 5-HT3 antagonist and dexamethasone in cycle 1</p> <p>Previous prophylactic regimen: Day 1: Granisetron 3mg IV + dexamethasone 20mg IV ± diphenhydramine 30mg IM q6h prn Additional days chemo was administered: Dexamethasone 5mg IV q12h ± diphenhydramine 30mg IM q6h prn</p> <p>Guideline consistent antiemetic prophylaxis: no</p>	<p>Day 1: Aprepitant 125mg PO Days 2-3: Aprepitant 80mg PO once daily + previous prophylactic regimen described</p>	<p>Proportion with complete control of vomiting: acute phase: 39/40 (97.5%) delayed phase: 26/40 (65%)</p> <p>Proportion with complete control of nausea: acute phase: 37/40 (92.5%) delayed phase: 24/40 (60%)</p> <p>Proportion with complete control of CINV: not reported</p> <p>Timeframe of assessments: acute and delayed phases (q24h x 6 days)</p>
Benzodiazepines (Clonazepam, Lorazepam, and Midazolam)				
Hayashi (2010)[42]	<ul style="list-style-type: none"> Prospective open-label trial Aim: Evaluate the efficacy of clonazepam in preventing CINV in refractory patients N = 7 (10 chemotherapy courses) Adults with cancer receiving cisplatin-based chemotherapy Median age: 61yrs; range: 43-73yrs CINV assessment: patient report Emetogenicity classification: highly emetogenic 	<p>Vomiting despite conventional antiemetic therapy</p> <p>Previous prophylactic regimen: Day 1: Granisetron 3mg IV + dexamethasone 12mg IV 60min prior to chemo Days 2-4: Dexamethasone 4mg IV once daily</p> <p>Guideline consistent antiemetic prophylaxis: no</p>	<p>Day -1: Clonazepam 0.5mg or 1mg PO beginning 12hrs prior to chemo Days 1-4: Clonazepam 0.5mg or 1mg PO once daily + previous prophylactic regimen described</p>	<p>Proportion of cycles with complete control of vomiting: acute phase: 8/10 (80%) delayed phase: 6/10 (60%)</p> <p>Proportion with complete control of nausea: not reported</p> <p>Proportion with complete control of CINV: not reported</p> <p>Timeframe of assessments: acute and delayed phases (q24h x 5 days)</p>
Mandala (2005)[43]	<ul style="list-style-type: none"> Prospective open-label trial Aim: evaluate the efficacy of the addition of midazolam to dexamethasone and granisetron for refractory acute CINV N = 26 Adults with cancer receiving cisplatin-based chemotherapy Median age: 58yrs; range: 30-70yrs CINV assessment: patient report and physician assessment Emetogenicity classification: highly emetogenic 	<p>Grade 2 acute nausea (oral intake significantly reduced) and/or vomiting (2-5 emetic episodes in 24hrs)</p> <p>Previous prophylactic regimen: Day 1: Granisetron 3mg IV + dexamethasone 20mg IV Days 2-5: Dexamethasone 4mg PO once daily + metoclopramide 20mg PO tid</p> <p>Guideline consistent antiemetic prophylaxis: no</p>	<p>Midazolam 0.04mg/kg continuous infusion during administration of chemo + previous prophylactic regimen described</p>	<p>Proportion with complete control of vomiting: acute phase: 6/26 (23%) delayed phase: 9/26 (34.6%)</p> <p>Proportion with complete control of nausea: acute phase: 5/26 (19.2%) delayed phase: 6/26 (23%)</p> <p>Proportion with complete control of CINV: not reported</p> <p>Timeframe of assessments: acute and delayed phases (q24h, duration not reported)</p>

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Mughal (1983)[44]	<ul style="list-style-type: none"> ▪ Prospective open-label trial ▪ Aim: Evaluate the antiemetic efficacy of lorazepam in patients who failed to benefit from standard antiemetics ▪ N = 24 ▪ Adolescents and adults with lymphoma receiving chemotherapy ▪ Age range: 14-60yrs ▪ CINV assessment: patient report ▪ Emetogenicity classification: moderately or highly emetogenic 	<p>Severe vomiting for several hrs after chemo ± anticipatory vomiting</p> <p>Previous prophylactic regimen: Prochlorperazine 10-15mg/m² IV ± metoclopramide 10-15mg/m² IV</p> <p>Guideline consistent antiemetic prophylaxis: no</p>	Lorazepam 3mg/m ² PO 30min prior to chemo + prochlorperazine 10mg IV	<p>Proportion with complete control of vomiting: 17/24 (71%)</p> <p>Proportion with complete control of nausea: not reported</p> <p>Proportion with complete control of CINV: not reported</p> <p>Timeframe of assessments: acute phase (1-2hrs after chemo)</p>
Dexamethasone				
Aapro (1981)[45]	<ul style="list-style-type: none"> ▪ Prospective open-label trial ▪ Aim: Evaluate high-dose dexamethasone for CIV ▪ N = 10 ▪ Adults with cancer receiving chemotherapy ▪ Median age: not reported for refractory cohort ▪ CINV assessment: patient report ▪ Emetogenicity classification: unable to determine/not reported (28 patients received highly emetogenic chemotherapy) 	<p>Previous failure to respond to other antiemetics</p> <p>Previous prophylactic regimen: not reported</p> <p>Guideline consistent antiemetic prophylaxis: unable to determine/not reported</p>	Dexamethasone 8mg PO the night before chemo, then dexamethasone 4mg PO q4-6h on the day of treatment + dexamethasone 10mg IV prior to chemo ± droperidol or haloperidol 2-2.5mg IV	<p>Proportion with complete control of vomiting: not reported</p> <p>Proportion with complete control of nausea: not reported</p> <p>Proportion with complete control of CINV (defined as no symptoms or slight nausea): 3/10 (30%)</p> <p>Timeframe of assessments: not reported/unable to determine</p>

