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**Guideline for the Treatment of Breakthrough and the Prevention of Refractory Chemotherapy-induced Nausea and Vomiting in Children with Cancer**

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Manuscripts

1 **Guideline for the Treatment of Breakthrough and the Prevention of Refractory**  
2 **Chemotherapy-induced Nausea and Vomiting in Children with Cancer**

3  
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37

38

39

Abbreviation	Full Term
CINV	Chemotherapy-induced nausea and vomiting
CIV	Chemotherapy-induced vomiting
EPS	Extrapyramidal symptoms
HEC	Highly emetogenic chemotherapy
MEC	Moderately emetogenic chemotherapy

40

## 41 Abstract

42 This clinical practice guideline provides an approach to the treatment of breakthrough  
43 chemotherapy-induced nausea and vomiting (CINV) and the prevention of refractory CINV in  
44 children. It was developed by an international, inter-professional panel and is based on  
45 systematic literature reviews. Evidence-based interventions for treatment of breakthrough and  
46 prophylaxis of refractory CINV are recommended. Gaps in the evidence used to support the  
47 recommendations made in this clinical practice guideline were identified. The contribution of  
48 these recommendations to breakthrough and refractory CINV control in children requires  
49 prospective evaluation.

50

51

52

53

For Peer Review

## 54 **Introduction**

55 Children commonly experience chemotherapy-induced nausea and vomiting (CINV) despite  
56 administration of modern, guideline-consistent antiemetic agents. Children who experience  
57 CINV in previous chemotherapy blocks despite administration of prophylaxis (breakthrough  
58 CINV) which does not respond to treatment or to changes in CINV prophylaxis are deemed to  
59 have refractory CINV. Achieving complete CINV control may be more difficult in these  
60 patients[1] and finding effective antiemetic interventions for them can be challenging. An  
61 evidence-based approach to optimizing CINV control in these patients is therefore essential.

62  
63 The overall objective of this clinical practice guideline is to optimize breakthrough and  
64 refractory CINV control in children. This guideline applies to children aged 1 month to 18 years  
65 receiving chemotherapy. The target users of this guideline are all healthcare providers who care  
66 for these children. For the purpose of this guideline, optimal control of breakthrough CINV is  
67 defined as acute relief of nausea or vomiting during the current chemotherapy block. Optimal  
68 control of refractory CINV is defined as no vomiting, no retching, no nausea, no use of  
69 antiemetic agents other than those given for CINV prevention and no nausea-related change in  
70 the child's usual appetite and diet.

71  
72 This guideline represents the fourth guideline in a series to address CINV in children. The three  
73 previously published guidelines address chemotherapy emetogenicity, prevention of acute  
74 CINV and management of anticipatory CINV in children with cancer.[2-4] Complete versions of  
75 all four guidelines may be viewed at: <http://www.pogo.ca/healthcare/practiceguidelines/>. Our  
76 recommendations are based on the assumption that children are receiving CINV prophylaxis that  
77 is consistent with the previously published guidelines.

## 79 **Methods**

80 Guideline panel and development of clinical questions

81 Guideline panel members were chosen to represent inter-professional staff from Pediatric  
82 Oncology Group of Ontario centers and from internationally recognized experts in pediatric  
83 supportive care. Once chosen, the panel members developed the specific health questions (Table  
84 I) to be addressed by this guideline.

85

86 Systematic literature searches

87 In March 2015, computerized searches (Supplementary Table I) were performed with the  
88 assistance of a library scientist to identify guidelines which could be endorsed for the treatment  
89 of breakthrough CINV and for the prevention of refractory CINV in children. 4,451 citations  
90 were identified and screened. Since none met the inclusion criteria (Table II) for endorsement  
91 assessment, the guideline panel proceeded to develop a *de novo* guideline. Systematic reviews of  
92 primary studies evaluating interventions for the treatment of breakthrough CINV and the  
93 prevention of refractory CINV were conducted.

94

95 Evidence identification and synthesis

96 We searched for primary studies pertinent to the guideline topics (Supplementary Tables II and  
97 III) as of March 13, 2015. Eligibility was not restricted by age or language. All primary study  
98 designs, except single case reports were eligible. Citations were screened independently by two  
99 reviewers. Conflicts were resolved by a third. Potentially relevant citations were included for  
100 full-text screening. Two reviewers independently evaluated the full-text papers to determine  
101 whether they met the inclusion criteria (Table II). Disagreements were resolved by a third  
102 reviewer. Evidence tables were compiled.

103

104 During the guideline development process, it became apparent that understanding the safety of  
105 specific medications in children with cancer was required to better inform recommendations.  
106 Therefore systematic reviews evaluating the safety of metoclopramide[5] and  
107 prochlorperazine[6] were undertaken, and an existing systematic review of the safety of  
108 olanzapine[7] in children was considered by the panel. Primary studies relating to the safety of  
109 methotrimeprazine in children were also searched (Supplementary Table III) as of March 9, 2015  
110 with the assistance of a library scientist. Citations were screened, full-text papers were evaluated  
111 to determine if they met the inclusion criteria (Table II) and evidence summary tables were  
112 compiled as described above.

113

114 Decisions were taken through panel discussions; any differences in opinion were resolved by  
115 consensus. The quality of evidence and strength of recommendations were assessed using the

116 GRADE system.[8,9] In formulating recommendations, health benefits, adverse effects and risks  
117 were explicitly considered.

118

119 External review and consultation process

120 The draft guideline underwent a two-stage external review: first by international experts in CINV  
121 and then by stakeholders from the Ontario pediatric oncology community. Six content experts  
122 provided a review; their comments were discussed in detail by the panel and a decision on each  
123 point was taken by consensus. Ten Ontario pediatric oncology stakeholders also provided  
124 comments. These identified the need to development guideline implementation tools.

125

126 Procedure for updating the guideline

127 This guideline will be formally updated five years from publication or earlier should new,  
128 significant evidence become available.

129

## 130 **Results**

131 A total of 4,654 references were identified from the database searches. Of these, 116 papers were  
132 reviewed in full-text and 59 (breakthrough CINV: 13; refractory CINV: 46) satisfied the  
133 eligibility criteria (Figure 1) and were included in the systematic review.

134

135 **Health Question #1: What interventions are recommended to treat breakthrough CINV in**  
136 **children?**

137 Breakthrough CINV is defined as nausea and/or vomiting presumed to be attributable to  
138 antineoplastic chemotherapy and with no other pathological cause which occurs during the acute  
139 or delayed phase despite CINV prophylaxis.

140

141 No studies were identified that described the treatment of breakthrough CINV exclusively in  
142 children. Thirteen studies in adults met criteria for inclusion (four randomized trials, two non-  
143 randomized comparative studies, and seven prospective single arm studies).

144

145 Evidence describing the treatment of breakthrough CINV in adults is summarized in  
146 Supplementary Table IV. The guideline recommendations are summarized in Table I. Studies



147 evaluating ABH gel, 5-HT<sub>3</sub> antagonists and prochlorperazine were included in the evidence  
148 summary but were omitted from the recommendations due to poor systemic bioavailability,[10]  
149 inclusion as standard acute CINV prophylaxis[11] and safety concerns,[6] respectively.

150

151 **Recommendation 1.1:** For children receiving acute CINV prophylaxis recommended for  
152 minimally, low, or moderately emetogenic chemotherapy, clinicians should upgrade or escalate  
153 the acute CINV prophylaxis provided to that recommended for chemotherapy of the next higher  
154 level of emetogenic risk.

155

156 No specific evidence was identified that evaluated the escalation of CINV prophylaxis as  
157 treatment for breakthrough CINV in children. This recommendation is grounded in the evidence  
158 supporting the interventions recommended for acute CINV prophylaxis in children. [11]

159

160 This recommendation places a high value on the possible control of breakthrough CINV in the  
161 acute phase by providing antiemetic interventions (pharmacological and non-pharmacological)  
162 known to be effective in the setting of more emetogenic chemotherapy. It is a strong  
163 recommendation because the panel is certain that the benefits of acute CINV prophylaxis  
164 escalation outweigh the low risk of harms associated with these interventions.

165

166 **Recommendation 1.2:** For children receiving acute CINV prophylaxis recommended for highly  
167 emetogenic chemotherapy (HEC), we suggest that olanzapine be added to guideline-consistent  
168 CINV prophylaxis.

169

170 **Adult Patients**

171 Two primary studies evaluated the use of olanzapine for the treatment of breakthrough  
172 CINV.[12,13] In a double-blind, randomized controlled trial, Navari et al evaluated the efficacy  
173 of olanzapine vs. metoclopramide for the treatment of breakthrough CINV in adult  
174 chemotherapy-naive patients receiving HEC and CINV prophylaxis with palonosetron,  
175 dexamethasone and fosaprepitant.[13] At the onset of breakthrough CINV, patients were  
176 randomized to receive olanzapine (10 mg orally daily for three days) or metoclopramide (10 mg  
177 orally TID for three days). Dexamethasone was stopped when olanzapine or metoclopramide

178 was initiated. The proportions of patients achieving complete control of breakthrough vomiting  
179 over the 72 hour observation period in the olanzapine and metoclopramide arms were 70% and  
180 31% ( $p < 0.01$ ), respectively. Similarly, a greater proportion of patients who received olanzapine  
181 (68%) achieved complete control of nausea compared to those patients receiving  
182 metoclopramide (23%,  $p < 0.01$ ).

183

184 Chanthawong et al described the efficacy of olanzapine for the treatment of breakthrough  
185 vomiting in adults receiving moderately emetogenic chemotherapy (MEC) or HEC.[12] In this  
186 prospective, open-label study, olanzapine (5 mg orally q12h for two doses) was administered to  
187 patients experiencing breakthrough emesis despite prophylaxis with ondansetron, a  
188 corticosteroid, and metoclopramide. Complete control of breakthrough vomiting was  
189 experienced by 28 of 46 patients (61%) after olanzapine administration. Nausea was not  
190 evaluated.

191

192 No clinically significant adverse effects were reported in either study that evaluated olanzapine  
193 for the treatment of breakthrough CINV in adults. Dizziness, fatigue, and dyspepsia, described  
194 as mild and tolerable, were reported by Chanthawong et al.[12]

195

#### 196 Pediatric Patients

197 No pediatric studies of olanzapine for the treatment of breakthrough CINV were identified from  
198 the literature search. The guideline panel is aware of one recent paper, published after the March  
199 2015 search end-date, which addresses the use of olanzapine in children. This multi-center,  
200 retrospective review described chemotherapy-induced vomiting (CIV) control and adverse  
201 effects in children receiving olanzapine.[14] In this cohort, 20 children received olanzapine for  
202 breakthrough CINV during 21 chemotherapy blocks. Complete CIV control was reported the  
203 day following the first olanzapine dose in 12 chemotherapy blocks (57%). Nausea control was  
204 not assessed.

205

206 In a systematic review and meta-analysis, weight gain and sedation (78% (95% confidence  
207 interval (CI): 63 to 95%) and 48% (95% CI: 35 to 67%), respectively) were commonly  
208 associated with the use of olanzapine in children less than 13 years old.[7] Extrapyramidal

209 symptoms (EPS) and electrocardiograph abnormalities were reported less frequently (9% (95%  
210 CI: 4 to 21%) and 14% (95% CI: 7 to 26%), respectively). Most adverse effects associated with  
211 olanzapine use were of minor clinical significance; no fatalities attributable to olanzapine were  
212 identified.