First Author (Year)	Study Design, Objective and Population	Definition of Refractory CINV and CINV Prophylaxis Provided During Previous Chemo Blocks	Antiemetic Interventions	Proportion with Complete Control of Refractory Nausea and/or Vomiting
Joss (1994)[46]	<ul style="list-style-type: none"> Randomized, double-blind trial Aim: Assess whether the addition of dexamethasone leads to improved control of CINV N = 96 Adults with cancer receiving chemotherapy Median age: <ul style="list-style-type: none"> G1: 44yrs; range: 17-79yrs G2: 52yrs; range: 17-69yrs CINV assessment: patient report (daily) and nursing assessment (first 24 hrs) Emetogenicity classification: unable to determine/not reported 	<p>> 5 vomiting episodes over 24hrs</p> <p>Previous prophylactic regimen: Day 1: Ondansetron 8mg IV x 3 doses Days 2-5: Ondansetron 8mg PO once daily</p> <p>Guideline consistent antiemetic prophylaxis: unable to determine/not reported</p>	<p>G1: Placebo G2: Day 1: Dexamethasone 20mg IV once Days 2-5: Dexamethasone 4mg PO tid + previous prophylactic regimen described</p> <p>Patients receiving multiple-days of chemo received IV antiemetics on the days of chemo and PO treatment as described afterward</p>	<p>Proportion with complete control of vomiting: acute phase: G1: 25/52 (48.1%) G2: 31/44 (70.5%) (p = 0.03)</p> <p>Proportion with complete control of nausea: acute phase: G1: 22/52 (42.3%) G2: 27/44 (61.3%) (p = 0.06)</p> <p>Proportion with complete control of CINV: acute phase: G1: 18/52 (34.6%) G2: 24/44 (54.5%) (p = 0.05)</p> <p>Timeframe of assessments: acute and delayed phases (q24h x 5 days)</p>
Prochlorperazine				
Johansson (1982)[47]	<ul style="list-style-type: none"> Randomized, double-blind, cross-over trial Aim: Compare the antiemetic efficacy of nabilone to prochlorperazine N = 18 Adults with cancer receiving chemotherapy Median age: not reported CINV assessment: patient report Emetogenicity classification: highly emetogenic 	<p>Uncontrolled nausea and vomiting despite use of standard antiemetic drugs</p> <p>Previous prophylactic regimen: not reported</p> <p>Guideline consistent antiemetic prophylaxis: unable to determine/not reported</p>	<p>G1: Nabilone 2mg PO bid x 4 doses G2: Prochlorperazine 10mg PO bid x 4 doses</p>	<p>Proportion with complete control of vomiting: G1: 3/18 (17%) G2: 0/18 (0%)</p> <p>Proportion with complete control of nausea: G1: 3/18 (17%) G2: 0/18 (0%)</p> <p>Proportion with complete control of CINV: not reported</p> <p>Timeframe of assessments: acute phase (q24h x 2 days)</p>

First Author (Year)	Study Design, Objective and Population	Definition of Refractory CINV and CINV Prophylaxis Provided During Previous Chemo Blocks	Antiemetic Interventions	Proportion with Complete Control of Refractory Nausea and/or Vomiting
McCabe (1988)[48]	<ul style="list-style-type: none"> Randomized, cross-over trial Aim: Compare the antiemetic activity of THC versus prochlorperazine in refractory patients N = 36 Adults with cancer receiving chemotherapy Median age: 48yrs; range: 18-69yrs CINV assessment: patient report Emetogenicity classification: moderately or highly emetogenic 	<p>Severe nausea and vomiting refractory to standard antiemetics</p> <p>Previous prophylactic regimen: Prochlorperazine: 34 pts Thiethylperazine: 2 pts</p> <p>Guideline consistent antiemetic prophylaxis: no</p>	<p>G1: THC 15mg/m² PO prior to chemo then q4h for 24hrs</p> <p>G2: Prochlorperazine 10mg PO prior to chemo then q4h for 24hrs</p>	<p>Proportion with complete control of vomiting: not reported</p> <p>Proportion with complete control of nausea: not reported</p> <p>Proportion with complete control of CINV: acute phase: G1: 9/36 (25%) G2: 0/36 (0%)</p> <p>Timeframe of assessments: acute phase (over 24hrs)</p>
THC Compounds (Levonantradol, Nabilone, Tetrahydrocannabinol)				
Cronin (1981)[49]	<ul style="list-style-type: none"> Prospective open-label trial Aim: Evaluate the effectiveness of IM levonantradol in refractory patients N = 28 Adults with cancer receiving chemotherapy Median age: not reported for evaluable patients (33yrs; range: 11-68yrs for all 31 patients initially enrolled) CINV assessment: patient report and investigator monitoring Emetogenicity classification: moderately or highly emetogenic 	<p>Refractory to the aggressive use of conventional antiemetic therapy</p> <p>Previous prophylactic regimen: Parenteral phenothiazines</p> <p>Guideline consistent antiemetic prophylaxis: no</p>	Levonantradol 0.5mg, 1mg, or 1.5mg IM q4h	<p>Proportion with complete control of vomiting: not reported</p> <p>Proportion with complete control of nausea: not reported</p> <p>Proportion with complete control of CINV: 5/28 (18%)</p> <p>Timeframe of assessments: acute phase (over 24hrs)</p>
Diasio (1981)[50]	<ul style="list-style-type: none"> Prospective open-label trial Aim: Report on the antiemetic efficacy of levonantradol in refractory patients N = 22 (26 courses of chemotherapy) Adults with cancer receiving chemotherapy Median age: not reported for refractory cohort CINV assessment: patient report and nurse monitoring Emetogenicity classification: unable to determine/not reported 	<p>Moderate to severe nausea and vomiting unrelieved by standard antiemetics</p> <p>Previous prophylactic regimen: not reported</p> <p>Guideline consistent antiemetic prophylaxis: unable to determine/not reported</p>	<p>G1: Levonantradol 0.5mg PO q4h x 3-27 doses (n=14)</p> <p>G2: Levonantradol 1mg PO q4h x 3-27 doses (n=11)</p> <p>G3: Levonantradol 1.5mg PO q4h x 3-27 doses (n=11)</p>	<p>Proportion of courses with complete control of vomiting: G1: 1/14 (7%) G2: 3/11 (27%) G3: 0/1 (0%)</p> <p>Proportion with complete control of nausea: not reported</p> <p>Proportion with complete control of CINV: not reported</p> <p>Timeframe of assessments: acute phase (4hrs following administration of levonantradol)</p>

First Author (Year)	Study Design, Objective and Population	Definition of Refractory CINV and CINV Prophylaxis Provided During Previous Chemo Blocks	Antiemetic Interventions	Proportion with Complete Control of Refractory Nausea and/or Vomiting
Gerhartz (1983)[51]	<ul style="list-style-type: none"> Prospective open-label trial Aim: Report on experience with levonantradol in refractory patients N = 20 Adults with cancer receiving chemotherapy Mean age: 43yrs; range 19-63yrs CINV assessment: patient report Emetogenicity classification: moderately or highly emetogenic 	<p>Severe CINV despite conventional antiemetic therapy</p> <p>Previous prophylactic regimen: Levomopromazine 50mg IV/PO ± metoclopramide 10mg ± triflupromazine ± dimenhydrinate pre-chemo</p> <p>Guideline consistent antiemetic prophylaxis: no</p>	Levonantradol 0.5-1mg SC 30min prior to chemo ± additional doses 4-8hrs later	<p>Proportion with complete control of vomiting: 8/20 (40%)</p> <p>Proportion with complete control of nausea: 5/20 (25%)</p> <p>Proportion with complete control of CINV: not reported</p> <p>Timeframe of assessments: unable to determine/not reported (pts reported on their experience when the experimental cycle was finished)</p>
Heim (1982)[52]	<ul style="list-style-type: none"> Prospective open-label trial Aim: Determine the antiemetic efficacy of levonantradol N = 20 Adults with cancer receiving chemotherapy Median age: not reported; range: 19-66yrs CINV assessment: Patient report Emetogenicity classification: moderately or highly emetogenic 	<p>“Patients treated without sufficient success of nausea and vomiting when treated with other antiemetics”</p> <p>Previous prophylactic regimen: Meclizine, metoclopramide, haloperidol, triflupromazine, flupentixol, and/or levomepromazine</p> <p>Guideline consistent antiemetic prophylaxis: no</p>	Levonantradol 1mg (0.5mg for patients weighing less than 50kg) IM 8hrs prior to chemo, then the same dose repeated at 2hrs and 6hrs post-chemo	<p>Proportion with complete control of vomiting: not reported</p> <p>Proportion with complete control of nausea: not reported</p> <p>Proportion with complete control of CINV: 5/20 (25%)</p> <p>Timeframe of assessments: acute phase (q24h x 2 days)</p>
Herman (1977)[53]	<ul style="list-style-type: none"> Prospective open-label trial Aim: Determine the antiemetic efficacy of nabilone and evaluate side effects N = 13 Adults with cancer receiving chemotherapy Median age: not reported CINV assessment: patient report Emetogenicity classification: moderately or highly emetogenic 	<p>Severe nausea and vomiting from chemo not controlled by standard antiemetics</p> <p>Previous Prophylactic regimen: Prochlorperazine</p> <p>Guideline consistent antiemetic prophylaxis: no</p>	Nabilone 1-2mg PO q8h x 5 days with 2 doses administered prior to chemo	<p>Proportion with complete control of vomiting: not reported</p> <p>Proportion with complete control of nausea: not reported</p> <p>Proportion with complete control of CINV (defined as an average daily rating of zero for nausea and vomiting): 2/13 (15%)</p> <p>Timeframe of assessments: acute and delayed phases (q24h x 5 days)</p>