213  
214 This recommendation is consistent with adult guidelines for the treatment of breakthrough CINV  
215 in adult cancer patients.[15,16] It places value on the high quality evidence of the efficacy of  
216 olanzapine in adults receiving contemporary CINV prophylaxis. It is a weak recommendation  
217 because direct evidence of efficacy of olanzapine for prevention or treatment of CINV in  
218 children and of its safety in children receiving chemotherapy is limited or indirect. Furthermore,  
219 the optimal pediatric dose for this indication is uncertain. It may be reasonable to give  
220 olanzapine 0.1 mg/kg/dose (maximum 10 mg/dose) once daily by mouth. This dose is based on  
221 the results of the retrospective review[14] and uses the adult dose as the maximum dose. If CINV  
222 is not controlled and sedation does not occur or is not troublesome, the dose could potentially be  
223 increased to 0.14 mg/kg/dose (maximum 10 mg/dose). Olanzapine injection should not be  
224 administered for CINV control since it has not been evaluated for this indication. Olanzapine  
225 should be avoided in patients receiving CYP1A2 inducers (e.g. carbamazepine, rifampin) or  
226 inhibitors (e.g. ciprofloxacin, fluvoxamine) as olanzapine is primarily metabolized via this  
227 enzymatic pathway.[17]

228  
229 **Recommendation 1.3:** For children receiving acute CINV prophylaxis recommended for HEC  
230 and who cannot receive olanzapine, we suggest that **one** of the following antiemetic agents be  
231 added to guideline-consistent CINV prophylaxis: methotrimeprazine (also known as  
232 levomepromazine) **or** metoclopramide (in children older than 1 year)

### 233 234 *Addition of methotrimeprazine*

#### 235 Adult Patients

236 One prospective open-label study was identified which evaluated methotrimeprazine for the  
237 treatment of breakthrough CINV in 32 patients. McCabe et al evaluated the efficacy of a single  
238 25 mg subcutaneous dose of methotrimeprazine for the treatment of breakthrough CINV  
239 occurring in the delayed phase in adult cancer patients receiving HEC.[18] The proportion of

240 patients achieving complete control of breakthrough vomiting over the first 24 and 48 hours of  
241 methotrimeprazine administration was 88% and 94%, respectively. The proportion of patients  
242 achieving complete control of breakthrough nausea in 24 and 48 hours with administration of  
243 methotrimeprazine was 75% and 94%, respectively.

244

245 Drowsiness, dry mouth, and constipation are the most commonly reported adverse effects of  
246 methotrimeprazine in adult psychiatric patients[19]. Sedation (12/32 patients), hypotension  
247 (8/32), and induration at the site of methotrimeprazine administration (32/32) were the most  
248 commonly reported adverse effects experienced by patients included in the previously described  
249 study. [18]

250

#### 251 Pediatric Patients

252 No evidence was identified that described the use of methotrimeprazine in children for the  
253 treatment of breakthrough CINV. Despite being licensed for use in children in Canada,[19]  
254 information regarding the use of methotrimeprazine in pediatric patients for any indication is  
255 limited. The pediatric dose recommended by the manufacturer is 0.25 mg/kg/day by mouth in 2  
256 or 3 divided doses initially and increasing to a maximum of 40 mg/day in children 12 years of  
257 age or less.[19]

258

259 Four studies (two retrospective reviews, 1 case series and 1 case report) involving 30 children  
260 were included in a systematic review of the safety of methotrimeprazine in children  
261 (Supplementary Table V). No persistent adverse effects or fatalities were attributable to  
262 methotrimeprazine in these studies.

263

#### 264 *Addition of metoclopramide*

##### 265 Adult Patients

266 Two studies (a randomized controlled trial and a prospective observational study) were included.  
267 The randomized trial evaluating the efficacy of olanzapine vs. metoclopramide for the treatment  
268 of breakthrough CINV in chemotherapy-naive adults receiving HEC has been described  
269 previously.[13] Musso et al also evaluated the efficacy of metoclopramide (20 mg IV q6h or  
270 q12h) vs. a second dose of palonosetron (0.25 mg IV) in adults receiving either MEC or

271 HEC.[20] Patients assigned to the metoclopramide arm received prophylaxis with ondansetron  
272 plus dexamethasone, while those in the palonosetron group received palonosetron plus  
273 dexamethasone. The proportion of patients achieving complete control of breakthrough CINV in  
274 the metoclopramide group was 22%, vs. 67% in the palonosetron group ( $p = 0.039$ ).

275

276 Navari et al[13] reported no grade 3 or 4 toxicities attributable to metoclopramide and Musso et  
277 al stated that no serious adverse events observed in their study were attributable to antiemetic  
278 treatment.[20]

279

280 Pediatric Patients

281 No evidence was identified that described the use of metoclopramide exclusively in pediatric  
282 patients for the treatment of breakthrough CINV. However, it is recommended for acute CINV  
283 prophylaxis in children as an alternate to dexamethasone.[11]

284

285 In a recent systematic review and meta-analysis of adverse effects of metoclopramide in  
286 children, the mean proportion of children reported to have EPS was 9% (95% CI: 5 to 17%) or  
287 diarrhea was 6% (95% CI: 3 to 9%).[5] In single-dose and multiple-dose metoclopramide  
288 studies, the mean proportion of children reported to experience sedation was 2% (95% CI: 1 to  
289 5%) and 6% (95% CI: 3 to 12%), respectively. Since Health Canada and the European  
290 Medicines Agency have recently issued warnings regarding the risk of EPS in young children  
291 receiving metoclopramide, the panel recommends that metoclopramide be avoided in children  
292 less than 1 year old[21].

293

294 Methotrimeprazine is a phenothiazine similar to chlorpromazine. It is marketed in Canada,  
295 Europe, and Australia. Current CINV prophylaxis guidelines recommend the use of  
296 metoclopramide for the treatment of breakthrough CINV in adults.[15,16] The panel recognizes  
297 that the evidence base for these agents consists of studies in adults that were not conducted in the  
298 context of currently recommended CINV prophylaxis. Despite these limitations and although  
299 direct evidence of efficacy of these agents for treatment of breakthrough CINV in children is not  
300 available, the guideline panel placed a high value on the possible benefit of these agents in the  
301 setting of breakthrough CINV. A lower value was placed on the potential for toxicity secondary

302 to these agents because EPS are generally amenable to intervention and, although possibly  
303 distressing if not anticipated, are short-lived.

304

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

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

311

312 Two studies were identified that described the prevention of refractory CINV in children: one  
313 prospective study evaluating the use of tropisetron[22] and a retrospective review evaluating the  
314 use of aprepitant.[23] Forty-one studies in adults met criteria for inclusion in this evidence base  
315 (five randomized trials, four non-randomized prospective comparative studies, 31 prospective  
316 single arm studies, and one case series). Evidence describing the prevention of refractory CINV  
317 in children and adults is summarized in Supplementary Table VI. Dexamethasone,  
318 tetrahydrocannabinol, levonantradol, Sancuso®, benzodiazepines, medroxyprogesterone,  
319 nabilone and propofol were included in the evidence summary but were omitted from the  
320 recommendations. Similarly, placebo-controlled trials, dosage form comparison studies or single  
321 arm studies evaluating 5-HT<sub>3</sub> antagonists other than palonosetron were omitted from the  
322 recommendations. This decision was taken for one or more of the following reasons: 1) the agent  
323 is currently recommended for acute CINV prophylaxis; 2) it is not available in a dosage form  
324 suitable for pediatric use; 3) outcome data have only been reported in an extremely small number  
325 of patients; 4) there is a lack efficacy data in the context of modern CINV prophylaxis or 5) the  
326 agent is difficult to administer safely.

327

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

332

333 No specific evidence was identified that evaluated the escalation of CINV prophylaxis as a  
334 preventative measure for refractory CINV in children. The panel felt that escalation of  
335 prophylaxis is a logical approach that is grounded in the evidence described previously in  
336 Recommendation 1.1.

337  
338 This recommendation places a high value on the possible control of refractory CINV in the acute  
339 phase by provision of acute CINV prophylaxis (pharmacological and non-pharmacological)  
340 known to be effective in the setting of more emetogenic chemotherapy. It is a strong  
341 recommendation because the guideline panel is certain that the benefits of acute CINV  
342 prophylaxis escalation outweigh the low risk of harms associated with the interventions.

343  
344 **Recommendation 2.2:** For children receiving acute CINV prophylaxis recommended for HEC,  
345 we suggest that the 5-HT<sub>3</sub> antagonist given for CINV prophylaxis be changed from ondansetron  
346 or granisetron to palonosetron. In jurisdictions where palonosetron is not available, we suggest  
347 that granisetron be substituted for ondansetron.

348  
349 ***Switching from ondansetron or granisetron to palonosetron***

350 **Adult Patients**

351 Two prospective open-label studies were identified. The first evaluated the efficacy and safety of  
352 a single IV dose of palonosetron in adults receiving chemotherapy with low emetogenic potential  
353 who had experienced refractory CINV.[24] Complete acute CINV control was achieved in 29 of  
354 34 (85.3%) patients. A second study evaluated the efficacy of palonosetron in preventing  
355 refractory CINV in adults who had previously received CINV prophylaxis with either  
356 granisetron or ondansetron.[25] Complete CINV control rates in the acute and delayed phases of  
357 77% and 81% were observed, respectively. The most commonly reported adverse effects  
358 reported by patients in this study were constipation and anxiety; no patient experienced severe  
359 toxicity.

360

361 **Pediatric Patients**

362 No evidence was identified that described switching from ondansetron or granisetron to  
363 palonosetron in children for the prevention of refractory CINV. Palonosetron was recently



364 approved for use in pediatric patients in the United States for prevention of acute CINV as a  
365 single dose of 20 µg/kg (max 1.5 mg) prior to chemotherapy[26]. The limited, peer-reviewed,  
366 published evidence to support its use in children has been summarized previously.[11]

367

368 This recommendation is consistent with adult guidelines related to palonosetron since it is  
369 considered the 5-HT<sub>3</sub> antagonist of choice in adults receiving MEC.[15,27]It places a high value  
370 on the improved CINV control seen in adult cancer patients receiving palonosetron. It places  
371 less value on drug cost in the scenario where less expensive alternatives have been ineffective. It  
372 is a weak recommendation because direct evidence of the comparative efficacy of palonosetron  
373 for prevention of refractory CINV in children is not available. However, the available  
374 information (including approval by the US Food and Drug Administration for the prevention of  
375 CINV in children) indicates that palonosetron can be used safely in pediatric cancer patients.

376

### 377 ***Switching from ondansetron to granisetron***

378 Either ondansetron or granisetron is recommended for acute CINV prophylaxis in all children  
379 receiving chemotherapy of low, moderate or high emetogenic risk.[11] There is no evidence to  
380 support use of one first generation 5-HT<sub>3</sub> receptor antagonist over the other in children.

381 However, ondansetron is primarily metabolized via the cytochrome P450 CYP 2D6 enzyme and  
382 studies in adults have shown that polymorphisms in this enzyme predispose patients to poor  
383 CINV control secondary to rapid ondansetron metabolism.[28]

384

#### 385 **Adult Patients**

386 A single study was identified that evaluated the efficacy of granisetron after CINV failure while  
387 receiving ondansetron in adults receiving HEC.[29] The authors reported complete CINV control  
388 (no vomiting and no or mild nausea) in 47% (9/19) of patients who received granisetron while  
389 only 5% (1/21) of patients who continued to receive ondansetron experienced complete CINV  
390 control (p = 0.005).

391

#### 392 **Pediatric Patients**

393 No evidence was identified that described switching from ondansetron to granisetron in children  
394 for the prevention of refractory CINV.