First Author (Year)	Study Design, Objective and Population	Definition of Refractory CINV and CINV Prophylaxis Provided During Previous Chemo Blocks	Antiemetic Interventions	Proportion with Complete Control of Refractory Nausea and/or Vomiting
Johansson (1982)[47]	<ul style="list-style-type: none"> Randomized, double-blind, cross-over trial Aim: Compare the antiemetic efficacy of nabilone to prochlorperazine N = 18 Adults with cancer receiving chemotherapy Median age: not reported CINV assessment: patient report Emetogenicity classification: highly emetogenic 	<p>Uncontrolled nausea and vomiting despite use of standard antiemetic drugs</p> <p>Previous prophylactic regimen: not reported</p> <p>Guideline consistent antiemetic prophylaxis: unable to determine/not reported</p>	<p>G1: Nabilone 2mg PO bid x 4 doses</p> <p>G2: Prochlorperazine 10mg PO bid x 4 doses</p>	<p>Proportion with complete control of vomiting: G1: 3/18 (17%) G2: 0/18 (0%)</p> <p>Proportion with complete control of nausea: G1: 3/18 (17%) G2: 0/18 (0%)</p> <p>Proportion with complete control of CINV: not reported</p> <p>Timeframe of assessments: acute phase (q24h x 2 days)</p>
Laszlo (1981)[54]	<ul style="list-style-type: none"> Prospective open-label trial Aim: Evaluate the effectiveness of parenteral levonantradol in refractory patients N = 33 Adults with cancer receiving chemotherapy Median age: not reported for refractory cohort CINV assessment: patient report and investigator monitoring Emetogenicity classification: unable to determine/not reported 	<p>Persistent nausea and vomiting despite the use of standard antiemetics</p> <p>Previous prophylactic regimen: PO or parenteral phenothiazines ± additional prn antiemetics</p> <p>Guideline consistent antiemetic prophylaxis: no</p>	<p>Levonantradol 0.5mg, 1mg, 1.5mg, or 2mg PO q4h x 3-27 doses</p>	<p>Proportion with complete control of vomiting: not reported</p> <p>Proportion with complete control of nausea: not reported</p> <p>Proportion with complete control of CINV: 3/33 (9%)</p> <p>Timeframe of assessments: acute phase (over the course of chemo)</p>
Lucas (1980)[55]	<ul style="list-style-type: none"> Prospective open-label trial Aim: Determine if PO THC is an effective antiemetic for refractory patients N = 53 Adults with cancer receiving chemotherapy Median age: 51yrs; range: 18-69yrs) CINV assessment: patient report and investigator monitoring Emetogenicity classification: unable to determine/not reported 	<p>Persistent severe nausea and vomiting in spite of aggressive use of standard antiemetics</p> <p>Previous Prophylactic regimen: "Drug therapy" beginning 10-12hrs prior to chemo and continuing throughout the course of chemo, ± additional doses of antiemetics</p> <p>Guideline consistent antiemetic prophylaxis: no</p>	<p>Δ9-tetrahydrocannabinol 15mg/m² PO q6h x 4 doses beginning 1hr prior to chemo OR 5mg/m² PO q4h beginning 8-12hrs prior to chemo and continuing for 24hrs after chemo</p>	<p>Proportion with complete control of vomiting: not reported</p> <p>Proportion with complete control of nausea: not reported</p> <p>Proportion with complete control of CINV: 10/53 (19%)</p> <p>Timeframe of assessments: not reported/unable to determine (pts observed by investigators over the course of chemo)</p>

First Author (Year)	Study Design, Objective and Population	Definition of Refractory CINV and CINV Prophylaxis Provided During Previous Chemo Blocks	Antiemetic Interventions	Proportion with Complete Control of Refractory Nausea and/or Vomiting
McCabe (1988)[48]	<ul style="list-style-type: none"> Randomized, cross-over trial Aim: Compare the antiemetic activity of THC versus prochlorperazine in refractory patients N = 36 Adults with cancer receiving chemotherapy Median age: 48yrs; range: 18-69yrs CINV assessment: patient report Emetogenicity classification: moderately or highly emetogenic 	<p>Severe nausea and vomiting refractory to standard antiemetics</p> <p>Previous prophylactic regimen: Prochlorperazine: 34 pts Thiethylperazine: 2 pts</p> <p>Guideline consistent antiemetic prophylaxis: no</p>	<p>G1: THC 15mg/m² PO prior to chemo then q4h for 24hrs</p> <p>G2: Prochlorperazine 10mg PO prior to chemo then q4h for 24hrs</p>	<p>Proportion with complete control of vomiting: not reported</p> <p>Proportion with complete control of nausea: not reported</p> <p>Proportion with complete control of CINV: acute phase: G1: 9/36 (25%) G2: 0/36 (25%)</p> <p>Timeframe of assessments: acute phase (over 24hrs)</p>
Stambaugh (1984)[56]	<ul style="list-style-type: none"> Randomized, double-blind, placebo-controlled trial Aim: Evaluate the efficacy and toxicity of intramuscular levonantradol N = 20 Adults with cancer receiving chemotherapy Median age: not reported CINV assessment: patient and observer report Emetogenicity classification: unable to determine/not reported 	<p>Persistent nausea and vomiting from chemo refractory to maximally recommended doses of conventional antiemetics</p> <p>Previous prophylactic regimen: not reported</p> <p>Guideline consistent antiemetic prophylaxis: unable to determine/not reported</p>	<p>Levonantradol 0.5mg, 1mg, 1.5mg, or 2mg IM 2hrs prior to chemo then q4h for 3 additional doses</p>	<p>Proportion with complete control of vomiting: not reported</p> <p>Proportion with complete control of nausea: not reported</p> <p>Proportion with complete control of CINV: acute phase: 11/20 (55%)</p> <p>Timeframe of assessments: acute phase (over 24hrs)</p>
Stuart-Harris (1983)[57]	<ul style="list-style-type: none"> Prospective open-label trial Aim: Determine the efficacy of levonantradol for CINV in refractory patients N = 22 Adults with cancer receiving chemotherapy Median age: 49yrs; range 20-70yrs CINV assessment: patient report and nurse monitoring Emetogenicity classification: unable to determine/not reported (6 patients received highly emetogenic chemotherapy) 	<p>Severe nausea and vomiting refractory to conventional antiemetic treatment</p> <p>Previous prophylactic regimen: Chlorpromazine 50-100mg IV/IM q4-6h: 13 pts Prochlorperazine 12.5-25mg IV q4-6h: 12 pts Metoclopramide 10-15mg IV q4h: 5 pts Thiethylperazine 10mg suppositories q6h: 2 pts Perphenazine 6mg PO q8h: 1 pt</p> <p>Guideline consistent antiemetic prophylaxis: no</p>	<p>Levonantradol 0.5mg IM 1 hour pre-chemo ± additional doses q4h prn</p>	<p>Proportion with complete control of vomiting: not reported</p> <p>Proportion with complete control of nausea: not reported</p> <p>Proportion with complete control of CINV: 3/22 (13.6%)</p> <p>Timeframe of assessments: not reported/unable to determine</p>

First Author (Year)	Study Design, Objective and Population	Definition of Refractory CINV and CINV Prophylaxis Provided During Previous Chemo Blocks	Antiemetic Interventions	Proportion with Complete Control of Refractory Nausea and/or Vomiting
Miscellaneous (Methotrimeprazine, Medroxyprogesterone, and Propofol)				
Borgeat (1994)[58]	<ul style="list-style-type: none"> ▪ Prospective open-label trial ▪ Aim: Determine the efficacy and safety of added low-dose propofol infusion in patients experiencing refractory CINV ▪ N = 20 ▪ Adults with breast cancer receiving non-cisplatin chemotherapy ▪ Median age: 56yrs; range: 45-72yrs ▪ CINV assessment: nurse report ▪ Emetogenicity classification: moderately emetogenic 	<p>> 5 emetic episodes in the first 24hrs despite antiemetic prophylaxis during their first cycle of chemo</p> <p>Prophylactic regimen: Ondansetron 8mg IV x 2 doses + dexamethasone 10mg IV once</p> <p>Guideline consistent antiemetic prophylaxis: yes</p>	<p>Propofol 1mg/kg/hr continuous infusion started 4 hrs prior to chemo and continuing for 24 hrs + previous prophylactic regimen described</p>	<p>Proportion with complete control of vomiting: not reported</p> <p>Proportion with complete control of nausea: not reported</p> <p>Proportion with complete control of CINV: acute phase: 18/20 (90%)</p> <p>Timeframe of assessments: acute phase (q2h starting 4hrs pre-chemo and continuing for 24 hrs after chemo)</p>
Borgeat (1993)[59]	<ul style="list-style-type: none"> ▪ Prospective open-label trial ▪ Aim: Determine the efficacy and safety of added low-dose propofol infusion in patients experiencing refractory CINV ▪ N = 20 ▪ Adults with cancer receiving cisplatin-based chemotherapy ▪ Median age: 52yrs; range: 30-70yrs ▪ CINV assessment: nurse report ▪ Emetogenicity classification: moderately emetogenic 	<p>> 5 emetic episodes in the first 24hrs despite antiemetic prophylaxis during their first cycle of chemo</p> <p>Previous prophylactic regimen: Ondansetron 8mg IV OR granisetron 3mg IV x 3 doses + dexamethasone 10mg IV once</p> <p>Guideline consistent antiemetic prophylaxis: yes</p>	<p>Propofol 1mg/kg/hr continuous infusion started 4 hours prior to chemo and continuing for 72hrs after + previous prophylactic regimen described</p>	<p>Proportion with complete control of vomiting: acute phase: 17/20 (85%) delayed phase: 15/20 (75%)</p> <p>Proportion with complete control of nausea: not reported</p> <p>Proportion with complete control of CINV: not reported</p> <p>Timeframe of assessments: acute and delayed phases (q2h starting 4hrs pre-chemo and continuing for 72hrs after chemo)</p>