395

396 If palonosetron is not available, it is suggested that granisetron be substituted for ondansetron in  
397 patients who experienced refractory CINV while receiving ondansetron. This recommendation  
398 is based on the potential for genetic variability in the enzymes responsible for metabolizing  
399 ondansetron. It places a high value on the improved CINV control seen in adult cancer patients  
400 receiving granisetron who have a genetic predisposition to a poor response to ondansetron at  
401 usual doses. It places less value on drug cost in the scenario where a less expensive alternative  
402 has been ineffective. It is a weak recommendation because direct evidence of using an alternative  
403 5HT-3 antagonist for prevention of refractory CINV in children is not available.

404

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

409

410 The use of aprepitant is currently recommended for acute CINV prophylaxis in children greater  
411 than or equal to 12 years of age receiving HEC which is not known or suspected to interact with  
412 this agent[11] and recent evidence supports its use in children as young as 6 months.[30]

413 Aprepitant is a CYP3A4 substrate and an inhibitor of CYP2C9/8 and CYP2C19. As a result, it  
414 may potentially interact with medications, including chemotherapy, metabolized via these  
415 pathways. The issues which must be considered when using aprepitant in pediatric patients have  
416 been summarized previously.[11] Interactions with chemotherapy which may lead to an  
417 increased risk of short and long-term toxicity are of primary concern. However, direct evidence  
418 of these interactions is often unavailable and interpretation of the results of available studies that  
419 do evaluate aprepitant/fosaprepitant interactions with chemotherapy varies.

420

421 Adult Patients

422 Six prospective, open-label studies were identified that evaluated the use of aprepitant in adults  
423 with refractory CINV receiving MEC or HEC. Since guidelines for CINV prophylaxis in adult  
424 cancer patients now recommend the use of aprepitant or its intravenous pro-drug fosaprepitant,

425 as prophylaxis for HEC and for some MEC regimens,[15,16,27] studies of aprepitant for  
426 breakthrough CINV will not be discussed since this approach is no longer applicable.

427

#### 428 Pediatric Patients

429 One study was identified describing the use of aprepitant in children and adolescents with  
430 refractory CINV.[23] Bauters et al retrospectively evaluated the addition of aprepitant using the  
431 recommended adult dose (125 mg on day one prior to chemotherapy followed by 80 mg once  
432 daily on days 2 and 3) to a 5-HT3 antagonist plus dexamethasone in 20 patients 8 - 16 years of  
433 age during 104 MEC or HEC blocks. Complete control of vomiting in the acute phase was  
434 achieved in 86% of chemotherapy blocks. The authors described aprepitant as well-tolerated in  
435 combination with other antiemetics.

436

437 Additional experience with the use of aprepitant in adolescents is summarized in the pediatric  
438 acute CINV prophylaxis guideline.[11] Information regarding the use of aprepitant in younger  
439 children is growing and it is now approved in the US for use in children **6 months of age and**  
440 **older**. [30-35] Published experience with fosaprepitant in children is limited[36].

441

442 This recommendation places a high value on improved CINV control when control is likely to be  
443 difficult to achieve and on the negative consequences of uncontrolled CINV. It is a weak  
444 recommendation since direct evidence of the efficacy of aprepitant in this context is lacking.  
445 The potential improvement in CINV control offered by the addition of aprepitant should be  
446 weighed against the short and long-term toxicities resulting from potential interactions with  
447 chemotherapy. It is essential to include the patient, when appropriate, and family in this  
448 discussion so their values can be incorporated into the decision-making process. The relative  
449 risks of aprepitant (potential for drug interaction with chemotherapy and altered chemotherapy  
450 exposure) and benefits (CINV control) should be determined on a case-by-case basis.

451

452 **Recommendation 2.4:** For children experiencing refractory CINV despite initiation of the  
453 previous recommendations, we suggest that **one** of the following interventions be added to the  
454 CINV prophylaxis provided: interventions that were employed successfully for the treatment of  
455 breakthrough CINV in previous treatment blocks (olanzapine, methotrimeprazine or

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

458

459 ***Inclusion of successful interventions aimed at breakthrough CINV in acute CINV prophylaxis***

460 No specific evidence was identified that evaluated the efficacy of incorporating successful  
461 breakthrough CINV interventions from previous treatment blocks into the CINV prophylaxis  
462 provided for future chemotherapy blocks in children. Again, the panel felt that this is a logical  
463 approach and is another example of providing individualized care for patients. Olanzapine has  
464 been recommended for the treatment of breakthrough CINV in Recommendation 1.2. For  
465 children who cannot receive olanzapine, methotrimeprazine and metoclopramide have been  
466 recommended. In one study,[37] 62% of adults with refractory CINV achieved complete CINV  
467 control after administration of methotrimeprazine.

468

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

474

475 ***Addition of acupressure or acupuncture to acute CINV prophylaxis***

476 Adult Patients

477 One study evaluating the use of acupressure, [38] and another evaluating the use of electro-  
478 acupuncture[39] in adults with cancer were identified. Both were prospective, open-label studies  
479 of Nei Guan (P6) stimulation. It was not possible to determine if the CINV prophylaxis given in  
480 combination with acupressure was consistent with contemporary recommendations. However,  
481 68% of patients had complete control of vomiting. Combining electro-acupuncture with CINV  
482 prophylaxis consistent with contemporary recommendations resulted in complete vomiting  
483 control in 37% of adult patients.

484

485

486 Pediatric patients

487 No evidence was identified that described the use of acupressure or electroacupuncture in  
488 children for the prevention of refractory CINV.

489

490 This recommendation places a high value on the possibility that acupressure or acupuncture may  
491 increase control of CINV in patients who have experienced refractory CINV with a low potential  
492 for harm. It is a weak recommendation because there is a single study to support the use of each  
493 intervention in adults and there is no direct information regarding the efficacy or safety of  
494 acupressure/acupuncture in children with refractory CINV.

495

#### 496 **Research Gaps**

497 The gaps in the evidence available to support recommendations for the control of breakthrough  
498 and refractory CINV in children are substantial. Examples are provided in Table III.

499

#### 500 **Conclusions**

501 Recommendations for the treatment of breakthrough CINV and prevention of refractory CINV in  
502 children are summarized in Table I. These recommendations are based on a systematic review of  
503 the literature. However, there are many gaps in the available evidence. Optimization of CINV  
504 control in children requires delivery of care based on the best available evidence and the  
505 prospective evaluation of both new and old antiemetic agents.

506

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518

519 **Conflict of Interest Statement**

520 None of the authors have a conflict of interest with respect to the content of this paper.

521

522

For Peer Review

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647

### 648 **Legends**

649 Figure 1: Interventions to treat breakthrough chemotherapy-induced nausea and vomiting

650 (CINV) or prevent CINV in refractory patients: flowchart of literature identification process

651 Supplementary Table I: Guideline Search Strategy

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

653 Supplementary Table III: Search Strategies for Systematic Reviews of Pediatric

654 Methotrimeprazine (Levomepromazine) Studies

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

656 Supplementary Table V: Adverse Effects Reported in Pediatric Studies Evaluating the Use of

657 Methotrimeprazine (Levopromazine) – Summary of Included Studies

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

659 Included Studies

660 Supplementary Table VII: Health questions, summary of recommendations and remarks for the

661 treatment of breakthrough chemotherapy-induced nausea and vomiting (CINV) and the

662 prevention of refractory CINV in children

TABLE I: Health questions and summary of recommendations for the treatment of breakthrough chemotherapy-induced nausea and vomiting (CINV) and the prevention of refractory CINV in children. A recommendation summary table that includes the remarks for each recommendation is presented in [Supplementary Table VII](#).

Health Questions and Recommendations	Strength of Recommendation & Level of Evidence <sup>9,10</sup>
<p><b>Health Question #1: What interventions are recommended to treat breakthrough CINV in children?</b></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><b>Recommendation 1.1:</b> 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>Strong Recommendation Very Low Quality Evidence</p>
<p><b>Recommendation 1.2:</b> For children receiving acute CINV prophylaxis recommended for highly emetogenic chemotherapy, we suggest that olanzapine be added to guideline-consistent CINV prophylaxis.</p>	<p>Weak Recommendation Low Quality Evidence</p>
<p><b>Recommendation 1.3:</b> 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"> <li>• methotrimeprazine (also known as levomepromazine) or</li> <li>• metoclopramide (in children older than 1 year)</li> </ul> <p><b>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.</b></p>	<p>Weak Recommendation Very Low Quality Evidence</p>

### **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

**Recommendation 2.2:** For children receiving acute CINV prophylaxis recommended for highly emetogenic chemotherapy, we suggest that the 5-HT<sub>3</sub> 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 for ondansetron.

Weak  
Recommendation  
Very Low Quality  
Evidence

**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

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

Weak  
Recommendation  
Very Low Quality  
Evidence

Weak  
Recommendation  
Very Low Quality  
Evidence

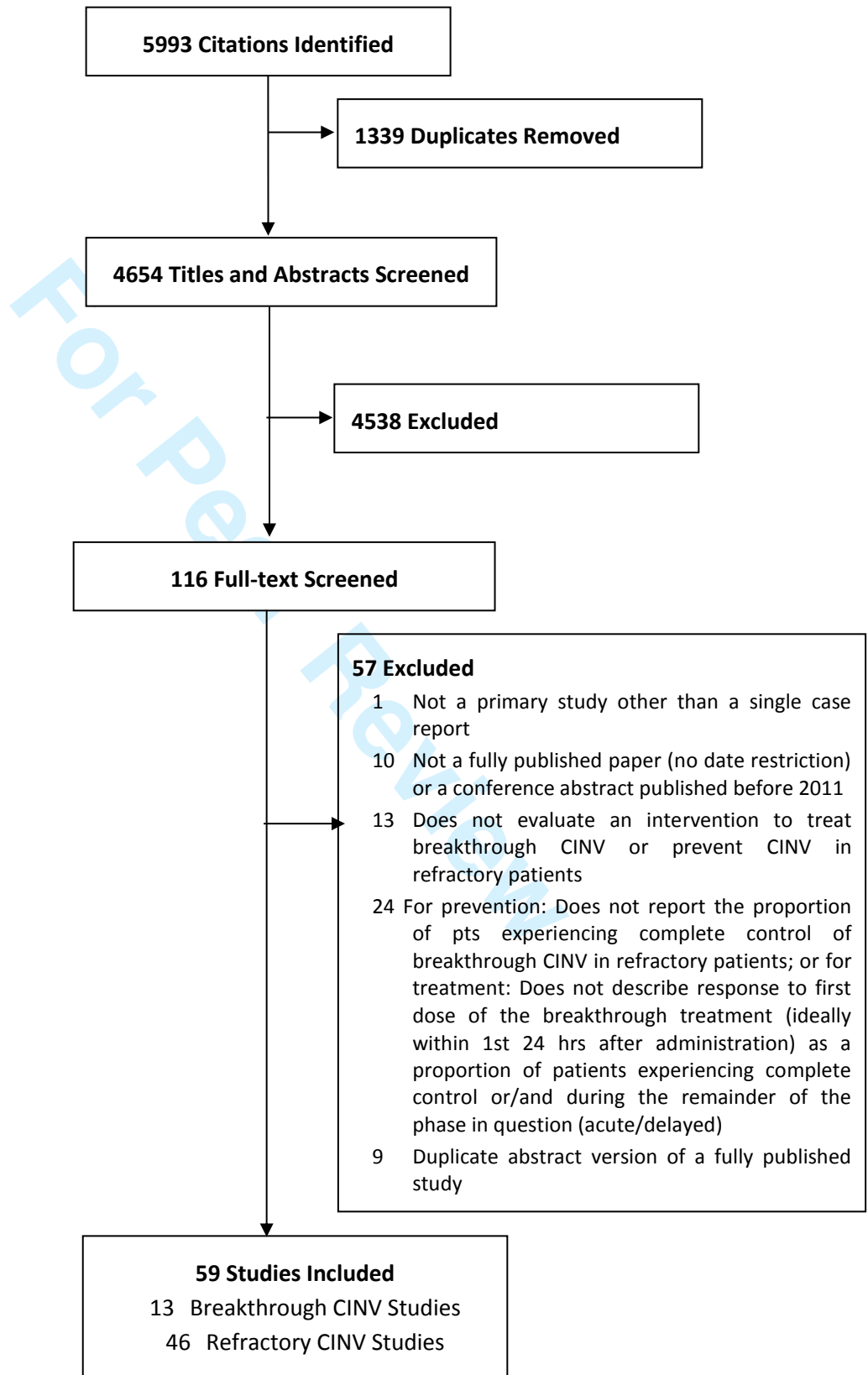
TABLE II: Study inclusion criteria for three systematic reviews undertaken

<b>Guidelines</b>	
(i)	provided recommendations specifically for the management of breakthrough and/or refractory CINV;
(ii)	were published in 2012 or more recently;
(iii)	were based on a systematic review of the literature and
(iv)	were published in English.
<b>Treatment of breakthrough CINV and prevention of CINV in patients who have experienced refractory CINV</b>	
(i)	were primary studies, other than single case reports;
(ii)	were either fully published studies (no date restriction) or conference abstracts published in 2011 or more recently;
(iii)	evaluated an intervention to treat breakthrough CINV or prevent CINV in refractory patients;
(iv)	for prevention interventions: reported the proportion of patients experiencing complete control of CINV in refractory patients; and
(v)	for treatment interventions: described the response to the first dose of the breakthrough treatment (ideally within the first 24 hrs after administration) as a proportion of patients experiencing complete control or/and during the remainder of the phase in question (acute/delayed).
<b>Safety of methotrimeprazine in children</b>	
(i)	published in English in a journal in full text or a letter to the editor reporting primary data;
(ii)	included patients $\leq 18$ years of age and either results were reported separately for patients $\leq 18$ years of age or the mean or median age of participants was $\leq 18$ years;
(iii)	described the adverse effects associated with the use of methotrimeprazine; and
(iv)	the methotrimeprazine dose used was provided or, in the case of poisoning where the dose ingested was not able to be determined, a blood methotrimeprazine concentration was reported.

TABLE III: Examples of research gaps identified in the domain of treatment of breakthrough chemotherapy-induced nausea and vomiting and the prevention of refractory CINV in children

Domain	Issues
Breakthrough CINV	<ul style="list-style-type: none"> <li>• efficacy of CINV prophylaxis escalation</li> </ul>
	<ul style="list-style-type: none"> <li>• optimal dose, efficacy and safety of olanzapine and methotrimeprazine</li> </ul>
	<ul style="list-style-type: none"> <li>• optimal dose, efficacy of metoclopramide and risk factors for toxicity</li> </ul>
Refractory CINV	<ul style="list-style-type: none"> <li>• optimal palonosetron dose in children receiving multiple day chemotherapy</li> </ul>
	<ul style="list-style-type: none"> <li>• extent and clinical significance of interactions between aprepitant and chemotherapy</li> </ul>

Figure 1: Interventions to treat breakthrough CINV or prevent CINV in refractory patients: flowchart of literature identification process



**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")

For Peer Review

**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
<b>Pediatric Studies</b>				
No studies identified				
<b>Adult Studies</b>				
<b>5HT-3 Antagonist - Granisetron</b>				
Jones (2011) [1]	<ul style="list-style-type: none"> <li>Prospective observational trial</li> <li>Aim: Describe the response to antiemetic therapy taken for breakthrough CINV</li> <li>N = 27</li> <li>Adults with cancer receiving chemotherapy</li> <li>Median age: 57 yrs; range: 30-72 yrs</li> <li>CINV assessment: patient report</li> <li>Emetogenicity classification: moderately or highly emetogenic</li> </ul>	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: <b>Prochlorperazine</b> 10mg PO (n=24)  G2: <b>5-HT antagonist</b> (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)
Marty (1990)[2]	<ul style="list-style-type: none"> <li>Prospective trial</li> <li>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</li> <li>N = 23</li> <li>Adults with cancer receiving chemotherapy</li> <li>Median age: Not reported for breakthrough cohort</li> <li>CINV assessment: patient and clinician report</li> <li>Emetogenicity classification: moderately or highly emetogenic</li> </ul>	Moderate or severe nausea	Prophylactic regimen: Granisetron 40mcg/kg IV (5 min pre-chemo)  *Guideline consistent antiemetic prophylaxis: <b>no</b>  Breakthrough intervention: Additional <b>Granisetron</b> doses of 40mcg/kg IV up to a maximum of 120mcg/kg	Proportion with complete control of breakthrough CINV after 1 additional granisetron dose: 11/23 (47.8%)  Proportion with complete control of breakthrough CINV after 2 additional granisetron doses: 4/8 (50%)  Time of occurrence of breakthrough CINV: acute phase  Timeframe of assessments: acute phase (30min after administration of additional granisetron doses)