First Author (Year)	Study Design, Objective and Population	Definition of Refractory CINV and CINV Prophylaxis Provided During Previous Chemo Blocks	Antiemetic Interventions	Proportion with Complete Control of Refractory Nausea and/or Vomiting
Hata (2012)[60]	<ul style="list-style-type: none"> ▪ Case series ▪ Aim: Describe 3 cases where medroxyprogesterone acetate was effective for cisplatin-induced refractory emesis ▪ N = 3 ▪ Adults with cancer receiving cisplatin + gemcitabine ▪ Median age: 58 yrs; range:58-67yrs ▪ CINV assessment: not reported ▪ Emetogenicity classification: highly emetogenic 	<p>Emesis occurring despite the use of antiemetic prophylaxis during the previous cycle</p> <p>Previous Prophylactic regimen:</p> <p>Pt 1: Day 1: Granisetron 3mg + aprepitant 125mg + dexamethasone 12mg Days 2-3: Aprepitant 80mg + dexamethasone 8mg Day 4: Dexamethasone 8mg</p> <p>Pt 2: Day 1: Granisetron 1mg + aprepitant 125mg + dexamethasone 8mg Days 2-3 and 9-10: Aprepitant 80mg + dexamethasone 4mg Day 8: Dexamethasone 8mg</p> <p>Pt 3: Day 1: Palonosetron 0.75mg + aprepitant 125mg + dexamethasone 12mg Days 2-3: Aprepitant 80mg + dexamethasone 8mg Day 4: Dexamethasone 8mg</p> <p>Guideline consistent antiemetic prophylaxis: Pt 1: yes Pt 2: yes Pt 3: yes</p>	<p>Pt 1: Day 1: Granisetron 3mg + dexamethasone 12mg Days 2-4: Medroxyprogesterone acetate 900mg PO + dexamethasone 8mg Day 5: Medroxyprogesterone acetate 900mg PO</p> <p>Pt 2: Day 1: Granisetron 1mg + dexamethasone 8mg Days 2-4: Medroxyprogesterone acetate 900mg PO + dexamethasone 4mg Day 5: Medroxyprogesterone acetate 900mg PO</p> <p>Pt 3: Day 1: Palonosetron 0.75mg + aprepitant 125mg + dexamethasone 12mg + Medroxyprogesterone acetate 900mg PO Days 2-3: Aprepitant 80mg + dexamethasone 8mg + Medroxyprogesterone acetate 900mg PO Day 4: Dexamethasone 8mg + Medroxyprogesterone acetate 900mg PO</p>	<p>Proportion with complete control of vomiting: 3/3 (100%)</p> <p>Proportion with complete control of nausea: not reported</p> <p>Proportion with complete control of CINV: not reported</p> <p>Timeframe of assessments: not reported</p>
Higi (1980)[61]	<ul style="list-style-type: none"> ▪ Prospective open-label trial ▪ Aim: Determine the antiemetic efficacy of oral methotrimeprazine ▪ N = 113 ▪ Adults with cancer receiving either cisplatin, ifosfamide, or adriamycin-containing chemotherapy combinations ▪ Median age: not reported ▪ CINV assessment: clinical observation ▪ Emetogenicity classification: moderately or highly emetogenic 	<p>Refractory to conventional antiemetics</p> <p>Previous prophylactic regimen: Metoclopramide ± triflupromazine ± other phenothiazines/antihistamines</p> <p>Guideline consistent antiemetic prophylaxis: no</p>	<p>Methotrimeprazine 8-15mg PO x 2 doses beginning 12hrs and 60 min prior to chemo</p>	<p>Proportion with complete control of vomiting: not reported</p> <p>Proportion with complete control of nausea: not reported</p> <p>Proportion with complete control of CINV: 70/113 (62%)</p> <p>Timeframe of assessments: not reported/unable to determine</p>