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"> <li>Prospective open-label study</li> <li>Aim: Compare the efficacy and safety of 3 different doses of granisetron, evaluation of rescue with a second dose of granisetron was evaluated secondarily</li> <li>N = 64</li> <li>Adult patients receiving cisplatin-containing chemotherapy</li> <li>Median age: Not reported for breakthrough cohort</li> <li>CINV assessment: patient and clinician report</li> <li>Emetogenicity classification: highly emetogenic</li> </ul>	Moderate or severe nausea (more than mild nausea or vomiting occurred)	<p>Prophylactic regimen for all patients (5 min pre-chemo):</p> <p>G1: Granisetron 2mcg/kg IV G2: Granisetron 10mcg/kg IV G3: Granisetron 40mcg/kg IV</p> <p>*Guideline consistent antiemetic prophylaxis: <b>no</b></p> <p>Breakthrough intervention: <b>Granisetron</b> 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:</p> <p>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:</p> <p>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"> <li>Prospective observational trial</li> <li>Aim: Determine the usefulness of granisetron rescue therapy for CINV</li> <li>N = 20</li> <li>Adults with urogenital malignant tumors receiving chemotherapy (including cisplatin)</li> <li>Mean age: 61.9 ± 15 yrs; range: 25-76 yrs</li> <li>CINV assessment: Not reported, patients examined by a healthcare professional q6h for 24hrs</li> <li>Emetogenicity classification: highly emetogenic</li> </ul>	No response to antiemetics or emesis	<p><b>Prophylactic regimen:</b> Not reported</p> <p>*Guideline consistent antiemetic prophylaxis: unable to determine/not reported</p> <p>Breakthrough intervention: <b>Granisetron</b> 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>
<b>5HT-3 Antagonist - Ondansetron</b>				
Ariyoshi (1992)[5]	<ul style="list-style-type: none"> <li>Double-blind randomized comparison with placebo</li> <li>Aim: Determine the antiemetic efficacy and safety of ondansetron tablets</li> <li>N = 12</li> <li>Adults with cancer receiving a single dose of cisplatin 50mg/m<sup>2</sup> or higher</li> <li>Median Age: Not reported for breakthrough cohort</li> <li>CINV assessment: Not reported, patients examined by a healthcare professional q6h for 24hrs</li> <li>Emetogenicity classification: highly emetogenic</li> </ul>	"Satisfactory" anti-emetic effects not obtained	<p><b>Prophylactic regimen:</b> Ondansetron 4mg PO once (2hrs pre-chemo)</p> <p>*Guideline consistent antiemetic prophylaxis: <b>no</b></p> <p>Breakthrough intervention: <b>Ondansetron</b> 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"> <li>Open-label randomized trial</li> <li>Aim: evaluate the efficacy and safety of two different schedules of ondansetron as rescue antiemetic treatment</li> <li>N = 44</li> <li>Adults with cancer receiving chemotherapy</li> <li>Median age: Not reported for breakthrough cohorts</li> <li>CINV assessment: patient report</li> <li>Emetogenicity classification: moderately emetogenic</li> </ul>	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: <b>yes</b></p> <p>Breakthrough intervention: G1: <b>Ondansetron</b> 8mg IM (n=22) G2: ODT <b>ondansetron</b> 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"> <li>Prospective observational trial</li> <li>Aim: Describe the response to antiemetic therapy taken for breakthrough CINV</li> <li>N = 27</li> <li>Adults with cancer receiving chemotherapy</li> <li>Median age: 57 yrs; range: 30-72 yrs</li> <li>CINV assessment: patient report</li> <li>Emetogenicity classification: moderately or highly emetogenic</li> </ul>	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: <b>Prochlorperazine</b> 10mg PO (n=24) G2: <b>5-HT antagonist</b> (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"> <li>Double-blind randomized comparison with placebo</li> <li>Aim: Determine the antiemetic efficacy and safety of IV ondansetron</li> <li>N = 7</li> <li>Adults with cancer receiving a single dose of cisplatin 50mg/m<sup>2</sup> or higher</li> <li>Median age: Not reported for breakthrough cohort</li> <li>CINV assessment: Not reported, patients examined by a healthcare professional q6h for 24hrs</li> <li>Emetogenicity classification: highly emetogenic</li> </ul>	Insufficient anti-emetic effect after initial dose of IV ondansetron	<p><b>Prophylactic regimen:</b> Ondansetron 4mg IV (15 min pre-chemo)</p> <p>*Guideline consistent antiemetic prophylaxis: <b>no</b></p> <p>Breakthrough intervention: <b>Ondansetron</b> 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
<b>5HT-3 Antagonist - Palonosetron</b>				
Musso (2009)[8]	<ul style="list-style-type: none"> <li>▪ Prospective observational trial</li> <li>▪ 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</li> <li>▪ N =27</li> <li>▪ Adolescents and adults with haematological malignancies receiving multiple day chemotherapy (2-7 days)</li> <li>▪ Median age: Not reported for breakthrough cohorts</li> <li>▪ CINV assessment: patient report</li> <li>▪ Emetogenicity classification: moderately or highly emetogenic</li> </ul>	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: <b>yes</b> for MEC, <b>no</b> for HEC</p> <p>Breakthrough intervention:</p> <p>G1: <b>Palonosetron</b> 0.25mg IV 72 hrs after administration of the first dose</p> <p>G2: <b>Metoclopramide</b> 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"> <li>▪ Prospective open-label trial</li> <li>▪ 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</li> <li>▪ N = 51</li> <li>▪ Adolescents and adults with haematological malignancies receiving conditioning for autologous stem cell transplant</li> <li>▪ Median age: Not reported for breakthrough cohorts</li> <li>▪ CINV assessment: patient reported</li> <li>▪ Emetogenicity classification: moderately or highly emetogenic</li> </ul>	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: <b>no</b></p> <p>Breakthrough intervention:</p> <p><b>Palonosetron</b> 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
<b>Methotrimeprazine</b>				
McCabe (2003)[10]	<ul style="list-style-type: none"> <li>▪ Prospective observational study</li> <li>▪ Aim: Evaluate the efficacy of levomepromazine for management of breakthrough CINV</li> <li>▪ N = 32</li> <li>▪ Adult patients with high grade delayed chemotherapy-induced emesis requiring hospital admission to control this</li> <li>▪ Median age: 58 yrs; range: 35-76 yrs</li> <li>▪ CINV assessment: patient report</li> <li>▪ Emetogenicity classification: highly emetogenic</li> </ul>	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: <b>Levomepromazine</b> 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>
<b>Metoclopramide</b>				
Musso (2009)[8]	<ul style="list-style-type: none"> <li>▪ Prospective observational trial</li> <li>▪ 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</li> <li>▪ N =27</li> <li>▪ Adolescents and adults with haematological malignancies receiving multiple day chemotherapy (2-7 days)</li> <li>▪ Median age: Not reported for breakthrough cohorts</li> <li>▪ CINV assessment: patient report</li> <li>▪ Emetogenicity classification: moderately or highly emetogenic</li> </ul>	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: <b>yes</b> for MEC, <b>no</b> for HEC</p> <p>Breakthrough intervention:</p> <p>G1: <b>Palonosetron</b> 0.25mg IV 72 hrs after administration of the first dose</p> <p>G2: <b>Metoclopramide</b> 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"> <li>▪ Double-blinded randomized trial</li> <li>▪ Aim: Compare the use of olanzapine vs metoclopramide for the treatment of breakthrough CINV</li> <li>▪ N = 108</li> <li>▪ Chemotherapy-naïve adults with cancer receiving chemotherapy (cisplatin <math>\geq 70\text{mg}/\text{m}^2</math> or doxorubicin <math>\geq 50\text{mg}/\text{m}^2</math> + cyclophosphamide <math>\geq 600\text{mg}/\text{m}^2</math>)</li> <li>▪ Median age: G1: 61 yrs; range: 38-75 yrs G2: 63 yrs; range: 42-79 yrs</li> <li>▪ CINV assessment: patient report</li> <li>▪ Emetogenicity classification: highly emetogenic</li> </ul>	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: <b>yes</b></p> <p>Breakthrough intervention: G1: <b>Olanzapine</b> 10mg PO once daily x 3 days (n=56) G2: <b>Metoclopramide</b> 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&lt;0.01</p> <p>Proportion with complete control of breakthrough nausea: G1: 38/56 (68%) G2: 12/52 (23%) p&lt;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>
<b>Olanzapine</b>				
Chanthawong (2014)[12]	<ul style="list-style-type: none"> <li>▪ Phase II open label pilot study</li> <li>▪ Aim: Evaluate the efficacy and safety of olanzapine for breakthrough CINV</li> <li>▪ N = 46</li> <li>▪ Adults with cancer receiving chemotherapy</li> <li>▪ Median age: 33.5 yrs (males; 18 yrs (females))</li> <li>▪ Emetogenicity classification: highly emetogenic</li> </ul>	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: <b>no</b></p> <p>Breakthrough intervention: <b>Olanzapine</b> 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"> <li>▪ Double-blinded randomized trial</li> <li>▪ Aim: Compare the use of olanzapine vs metoclopramide for the treatment of breakthrough CINV</li> <li>▪ N = 108</li> <li>▪ Chemotherapy-naïve adults with cancer receiving chemotherapy (cisplatin <math>\geq 70\text{mg}/\text{m}^2</math> or doxorubicin <math>\geq 50\text{mg}/\text{m}^2</math> + cyclophosphamide <math>\geq 600\text{mg}/\text{m}^2</math>)</li> <li>▪ Median age: G1: 61 yrs; range: 38-75 yrs G2: 63 yrs; range: 42-79 yrs</li> <li>▪ CINV assessment: patient report</li> <li>▪ Emetogenicity classification: highly emetogenic</li> </ul>	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: <b>yes</b></p> <p>Breakthrough intervention: G1: <b>Olanzapine</b> 10mg PO once daily x 3 days (n=56) G2: <b>Metoclopramide</b> 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&lt;0.01</p> <p>Proportion with complete control of breakthrough nausea: G1: 38/56 (68%) G2: 12/52 (23%) p&lt;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
<b>Prochlorperazine</b>				
Jones (2011)[1]	<ul style="list-style-type: none"> <li>Prospective observational trial</li> <li>Aim: Describe the response to antiemetic therapy taken for breakthrough CINV</li> <li>N = 27</li> <li>Adults with cancer receiving chemotherapy</li> <li>Median age: 57 yrs; range: 30-72 yrs</li> <li>CINV assessment: patient report</li> <li>Emetogenicity classification: moderately or highly emetogenic</li> </ul>	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: <b>Prochlorperazine</b> 10mg PO (n=24)  G2: <b>5-HT antagonist</b> (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)
<b>Other</b>				
Bleicher (2008)[13]	<ul style="list-style-type: none"> <li>2 prospective open-label trials</li> <li>Aim: Describe the efficacy of ABH gel in reducing breakthrough CINV</li> <li>N = 33</li> <li>Adults with cancer receiving chemotherapy</li> <li>Median age: Not reported</li> <li>CINV assessment: patient report</li> <li>Emetogenicity classification: highly emetogenic</li> </ul>	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 <b>ABH gel</b> 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
<b>Randomized or Non-Randomized Trials</b>							
None							
<b>Retrospective Reviews, Case Series and Case Reports</b>							
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
<b>Pediatric Studies</b>				
<b>5HT-3 Antagonist – Tropisetron</b>				
Hachimi-Idrissi (1993)[18]	<ul style="list-style-type: none"> <li>Prospective open-label trial</li> <li>Aim: Determine the efficacy and tolerability of ICS 205-930 (tropisetron) in children with refractory CINV</li> <li>N = 19 (169 chemotherapy courses)</li> <li>Children with cancer receiving chemotherapy over 1-5 days</li> <li>Median age: 9 yrs; range: 2-16yrs</li> <li>CINV assessment: parent report</li> <li>Emetogenicity classification: moderately or highly emetogenic</li> </ul>	<p>Grade 3 emesis (&gt; 4 episodes of vomiting/day)</p> <p><b>Previous prophylactic regimen:</b> Alizapride 4-6mg/kg/day or metoclopramide 5mg/kg day</p> <p>Guideline consistent antiemetic prophylaxis: no</p>	<b>Tropisetron</b> 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>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>
<b>Aprepitant</b>				
Bauters (2013)[19]	<ul style="list-style-type: none"> <li>Retrospective, observational study</li> <li>Aim: Determine the efficacy of aprepitant in children and adolescents with refractory CINV</li> <li>N = 20 (104 chemotherapy cycles)</li> <li>Children with cancer receiving chemotherapy</li> <li>Mean age: 14 yrs; range: 8-16yrs</li> <li>CINV assessment: Only vomiting evaluated</li> <li>Emetogenicity classification: moderately or highly emetogenic</li> </ul>	<p>Intolerable and uncontrollable emesis in the preceding chemo cycle</p> <p><b>Previous prophylactic regimen:</b> Tropisetron 0.2mg/kg IV once daily (max 5mg) or ondansetron 5-8mg/m<sup>2</sup> bid (max 8mg/dose) or granisetron 0.04mg/kg once daily (max 9mg) + dexamethasone 3mg/m<sup>2</sup> once-twice daily given at least 30 minutes prior to chemo</p> <p>Guideline consistent antiemetic prophylaxis: <b>yes</b> (no for patients receiving HEC &gt; 12yrs where aprepitant use permitted)</p>	<p>Day 1: <b>Aprepitant</b> 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/m<sup>2</sup> bid (max 8mg/dose) or granisetron 0.04mg/kg once daily (max 9mg) + dexamethasone 1.5mg/m<sup>2</sup> 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
<b>Adult Studies</b>				
<b>5HT-3 Antagonists – Granisetron</b>				
Arevalo-Araujo (2013)[20] [abstract]	<ul style="list-style-type: none"> <li>▪ Prospective trial (abstract)</li> <li>▪ Aim: Determine the antiemetic efficacy of APF530 (sustained formulation of granisetron) in refractory patients</li> <li>▪ N = 72</li> <li>▪ Adults with cancer receiving chemotherapy</li> <li>▪ Median age: not reported</li> <li>▪ CINV assessment: not reported</li> <li>▪ Emetogenicity classification: moderately or highly emetogenic</li> </ul>	<p>Failure to achieve a complete response (no emesis or rescue medication) with palonosetron during cycle 1</p> <p><b>Previous Prophylactic regimen:</b> Palonosetron 0.25mg IV</p> <p>Guideline consistent antiemetic prophylaxis: no</p>	<p><b>APF530</b> (sustained formulation of granisetron) 500mg SC</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 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"> <li>▪ Prospective open-label trial</li> <li>▪ Aim: evaluate the tolerability and antiemetic efficacy of granisetron in refractory patients</li> <li>▪ N = 456</li> <li>▪ Adults with cancer receiving chemotherapy</li> <li>▪ Median age: not reported for refractory cohort</li> <li>▪ CINV assessment: patient report and direct observation for a minimum of 2hrs from the onset of chemotherapy administration</li> <li>▪ Emetogenicity classification: unable to determine/not reported</li> </ul>	<p>Failed antiemetic therapy during the previous cycle</p> <p><b>Previous prophylactic regimens:</b> One or more of the following: metoclopramide, Dexamethasone, alizapride, ondansetron, chlorpromazine, "other"</p> <p>Guideline consistent antiemetic prophylaxis: unable to determine/not reported</p>	<p><b>Granisetron</b> 3mg IV once 5min prior to chemo + up to 2 additional doses of granisetron 3mg IV with at least 10min between doses</p>	<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"> <li>▪ Randomized, double-blind trial</li> <li>▪ Aim: evaluate the efficacy of crossing over to granisetron after CINV failure while receiving ondansetron</li> <li>▪ N = 40</li> <li>▪ Adults with cancer receiving cisplatin-or cyclophosphamide-based chemotherapy</li> <li>▪ Median age: G1: 46yrs; range: 29-71yrs G2: 46yrs; range: 30-73yrs</li> <li>▪ CINV assessment: patient report</li> <li>▪ Emetogenicity classification: highly emetogenic</li> </ul>	<p>≥ 2 vomits and/or severe nausea (no significant intake possible) or nausea lasting &gt; 4hrs</p> <p><b>Previous prophylactic regimen:</b> Day 1: Ondansetron 8mg IV + dexamethasone 10mg IV</p> <p>Guideline consistent antiemetic prophylaxis: no</p>	<p>G1: <b>Granisetron</b> 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"> <li>▪ Prospective open-label trial</li> <li>▪ Aim: Determine the antiemetic efficacy of granisetron + prednisolone + metopimazine in refractory patients</li> <li>▪ N = 25</li> <li>▪ Adults with breast cancer receiving cyclophosphamide + fluorouracil + either methotrexate or epirubicin</li> <li>▪ Median age: 45yrs; range: 29-66yrs</li> <li>▪ CINV assessment: patient report</li> <li>▪ Emetogenicity classification: moderately emetogenic</li> </ul>	<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><b>Previous prophylactic regimen:</b> 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><b>Granisetron</b> 3mg IV once + <b>prednisolone</b> 25mg PO once a day x 3 days + <b>metopimazine</b> 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
<b>5HT-3 Antagonists – Ondansetron</b>				
Campora (1991)[24]	<ul style="list-style-type: none"> <li>▪ Prospective open-label trial</li> <li>▪ Aim: Evaluate the efficacy of ondansetron for antiemetic prophylaxis in refractory patients</li> <li>▪ N = 24</li> <li>▪ Adults with cancer receiving chemotherapy</li> <li>▪ Median age: 53yrs; range: 21-70yrs</li> <li>▪ CINV assessment: patient report</li> <li>▪ Emetogenicity classification: moderately or highly emetogenic</li> </ul>	<p>&gt; 15 emetic episodes within 24hrs of therapy while receiving combination antiemetics</p> <p><b>Previous prophylactic regimen:</b> 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>	<p><b>Ondansetron</b> 8mg PO prior to chemo and repeated after 6 and 12hrs on day 1, then 8mg PO tid on days 2-5</p>	<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"> <li>▪ Randomized, double-blind trial</li> <li>▪ Aim: evaluate the efficacy of crossing over to granisetron after CINV failure while receiving ondansetron</li> <li>▪ N = 40</li> <li>▪ Adults with cancer receiving cisplatin-or cyclophosphamide-based chemotherapy</li> <li>▪ Median age: G1: 46yrs; range: 29-71yrs G2: 46yrs; range: 30-73yrs</li> <li>▪ CINV assessment: patient report</li> <li>▪ Emetogenicity classification: highly emetogenic</li> </ul>	<p>≥ 2 vomits and/or severe nausea (no significant intake possible) or nausea lasting &gt; 4hrs</p> <p><b>Previous prophylactic regimen:</b> Day 1: Ondansetron 8mg IV + dexamethasone 10mg IV</p> <p>Guideline consistent antiemetic prophylaxis: no</p>	<p>G1: <b>Granisetron</b> 3mg IV + dexamethasone 10mg IV (n=19) 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"> <li>▪ Prospective open-label trial</li> <li>▪ Aim: Determine the antiemetic efficacy of ondansetron</li> <li>▪ N = 17 (34 chemotherapy cycles)</li> <li>▪ Adults with cancer receiving platinum based chemotherapy</li> <li>▪ Median age: 63.5yrs; range 41-75yrs</li> <li>▪ CINV assessment: Patient report</li> <li>▪ Emetogenicity classification: highly emetogenic</li> </ul>	<p>Severe emesis refractory to standard antiemetic regimen</p> <p><b>Previous prophylactic regimen:</b> Metoclopramide (2-3mg/kg) ± additional antiemetics</p> <p>Guideline consistent antiemetic prophylaxis: no</p>	<p>Day 1: <b>Ondansetron</b> 8mg IV 30 min prior to chemo, then 1mg/hr as a continuous infusion over 8-24hrs 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"> <li>Prospective open-label trial</li> <li>Aim: Report on experience with ondansetron for antiemetic prophylaxis in refractory patients</li> <li>N = 25</li> <li>Adults with ovarian cancer or testicular germ cell tumors receiving carboplatin + etoposide</li> <li>Median age: 52yrs; range: 24-68yrs</li> <li>CINV assessment: patient report</li> <li>Emetogenicity classification: highly emetogenic</li> </ul>	<p>Multiple episodes of vomiting (<math>\geq 3</math>) during the first 24hrs of the previous course of chemo</p> <p><b>Previous prophylactic regimens:</b>            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><b>Ondansetron</b> 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"> <li>Prospective open-label trial</li> <li>Aim: Report on experience with ondansetron in refractory patients</li> <li>N = 91</li> <li>Adults with cancer receiving chemotherapy</li> <li>Median age:            G1 (non-cisplatin chemotherapy): 47 yrs; range: 19-72yrs            G2 (cisplatin-based chemotherapy): 33yrs; range: 18-44yrs</li> <li>CINV assessment: patient report (daily) and nurse report (first 24hrs)</li> <li>Emetogenicity classification: minimal, low, moderate and highly emetogenic agents</li> </ul>	<p>At least 3 (non-cisplatin chemo) or 5 (cisplatin-based chemo) episodes of vomiting in the first 24hrs following previous chemo</p> <p><b>Previous prophylactic regimen:</b>            G1: Metoclopramide &lt;0.5mg/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: <b>Ondansetron</b> 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"> <li>▪ Prospective open-label trial</li> <li>▪ Aim: Evaluate the efficacy of 2 dosage regimens of ondansetron for antiemetic prophylaxis in refractory patients</li> <li>▪ N = 35</li> <li>▪ Adults with cancer receiving chemotherapy</li> <li>▪ 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)</li> <li>▪ CINV assessment: patient report</li> <li>▪ Emetogenicity classification: moderately or highly emetogenic</li> </ul>	<p>&gt; 5 emetic episodes while receiving previous standard antiemetics</p> <p><b>Previous prophylactic regimen:</b> Alizapride or metoclopramide 5-6mg/kg/day</p> <p>Guideline consistent antiemetic prophylaxis: no</p>	<p>G1: <b>Ondansetron</b> 4mg IV and 4mg PO prior to chemo, then 4mg PO qid for an additional 4 days (n=19)</p> <p>G2: <b>Ondansetron</b> 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"> <li>▪ Prospective open-label trial</li> <li>▪ Aim: Assess the efficacy of ondansetron for antiemetic prophylaxis in patients receiving carboplatin</li> <li>▪ N = 16</li> <li>▪ Adults with ovarian cancer receiving carboplatin</li> <li>▪ Median age: 58yrs; range: 23-73yrs</li> <li>▪ CINV assessment: patient report</li> <li>▪ Emetogenicity classification: highly emetogenic</li> </ul>	<p>&gt;2 emetic episodes in the 24hrs following carboplatin</p> <p><b>Previous prophylactic regimen:</b> Days 1: dexamethasone 8mg PO tid + metoclopramide 20mg PO qid beginning prior to chemo</p> <p>Guideline consistent antiemetic prophylaxis: no</p>	<p><b>Ondansetron</b> 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
<b>5HT-3 Antagonists – Palonosetron</b>				
Hesketh (2012)[30]	<ul style="list-style-type: none"> <li>Prospective open-label trial</li> <li>Aim: Determine the efficacy and safety of a single IV dose of palonosetron for prevention of CINV</li> <li>N = 34</li> <li>Adults with cancer receiving chemotherapy who experienced refractory CINV</li> <li>Mean age: 64.6 ± 13.77yrs</li> <li>CINV assessment: patient report</li> <li>Emetogenicity classification: low emetogenicity</li> </ul>	<p>Vomiting and/or at least moderate nausea during cycle 1</p> <p><b>Previous prophylactic regimen:</b> not reported</p> <p>Guideline consistent antiemetic prophylaxis: unable to determine/not reported</p>	Day 1: <b>Palonosetron</b> 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"> <li>Prospective open label trial</li> <li>Aim: Determine if palonosetron is able to prevent CINV in refractory patients</li> <li>N = 47</li> <li>Adults with cancer receiving chemotherapy</li> <li>Mean age: 60.7 ± 3yrs; range: 32-89yrs</li> <li>CINV assessment: patient report</li> <li>Emetogenicity classification: moderately or highly emetogenic</li> </ul>	<p>Grade 3-4 CINV during the first course of chemo that failed to respond to a different 5-HT3 antagonist</p> <p><b>Previous prophylactic regimen:</b> 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: <b>yes for MEC</b>, no for HEC</p>	<p>D1: <b>Palonosetron</b> 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>

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
<b>5HT-3 Antagonists – Tropisetron</b>				
Bruntsch (1993)[32]	<ul style="list-style-type: none"> <li>Prospective, randomized, open-label trial</li> <li>Aim: Determine the efficacy of tropisetron in refractory patients compared to conventional antiemetic treatment</li> <li>N = 115</li> <li>Adults with cancer receiving chemotherapy</li> <li>Mean age: 49 yrs</li> <li>CINV assessment: patient report plus report by an additional individual for the first 24hrs</li> <li>Emetogenicity classification: low, moderate and highly emetogenic agents</li> </ul>	<p>≥ 3 vomiting episodes within 24hrs during previous chemo cycles</p> <p><b>Previous prophylactic regimen:</b> individually prescribed for each patient by investigator</p> <p>Guideline consistent antiemetic prophylaxis: unable to determine/not reported</p>	<p><b>Tropisetron</b> 5mg IV/PO beginning the day before chemo and continuing for at least 5 days (duration dependent on duration of chemo)</p>	<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"> <li>Prospective open-label trial</li> <li>Aim: Determine the antiemetic efficacy and safety of tropisetron in refractory patients</li> <li>N = 164</li> <li><b>Adolescents</b> and adults with cancer receiving chemotherapy</li> <li>Median age: 48yrs; range: 14-88yrs</li> <li>CINV assessment: patient report</li> <li>Emetogenicity classification: moderately emetogenic</li> </ul>	<p>≥ 5 nausea and vomiting episodes despite antiemetic treatment during previous courses of chemo</p> <p><b>Previous prophylactic regimens:</b></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: <b>Tropisetron</b> 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>

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
<b>Fosaprepitant</b>				
Covens [abstract] (2014)[34]	<ul style="list-style-type: none"> <li>▪ Prospective open-label study</li> <li>▪ Aim: Demonstrate that fosaprepitant improves vomiting control</li> <li>▪ N= 106</li> <li>▪ Adults with breast or gynaecological cancer with refractory CINV in the first cycle</li> <li>▪ Median age: 45 yrs (breast cancer); 55 yrs (gynaecological cancer)</li> <li>▪ CINV assessment: not reported</li> <li>▪ Emetogenicity: moderately or highly emetogenic</li> </ul>	<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>
<b>Aprepitant</b>				
Abbrederis (2009)[35]	<ul style="list-style-type: none"> <li>▪ Prospective open-label trial</li> <li>▪ 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</li> <li>▪ N = 7</li> <li>▪ Adults with gastrointestinal tumors</li> <li>▪ Median age: not reported for refractory cohort</li> <li>▪ CINV assessment: patient report</li> <li>▪ Emetogenicity classification: moderately or highly emetogenic</li> </ul>	<p>CINV ≥ grade 2 (NCI definition) during the first course of chemo</p> <p><b>Previous prophylactic regimen:</b> Day 1: Granisetron 1.5mg IV + dexamethasone 12mg IV Days 2-3: Dexamethasone 8mg PO once daily</p> <p>Guideline consistent antiemetic prophylaxis: <b>yes for MEC</b>, no for HEC</p>	<p>Day 1: <b>Aprepitant</b> 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>

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
Caranana [abstract] (2013) [36]	<ul style="list-style-type: none"> <li>▪ Prospective open-label trial</li> <li>▪ Aim: Evaluate efficacy of aprepitant in addition to standard antiemetic prophylaxis</li> <li>▪ N = 24</li> <li>▪ Adults with breast cancer receiving docetaxel 75mg/m<sup>2</sup> + cyclophosphamide 600mg/m<sup>2</sup> IV with refractory CINV in the first cycle</li> <li>▪ Median age: not reported for refractory cohort</li> <li>▪ CINV assessment: patient diary and Functional Living Index-Emesis questionnaire</li> <li>▪ Emetogenicity classification: moderately emetogenic</li> </ul>	<p>Vomiting or receipt of rescue antiemetic therapy despite prophylaxis with a 5-HT3 antagonist and dexamethasone in cycle 1</p> <p><b>Previous prophylactic regimen:</b>                      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: <b>Aprepitant</b> 125mg PO                      Days 2-3: <b>Aprepitant</b> 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"> <li>▪ Trial design: Prospective, open-label trial</li> <li>▪ Aim: evaluate the effect of aprepitant on acute and delayed nausea and vomiting</li> <li>▪ N = 13</li> <li>▪ Adults with colorectal cancer receiving chemotherapy</li> <li>▪ Mean age: 65±11yrs</li> <li>▪ CINV assessment: Patient report (diary)</li> <li>▪ Emetogenicity classification: moderately emetogenic</li> </ul>	<p>Definition: Delayed CINV occurring in the previous chemotherapy block</p> <p><b>Previous prophylactic regimen:</b>                      Granisetron 3mg IV + dexamethasone 8mg IV 30-60min pre-chemo</p> <p>Guideline consistent antiemetic prophylaxis: <b>yes</b></p>	<p>Day 1: <b>Aprepitant</b> 125mg PO + granisetron 3mg IV + dexamethasone 4mg IV 30-60min pre-chemo                      Days 2-3: <b>Aprepitant</b> 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&lt;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>