First Author (Year)	Study Design, Objective and Population	Definition of Refractory CINV and CINV Prophylaxis Provided During Previous Chemo Blocks	Antiemetic Interventions	Proportion with Complete Control of Refractory Nausea and/or Vomiting
Non-pharmacological Interventions - Acupressure/Acupuncture				
Choo (2006)[62]	<ul style="list-style-type: none"> ▪ Prospective open-label trial ▪ Aim: evaluate the efficacy of electroacupuncture in preventing refractory CINV ▪ N = 27 ▪ Adults with cancer receiving anthracycline-based chemotherapy for breast cancer ▪ Median age: 48yrs; range: 37-60yrs ▪ CINV assessment: patient report and physician assessment ▪ Emetogenicity classification: moderately emetogenic 	<p>More than 2 episodes of emesis occurring in the first 24hrs after chemo when antiemetic prophylaxis and rescue antiemetics were given</p> <p>Previous prophylactic regimen: Day 1: A 5-HT3 antagonist (ondansetron 8mg IV or granisetron 3mg IV) + dexamethasone 8mg IV Days 2-3: A 5-HT3 antagonist PO</p> <p>Breakthrough medications including PO metoclopramide, lorazepam and dexamethasone permitted</p> <p>Guideline consistent antiemetic prophylaxis: yes</p>	<p>Electroacupuncture at PC6 for 30min beginning 10min prior to chemo + previous prophylactic regimen described</p>	<p>Proportion with complete control of vomiting: 10/27 (37%)</p> <p>Proportion with complete control of nausea: 3/27 (11%)</p> <p>Proportion with complete control of CINV: not reported</p> <p>Timeframe of assessments: not reported</p>
Gardani (2007)[63]	<ul style="list-style-type: none"> ▪ Prospective open-label trial ▪ Aim: evaluate the efficacy of PC6 stimulation by acupressure for the treatment of refractory CIV ▪ N = 100 ▪ Adults with solid tumors ▪ Median age: 59yrs ▪ CINV assessment: not reported ▪ Emetogenicity classification: moderately or highly emetogenic 	<p>Grade 3-4 vomiting and no response to “conventional antiemetics” including 5-HT3 antagonists, corticosteroids, and antidopaminergic agents</p> <p>Previous prophylactic regimen: not reported</p> <p>Guideline consistent antiemetic prophylaxis: unable to determine/not reported</p>	<p>Stimulation of the PC6 acupoint by acupressure for 8hrs a day starting prior to chemo and continuing for at least 3 days after chemo</p>	<p>Proportion with complete control of vomiting: 68/100 (68%)</p> <p>Proportion with complete control of nausea: not reported</p> <p>Proportion with complete control of CINV: not reported</p> <p>Timeframe of assessments: not reported</p>

Emetogenicity classified according to the MASCC and ASCO guidelines

*Prophylaxis considered “guideline consistent” in adult studies based on current recommendations provided by MASCC and/or ASCO and/or NCCN and on the POGO Acute AINV guideline for paediatric studies

Complete control of vomiting = no vomiting, Complete control of nausea = no nausea, Complete control of CINV = no nausea or vomiting (unless defined otherwise)

Supplementary Table VII: Health questions, summary of recommendations and remarks for the treatment of breakthrough chemotherapy-induced nausea and vomiting (CINV) and the prevention of refractory CINV in children

Health Questions and Recommendations	Strength of Recommendation & Level of Evidence ^{9,10}
<p>Health Question #1: What interventions are recommended to treat breakthrough CINV in children?</p> <p><i>Breakthrough CINV is defined as nausea and/or vomiting presumed to be attributable to antineoplastic chemotherapy and with no other pathological cause which occurs during the acute or delayed phase despite CINV prophylaxis.</i></p>	
<p>Recommendation 1.1: For children receiving acute CINV prophylaxis recommended for minimally, low, or moderately emetogenic chemotherapy, clinicians should upgrade or escalate the acute CINV prophylaxis provided to that recommended for chemotherapy of the next higher level of emetogenic risk.</p> <p><u>Remarks:</u> This recommendation places a high value on the possible control of breakthrough CINV in the acute phase by provision of CINV prophylaxis (pharmacological and non-pharmacological) known to be effective in the setting of more emetogenic chemotherapy. It is a strong recommendation because the guideline panel is certain that the benefits of acute CINV prophylaxis escalation outweigh the low risk of harms associated with the interventions.</p>	<p>Strong Recommendation Very Low Quality Evidence</p>
<p>Recommendation 1.2: For children receiving acute CINV prophylaxis recommended for highly emetogenic chemotherapy, we suggest that olanzapine be added to guideline-consistent CINV prophylaxis.</p> <p><u>Remarks:</u> This recommendation places value on the high quality evidence of the efficacy of olanzapine as a therapeutic intervention in adults receiving contemporary CINV prophylaxis. It is a weak recommendation because direct evidence of efficacy of olanzapine for prevention or treatment of CINV in children and of its safety in children receiving chemotherapy is limited. Furthermore, the optimal pediatric dose for this indication is uncertain.</p>	<p>Weak Recommendation Low Quality Evidence</p>
<p>Recommendation 1.3: For children receiving acute CINV prophylaxis recommended for highly emetogenic chemotherapy and who cannot receive olanzapine, we suggest that one of the following antiemetic agents be added to guideline-consistent CINV prophylaxis:</p> <ul style="list-style-type: none"> • methotrimeprazine (also known as levomepromazine) <p>or</p>	<p>Weak Recommendation Very Low Quality Evidence</p>

- metoclopramide (in children older than 1 year)

Given the possibility of extrapyramidal reactions with these agents, the risks and benefits of their use should be weighed carefully and co-administration of prophylaxis aimed at preventing extrapyramidal symptoms (EPS) should be considered. Patients and families should also be educated about the possible occurrence of EPS.