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
Hesketh (2009)[38]	<ul style="list-style-type: none"> <li>Prospective open-label trial</li> <li>Aim: Determine the antiemetic activity of aprepitant when used as salvage antiemetic therapy</li> <li>N = 44</li> <li>Adults with breast cancer receiving anthracycline + cyclophosphamide</li> <li>Median age: not reported for refractory cohort</li> <li>CINV assessment: patient report</li> <li>Emetogenicity classification: moderately emetogenic</li> </ul>	<p>Any vomiting, nausea, or use of rescue antiemetic medications during cycle 1</p> <p><b>Previous Prophylactic regimen:</b>            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: <b>yes</b></p>	<p>Day 1: <b>Aprepitant</b> 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"> <li>Prospective open-label study</li> <li>Aim: Evaluate effectiveness of aprepitant in addition to standard antiemetic prophylaxis</li> <li>N = 25</li> <li>Adults with cancer receiving cisplatin 75mg/m<sup>2</sup>/dose with refractory CIV in the first cycle</li> <li>Median age: 61 yrs (range: 32 to 72 yrs)</li> <li>CINV assessment: patient diary</li> <li>Emetogenicity: highly emetogenic</li> </ul>	<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: <b>Aprepitant</b> 125mg PO</p> <p>Days 2-3: <b>Aprepitant</b> 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"> <li>Prospective open-label trial</li> <li>Aim: evaluate the efficacy of the addition of aprepitant in refractory patients</li> <li>N = 34</li> <li>Adults with cancer receiving chemotherapy</li> <li>Median age: 51yrs; range: 23-77yrs</li> <li>CINV assessment: patient report</li> <li>Emetogenicity classification: moderately or highly emetogenic</li> </ul>	<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><b>Previous prophylactic regimen:</b>            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: <b>yes For MEC, no for HEC</b></p>	<p>Day 1: <b>Aprepitant</b> 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"> <li>Prospective open-label trial</li> <li>Aim: Evaluate aprepitant as secondary antiemetic prophylaxis</li> <li>N = 40</li> <li>Adults with cancer receiving cisplatin + 5-fluorouracil ± other chemotherapy with refractory CINV</li> <li>Median age: not reported for refractory cohort</li> <li>CINV assessment: investigator (physicians and nurses) and patient report</li> <li>Emetogenicity classification: highly emetogenic</li> </ul>	<p>Failure to achieve complete protection from vomiting with a 5-HT3 antagonist and dexamethasone in cycle 1</p> <p><b>Previous prophylactic regimen:</b> 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: <b>Aprepitant</b> 125mg PO Days 2-3: <b>Aprepitant</b> 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>
<b>Benzodiazepines (Clonazepam, Lorazepam, and Midazolam)</b>				
Hayashi (2010)[42]	<ul style="list-style-type: none"> <li>Prospective open-label trial</li> <li>Aim: Evaluate the efficacy of clonazepam in preventing CINV in refractory patients</li> <li>N = 7 (10 chemotherapy courses)</li> <li>Adults with cancer receiving cisplatin-based chemotherapy</li> <li>Median age: 61yrs; range: 43-73yrs</li> <li>CINV assessment: patient report</li> <li>Emetogenicity classification: highly emetogenic</li> </ul>	<p>Vomiting despite conventional antiemetic therapy</p> <p><b>Previous prophylactic regimen:</b> 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: <b>Clonazepam</b> 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"> <li>Prospective open-label trial</li> <li>Aim: evaluate the efficacy of the addition of midazolam to dexamethasone and granisetron for refractory acute CINV</li> <li>N = 26</li> <li>Adults with cancer receiving cisplatin-based chemotherapy</li> <li>Median age: 58yrs; range: 30-70yrs</li> <li>CINV assessment: patient report and physician assessment</li> <li>Emetogenicity classification: highly emetogenic</li> </ul>	<p>Grade 2 acute nausea (oral intake significantly reduced) and/or vomiting (2-5 emetic episodes in 24hrs)</p> <p><b>Previous prophylactic regimen:</b> 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><b>Midazolam</b> 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>



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
Mughal (1983)[44]	<ul style="list-style-type: none"> <li>Prospective open-label trial</li> <li>Aim: Evaluate the antiemetic efficacy of lorazepam in patients who failed to benefit from standard antiemetics</li> <li>N = 24</li> <li><b>Adolescents</b> and adults with lymphoma receiving chemotherapy</li> <li>Age range: 14-60yrs</li> <li>CINV assessment: patient report</li> <li>Emetogenicity classification: moderately or highly emetogenic</li> </ul>	<p>Severe vomiting for several hrs after chemo ± anticipatory vomiting</p> <p><b>Previous prophylactic regimen:</b> Prochlorperazine 10-15mg/m<sup>2</sup> IV ± metoclopramide 10-15mg/m<sup>2</sup> IV</p> <p>Guideline consistent antiemetic prophylaxis: no</p>	<b>Lorazepam</b> 3mg/m <sup>2</sup> 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>
<b>Dexamethasone</b>				
Aapro (1981)[45]	<ul style="list-style-type: none"> <li>Prospective open-label trial</li> <li>Aim: Evaluate high-dose dexamethasone for CIV</li> <li>N = 10</li> <li>Adults with cancer receiving chemotherapy</li> <li>Median age: not reported for refractory cohort</li> <li>CINV assessment: patient report</li> <li>Emetogenicity classification: unable to determine/not reported (28 patients received highly emetogenic chemotherapy)</li> </ul>	<p>Previous failure to respond to other antiemetics</p> <p><b>Previous prophylactic regimen:</b> not reported</p> <p>Guideline consistent antiemetic prophylaxis: unable to determine/not reported</p>	<b>Dexamethasone</b> 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"> <li>▪ Randomized, double-blind trial</li> <li>▪ Aim: Assess whether the addition of dexamethasone leads to improved control of CINV</li> <li>▪ N = 96</li> <li>▪ Adults with cancer receiving chemotherapy</li> <li>▪ Median age: G1: 44yrs; range: 17-79yrs G2: 52yrs; range: 17-69yrs</li> <li>▪ CINV assessment: patient report (daily) and nursing assessment (first 24 hrs)</li> <li>▪ Emetogenicity classification: unable to determine/not reported</li> </ul>	<p>&gt; 5 vomiting episodes over 24hrs</p> <p><b>Previous prophylactic regimen:</b> 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: <b>Dexamethasone</b> 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>
<b>Prochlorperazine</b>				
Johansson (1982)[47]	<ul style="list-style-type: none"> <li>▪ Randomized, double-blind, cross-over trial</li> <li>▪ Aim: Compare the antiemetic efficacy of nabilone to prochlorperazine</li> <li>▪ N = 18</li> <li>▪ Adults with cancer receiving chemotherapy</li> <li>▪ Median age: not reported</li> <li>▪ CINV assessment: patient report</li> <li>▪ Emetogenicity classification: highly emetogenic</li> </ul>	<p>Uncontrolled nausea and vomiting despite use of standard antiemetic drugs</p> <p><b>Previous prophylactic regimen:</b> not reported</p> <p>Guideline consistent antiemetic prophylaxis: unable to determine/not reported</p>	<p>G1: <b>Nabilone</b> 2mg PO bid x 4 doses G2: <b>Prochlorperazine</b> 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"> <li>Randomized, cross-over trial</li> <li>Aim: Compare the antiemetic activity of THC versus prochlorperazine in refractory patients</li> <li>N = 36</li> <li>Adults with cancer receiving chemotherapy</li> <li>Median age: 48yrs; range: 18-69yrs</li> <li>CINV assessment: patient report</li> <li>Emetogenicity classification: moderately or highly emetogenic</li> </ul>	<p>Severe nausea and vomiting refractory to standard antiemetics</p> <p><b>Previous prophylactic regimen:</b> Prochlorperazine: 34 pts Thiethylperazine: 2 pts</p> <p>Guideline consistent antiemetic prophylaxis: no</p>	<p>G1: <b>THC</b> 15mg/m<sup>2</sup> PO prior to chemo then q4h for 24hrs</p> <p>G2: <b>Prochlorperazine</b> 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>
<b>THC Compounds (Levonantradol, Nabilone, Tetrahydrocannabinol)</b>				
Cronin (1981)[49]	<ul style="list-style-type: none"> <li>Prospective open-label trial</li> <li>Aim: Evaluate the effectiveness of IM levonantradol in refractory patients</li> <li>N = 28</li> <li>Adults with cancer receiving chemotherapy</li> <li>Median age: not reported for evaluable patients (33yrs; range: 11-68yrs for all 31 patients initially enrolled)</li> <li>CINV assessment: patient report and investigator monitoring</li> <li>Emetogenicity classification: moderately or highly emetogenic</li> </ul>	<p>Refractory to the aggressive use of conventional antiemetic therapy</p> <p><b>Previous prophylactic regimen:</b> Parenteral phenothiazines</p> <p>Guideline consistent antiemetic prophylaxis: no</p>	<b>Levonantradol</b> 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"> <li>Prospective open-label trial</li> <li>Aim: Report on the antiemetic efficacy of levonantradol in refractory patients</li> <li>N = 22 (26 courses of chemotherapy)</li> <li>Adults with cancer receiving chemotherapy</li> <li>Median age: not reported for refractory cohort</li> <li>CINV assessment: patient report and nurse monitoring</li> <li>Emetogenicity classification: unable to determine/not reported</li> </ul>	<p>Moderate to severe nausea and vomiting unrelieved by standard antiemetics</p> <p><b>Previous prophylactic regimen:</b> not reported</p> <p>Guideline consistent antiemetic prophylaxis: unable to determine/not reported</p>	<p>G1: <b>Levonantradol</b> 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"> <li>▪ Prospective open-label trial</li> <li>▪ Aim: Report on experience with levonantradol in refractory patients</li> <li>▪ N = 20</li> <li>▪ Adults with cancer receiving chemotherapy</li> <li>▪ Mean age: 43yrs; range 19-63yrs</li> <li>▪ CINV assessment: patient report</li> <li>▪ Emetogenicity classification: moderately or highly emetogenic</li> </ul>	<p>Severe CINV despite conventional antiemetic therapy</p> <p><b>Previous prophylactic regimen:</b> Levomopromazine 50mg IV/PO ± metoclopramide 10mg ± triflupromazine ± dimenhydrinate pre-chemo</p> <p>Guideline consistent antiemetic prophylaxis: no</p>	<p><b>Levonantradol</b> 0.5-1mg SC 30min prior to chemo ± additional doses 4-8hrs later</p>	<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"> <li>▪ Prospective open-label trial</li> <li>▪ Aim: Determine the antiemetic efficacy of levonantradol</li> <li>▪ N = 20</li> <li>▪ Adults with cancer receiving chemotherapy</li> <li>▪ Median age: not reported; range: 19-66yrs</li> <li>▪ CINV assessment: Patient report</li> <li>▪ Emetogenicity classification: moderately or highly emetogenic</li> </ul>	<p>“Patients treated without sufficient success of nausea and vomiting when treated with other antiemetics”</p> <p><b>Previous prophylactic regimen:</b> Meclizine, metoclopramide, haloperidol, triflupromazine, flupentixol, and/or levomopromazine</p> <p>Guideline consistent antiemetic prophylaxis: no</p>	<p><b>Levonantradol</b> 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>	<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"> <li>▪ Prospective open-label trial</li> <li>▪ Aim: Determine the antiemetic efficacy of nabilone and evaluate side effects</li> <li>▪ N = 13</li> <li>▪ Adults with cancer receiving chemotherapy</li> <li>▪ Median age: not reported</li> <li>▪ CINV assessment: patient report</li> <li>▪ Emetogenicity classification: moderately or highly emetogenic</li> </ul>	<p>Severe nausea and vomiting from chemo not controlled by standard antiemetics</p> <p><b>Previous Prophylactic regimen:</b> Prochlorperazine</p> <p>Guideline consistent antiemetic prophylaxis: no</p>	<p><b>Nabilone</b> 1-2mg PO q8h x 5 days with 2 doses administered 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 (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"> <li>▪ Randomized, double-blind, cross-over trial</li> <li>▪ Aim: Compare the antiemetic efficacy of nabilone to prochlorperazine</li> <li>▪ N = 18</li> <li>▪ Adults with cancer receiving chemotherapy</li> <li>▪ Median age: not reported</li> <li>▪ CINV assessment: patient report</li> <li>▪ Emetogenicity classification: highly emetogenic</li> </ul>	<p>Uncontrolled nausea and vomiting despite use of standard antiemetic drugs</p> <p><b>Previous prophylactic regimen:</b> not reported</p> <p>Guideline consistent antiemetic prophylaxis: unable to determine/not reported</p>	<p>G1: <b>Nabilone</b> 2mg PO bid x 4 doses</p> <p>G2: <b>Prochlorperazine</b> 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"> <li>▪ Prospective open-label trial</li> <li>▪ Aim: Evaluate the effectiveness of parenteral levontradol in refractory patients</li> <li>▪ N = 33</li> <li>▪ Adults with cancer receiving chemotherapy</li> <li>▪ Median age: not reported for refractory cohort</li> <li>▪ CINV assessment: patient report and investigator monitoring</li> <li>▪ Emetogenicity classification: unable to determine/not reported</li> </ul>	<p>Persistent nausea and vomiting despite the use of standard antiemetics</p> <p><b>Previous prophylactic regimen:</b> PO or parenteral phenothiazines ± additional prn antiemetics</p> <p>Guideline consistent antiemetic prophylaxis: no</p>	<p><b>Levontradol</b> 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"> <li>▪ Prospective open-label trial</li> <li>▪ Aim: Determine if PO THC is an effective antiemetic for refractory patients</li> <li>▪ N = 53</li> <li>▪ Adults with cancer receiving chemotherapy</li> <li>▪ Median age: 51yrs; range: 18-69yrs)</li> <li>▪ CINV assessment: patient report and investigator monitoring</li> <li>▪ Emetogenicity classification: unable to determine/not reported</li> </ul>	<p>Persistent severe nausea and vomiting in spite of aggressive use of standard antiemetics</p> <p><b>Previous Prophylactic regimen:</b> "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><b>Δ9-tetrahydrocannabinol</b> 15mg/m<sup>2</sup> PO q6h x 4 doses beginning 1hr prior to chemo OR 5mg/m<sup>2</sup> 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"> <li>▪ Randomized, cross-over trial</li> <li>▪ Aim: Compare the antiemetic activity of THC versus prochlorperazine in refractory patients</li> <li>▪ N = 36</li> <li>▪ Adults with cancer receiving chemotherapy</li> <li>▪ Median age: 48yrs; range: 18-69yrs</li> <li>▪ CINV assessment: patient report</li> <li>▪ Emetogenicity classification: moderately or highly emetogenic</li> </ul>	<p>Severe nausea and vomiting refractory to standard antiemetics</p> <p><b>Previous prophylactic regimen:</b>            Prochlorperazine: 34 pts            Thiethylperazine: 2 pts</p> <p>Guideline consistent antiemetic prophylaxis: no</p>	<p>G1: <b>THC</b> 15mg/m<sup>2</sup> PO prior to chemo then q4h for 24hrs</p> <p>G2: <b>Prochlorperazine</b> 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"> <li>▪ Randomized, double-blind, placebo-controlled trial</li> <li>▪ Aim: Evaluate the efficacy and toxicity of intramuscular levonantradol</li> <li>▪ N = 20</li> <li>▪ Adults with cancer receiving chemotherapy</li> <li>▪ Median age: not reported</li> <li>▪ CINV assessment: patient and observer report</li> <li>▪ Emetogenicity classification: unable to determine/not reported</li> </ul>	<p>Persistent nausea and vomiting from chemo refractory to maximally recommended doses of conventional antiemetics</p> <p><b>Previous prophylactic regimen:</b> not reported</p> <p>Guideline consistent antiemetic prophylaxis: unable to determine/not reported</p>	<p><b>Levonantradol</b> 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"> <li>▪ Prospective open-label trial</li> <li>▪ Aim: Determine the efficacy of levonantradol for CINV in refractory patients</li> <li>▪ N = 22</li> <li>▪ Adults with cancer receiving chemotherapy</li> <li>▪ Median age: 49yrs; range 20-70yrs</li> <li>▪ CINV assessment: patient report and nurse monitoring</li> <li>▪ Emetogenicity classification: unable to determine/not reported (6 patients received highly emetogenic chemotherapy)</li> </ul>	<p>Severe nausea and vomiting refractory to conventional antiemetic treatment</p> <p><b>Previous prophylactic regimen:</b>            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><b>Levonantradol</b> 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>