Remarks: The panel recognizes that the evidence base for these agents in adult patients consists of older studies that were not conducted in the context of currently recommended CINV prophylaxis and is of low quality. Despite these limitations and although direct evidence of efficacy of these agents for treatment of breakthrough CINV in children is not available, the guideline panel made a weak recommendation for use of these agents. The panel placed a high value on the possible benefit of these agents in the setting of CINV prophylaxis failure. A lower value was placed on the potential for toxicity secondary to these agents because EPS are generally amenable to intervention and, although it may be distressing if not anticipated, is short-lived.

Health Question #2: What interventions are recommended to prevent CINV in children who have refractory CINV?

Refractory CINV is defined as nausea and/or vomiting presumed to be attributable to antineoplastic chemotherapy and with no other pathological cause which occurs during the acute or delayed phase despite CINV prophylaxis in patients who have experienced breakthrough CINV in a previous chemotherapy block.

Recommendation 2.1: For children receiving acute CINV prophylaxis recommended for minimally, low, or moderately emetogenic chemotherapy, clinicians should upgrade or escalate the acute CINV prophylaxis provided to that recommended for chemotherapy of the next higher level of emetogenic risk.

Strong
Recommendation
Very Low Quality
Evidence

Remarks: This recommendation places a high value on the possible control of refractory CINV in the acute phase by provision of CINV prophylaxis (pharmacological and non-pharmacological) known to be effective in the setting of more emetogenic chemotherapy. It is a strong recommendation because the guideline panel is certain that the benefits of acute CINV prophylaxis escalation outweigh the low risk of harms associated with the interventions.

Recommendation 2.2: For children receiving acute CINV prophylaxis recommended for highly emetogenic chemotherapy, we suggest that the 5-HT3 antagonist given for CINV prophylaxis be changed from ondansetron or granisetron to palonosetron. In jurisdictions where palonosetron is not available, we suggest that granisetron be substituted

Weak
Recommendation
Very Low Quality
Evidence

for ondansetron.

Remarks: This recommendation places a high value on the improved CINV control seen in adult cancer patients receiving palonosetron and in adult patients receiving granisetron who have a genetic predisposition to a poor response to ondansetron at usual doses. It places less value on drug cost in the scenario where less expensive alternatives have been ineffective. It is a weak recommendation because direct evidence of the comparative efficacy of palonosetron or of using an alternative 5HT-3 antagonist for prevention of refractory CINV in children is not available.

Recommendation 2.3: For children experiencing refractory CINV despite initiation of previous recommendations and who have not previously received aprepitant because it is known or suspected to interact with the chemotherapeutic agent(s) being given, we suggest that the addition of aprepitant to acute CINV prophylaxis be considered.

Weak
Recommendation
Low Quality
Evidence

Remarks: This recommendation places a high value on improved CINV control when control is likely to be difficult to achieve and on the negative consequences of uncontrolled CINV. It is a weak recommendation since direct evidence of the efficacy of aprepitant in this context is lacking. Furthermore, the relative risks of aprepitant (potential for drug interaction with chemotherapy and altered chemotherapy exposure) and benefits (CINV control) should be determined on a case-by-case basis.

Recommendation 2.4: For children experiencing refractory CINV despite initiation of the previous recommendations, we suggest that one of the following interventions be added to the CINV prophylaxis provided:

- interventions that were employed successfully for the treatment of breakthrough CINV in previous treatment blocks (olanzapine, methotrimeprazine or metoclopramide); or

Weak
Recommendation
Very Low Quality
Evidence

Remarks: This recommendation places a high value on the potential for continued CINV control using interventions that were used successfully and without significant adverse effects in patients who previously experienced breakthrough CINV. It is a weak recommendation because the impact of the recommended action has not been evaluated.

- stimulation of Nei Guan (P6) by means of acupressure or electro-acupuncture.

Weak
Recommendation
Very Low Quality
Evidence

Remarks: This recommendation places a high value on the possibility that acupressure or electro-acupuncture may increase control of

CINV in patients who have experienced refractory CINV with a low potential for harm. It is a weak recommendation because of imprecision of estimates, inability to evaluate consistency and indirectness since there is a single study to support the use of each intervention in adults and there is no direct information regarding the efficacy or safety of acupressure or electro-acupuncture in children with refractory CINV.

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