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<b>Miscellaneous (Methotrimeprazine, Medroxyprogesterone, and Propofol)</b>				
Borgeat (1994)[58]	<ul style="list-style-type: none"> <li>▪ Prospective open-label trial</li> <li>▪ Aim: Determine the efficacy and safety of added low-dose propofol infusion in patients experiencing refractory CINV</li> <li>▪ N = 20</li> <li>▪ Adults with breast cancer receiving non-cisplatin chemotherapy</li> <li>▪ Median age: 56yrs; range: 45-72yrs</li> <li>▪ CINV assessment: nurse report</li> <li>▪ Emetogenicity classification: moderately emetogenic</li> </ul>	<p>&gt; 5 emetic episodes in the first 24hrs despite antiemetic prophylaxis during their first cycle of chemo</p> <p><b>Prophylactic regimen:</b> Ondansetron 8mg IV x 2 doses + dexamethasone 10mg IV once</p> <p>Guideline consistent antiemetic prophylaxis: <b>yes</b></p>	<p><b>Propofol</b> 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"> <li>▪ Prospective open-label trial</li> <li>▪ Aim: Determine the efficacy and safety of added low-dose propofol infusion in patients experiencing refractory CINV</li> <li>▪ N = 20</li> <li>▪ Adults with cancer receiving cisplatin-based chemotherapy</li> <li>▪ Median age: 52yrs; range: 30-70yrs</li> <li>▪ CINV assessment: nurse report</li> <li>▪ Emetogenicity classification: moderately emetogenic</li> </ul>	<p>&gt; 5 emetic episodes in the first 24hrs despite antiemetic prophylaxis during their first cycle of chemo</p> <p><b>Previous prophylactic regimen:</b> Ondansetron 8mg IV OR granisetron 3mg IV x 3 doses + dexamethasone 10mg IV once</p> <p>Guideline consistent antiemetic prophylaxis: <b>yes</b></p>	<p><b>Propofol</b> 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"> <li>▪ Case series</li> <li>▪ Aim: Describe 3 cases where medroxyprogesterone acetate was effective for cisplatin-induced refractory emesis</li> <li>▪ N = 3</li> <li>▪ Adults with cancer receiving cisplatin + gemcitabine</li> <li>▪ Median age: 58 yrs; range:58-67yrs</li> <li>▪ CINV assessment: not reported</li> <li>▪ Emetogenicity classification: highly emetogenic</li> </ul>	<p>Emesis occurring despite the use of antiemetic prophylaxis during the previous cycle</p> <p><b>Previous Prophylactic regimen:</b></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: <b>yes</b> Pt 2: <b>yes</b> Pt 3: <b>yes</b></p>	<p>Pt 1: Day 1: Granisetron 3mg + dexamethasone 12mg Days 2-4: <b>Medroxyprogesterone acetate</b> 900mg PO + dexamethasone 8mg Day 5: Medroxyprogesterone acetate 900mg PO</p> <p>Pt 2: Day 1: Granisetron 1mg + dexamethasone 8mg Days 2-4: <b>Medroxyprogesterone acetate</b> 900mg PO + dexamethasone 4mg Day 5: Medroxyprogesterone acetate 900mg PO</p> <p>Pt 3: Day 1: Palonosetron 0.75mg + aprepitant 125mg + dexamethasone 12mg + <b>Medroxyprogesterone acetate</b> 900mg PO Days 2-3: Aprepitant 80mg + dexamethasone 8mg + <b>Medroxyprogesterone acetate</b> 900mg PO Day 4: Dexamethasone 8mg + <b>Medroxyprogesterone acetate</b> 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"> <li>▪ Prospective open-label trial</li> <li>▪ Aim: Determine the antiemetic efficacy of oral methotrimeprazine</li> <li>▪ N = 113</li> <li>▪ Adults with cancer receiving either cisplatin, ifosfamide, or adriamycin-containing chemotherapy combinations</li> <li>▪ Median age: not reported</li> <li>▪ CINV assessment: clinical observation</li> <li>▪ Emetogenicity classification: moderately or highly emetogenic</li> </ul>	<p>Refractory to conventional antiemetics</p> <p><b>Previous prophylactic regimen:</b> Metoclopramide ± triflupromacine ± other phenothiazines/antihistamines</p> <p>Guideline consistent antiemetic prophylaxis: no</p>	<p><b>Methotrimeprazine</b> 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
<b>Non-pharmacological Interventions - Acupressure/Acupuncture</b>				
Choo (2006)[62]	<ul style="list-style-type: none"> <li>▪ Prospective open-label trial</li> <li>▪ Aim: evaluate the efficacy of electroacupuncture in preventing refractory CINV</li> <li>▪ N = 27</li> <li>▪ Adults with cancer receiving anthracycline-based chemotherapy for breast cancer</li> <li>▪ Median age: 48yrs; range: 37-60yrs</li> <li>▪ CINV assessment: patient report and physician assessment</li> <li>▪ Emetogenicity classification: moderately emetogenic</li> </ul>	<p>More than 2 episodes of emesis occurring in the first 24hrs after chemo when antiemetic prophylaxis and rescue antiemetics were given</p> <p><b>Previous prophylactic regimen:</b>            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: <b>yes</b></p>	<b>Electroacupuncture</b> at PC6 for 30min beginning 10min prior to chemo + previous prophylactic regimen described	<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"> <li>▪ Prospective open-label trial</li> <li>▪ Aim: evaluate the efficacy of PC6 stimulation by acupressure for the treatment of refractory CIV</li> <li>▪ N = 100</li> <li>▪ Adults with solid tumors</li> <li>▪ Median age: 59yrs</li> <li>▪ CINV assessment: not reported</li> <li>▪ Emetogenicity classification: moderately or highly emetogenic</li> </ul>	<p>Grade 3-4 vomiting and no response to "conventional antiemetics" including 5-HT3 antagonists, corticosteroids, and antidopaminergic agents</p> <p><b>Previous prophylactic regimen:</b> not reported</p> <p>Guideline consistent antiemetic prophylaxis: unable to determine/not reported</p>	Stimulation of the PC6 acupoint by <b>acupressure</b> for 8hrs a day starting prior to chemo and continuing for at least 3 days after chemo	<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 <sup>9,10</sup>
<p><b>Health Question #1: What interventions are recommended to treat breakthrough CINV in children?</b></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><b>Recommendation 1.1:</b> 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><b>Recommendation 1.2:</b> 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><b>Recommendation 1.3:</b> 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"> <li>• methotrimeprazine (also known as levomepromazine)</li> </ul> <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-HT<sub>3</sub> 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.

For Peer Review

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