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

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

Abstract

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

Introduction

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

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

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

Methods

Guideline panel and development of clinical questions

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

Systematic literature searches

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

Evidence identification and synthesis

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

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

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

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

External review and consultation process

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

Procedure for updating the guideline

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

Results

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

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

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.

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

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

evaluating ABH gel, 5-HT3 antagonists and prochlorperazine were included in the evidence summary but were omitted from the recommendations due to poor systemic bioavailability,[10] inclusion as standard acute CINV prophylaxis[11] and safety concerns,[6] respectively.

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

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

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

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

Adult Patients

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

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

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

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

Pediatric Patients

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

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

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

This recommendation is consistent with adult guidelines for the treatment of breakthrough CINV in adult cancer patients.[15,16] It places value on the high quality evidence of the efficacy of olanzapine 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 or indirect. Furthermore, the optimal pediatric dose for this indication is uncertain. It may be reasonable to give olanzapine 0.1 mg/kg/dose (maximum 10 mg/dose) once daily by mouth. This dose is based on the results of the retrospective review[14] and uses the adult dose as the maximum dose. If CINV is not controlled and sedation does not occur or is not troublesome, the dose could potentially be increased to 0.14 mg/kg/dose (maximum 10 mg/dose). Olanzapine injection should not be administered for CINV control since it has not been evaluated for this indication. Olanzapine should be avoided in patients receiving CYP1A2 inducers (e.g. carbamazepine, rifampin) or inhibitors (e.g. ciprofloxacin, fluvoxamine) as olanzapine is primarily metabolized via this enzymatic pathway.[17]

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

Addition of methotrimeprazine

Adult Patients

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

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

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

Pediatric Patients

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

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

Addition of metoclopramide

Adult Patients

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

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

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

Pediatric Patients

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

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

Methotrimeprazine is a phenothiazine similar to chlorpromazine. It is marketed in Canada, Europe, and Australia. Current CINV prophylaxis guidelines recommend the use of metoclopramide for the treatment of breakthrough CINV in adults.[15,16] The panel recognizes that the evidence base for these agents consists of studies in adults that were not conducted in the context of currently recommended CINV prophylaxis. 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 placed a high value on the possible benefit of these agents in the setting of breakthrough CINV. A lower value was placed on the potential for toxicity secondary

to these agents because EPS are generally amenable to intervention and, although possibly distressing if not anticipated, are 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.

Two studies were identified that described the prevention of refractory CINV in children: one prospective study evaluating the use of tropisetron[22] and a retrospective review evaluating the use of aprepitant.[23] Forty-one studies in adults met criteria for inclusion in this evidence base (five randomized trials, four non-randomized prospective comparative studies, 31 prospective single arm studies, and one case series). Evidence describing the prevention of refractory CINV in children and adults is summarized in Supplementary Table VI. Dexamethasone, tetrahydrocannabinol, levonantradol, Sancuso®, benzodiazepines, medroxyprogesterone, nabilone and propofol were included in the evidence summary but were omitted from the recommendations. Similarly, placebo-controlled trials, dosage form comparison studies or single arm studies evaluating 5-HT3 antagonists other than palonosetron were omitted from the recommendations. This decision was taken for one or more of the following reasons: 1) the agent is currently recommended for acute CINV prophylaxis; 2) it is not available in a dosage form suitable for pediatric use; 3) outcome data have only been reported in an extremely small number of patients; 4) there is a lack efficacy data in the context of modern CINV prophylaxis or 5) the agent is difficult to administer safely.

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.

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

This recommendation places a high value on the possible control of refractory CINV in the acute phase by provision of acute 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 HEC, we suggest that the 5-HT3 antagonist given for CINV prophylaxis be changed from ondansetron or granisetron to palonosetron. In jurisdictions where palonosetron is not available, we suggest that granisetron be substituted for ondansetron.

Switching from ondansetron or granisetron to palonosetron

Adult Patients

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

Pediatric Patients

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

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

This recommendation is consistent with adult guidelines related to palonosetron since it is considered the 5-HT3 antagonist of choice in adults receiving MEC.[15,27]It places a high value on the improved CINV control seen in adult cancer patients receiving palonosetron. 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 for prevention of refractory CINV in children is not available. However, the available information (including approval by the US Food and Drug Administration for the prevention of CINV in children) indicates that palonosetron can be used safely in pediatric cancer patients.

Switching from ondansetron to granisetron

Either ondansetron or granisetron is recommended for acute CINV prophylaxis in all children receiving chemotherapy of low, moderate or high emetogenic risk.[11] There is no evidence to support use of one first generation 5-HT3 receptor antagonist over the other in children. However, ondansetron is primarily metabolized via the cytochrome P450 CYP 2D6 enzyme and studies in adults have shown that polymorphisms in this enzyme predispose patients to poor CINV control secondary to rapid ondansetron metabolism.[28]

Adult Patients

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

Pediatric Patients

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

If palonosetron is not available, it is suggested that granisetron be substituted for ondansetron in patients who experienced refractory CINV while receiving ondansetron. This recommendation is based on the potential for genetic variability in the enzymes responsible for metabolizing ondansetron. It places a high value on the improved CINV control seen in adult cancer 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 a less expensive alternative has been ineffective. It is a weak recommendation because direct evidence 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.

The use of aprepitant is currently recommended for acute CINV prophylaxis in children greater than or equal to 12 years of age receiving HEC which is not known or suspected to interact with this agent[11] and recent evidence supports its use in children as young as 6 months.[30] Aprepitant is a CYP3A4 substrate and an inhibitor of CYP2C9/8 and CYP2C19. As a result, it may potentially interact with medications, including chemotherapy, metabolized via these pathways. The issues which must be considered when using aprepitant in pediatric patients have been summarized previously.[11] Interactions with chemotherapy which may lead to an increased risk of short and long-term toxicity are of primary concern. However, direct evidence of these interactions is often unavailable and interpretation of the results of available studies that do evaluate aprepitant/fosaprepitant interactions with chemotherapy varies.

Adult Patients

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

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

Pediatric Patients

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

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

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. The potential improvement in CINV control offered by the addition of aprepitant should be weighed against the short and long-term toxicities resulting from potential interactions with chemotherapy. It is essential to include the patient, when appropriate, and family in this discussion so their values can be incorporated into the decision-making process. 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 stimulation of Nei Guan (P6) by means of acupressure or electro-acupuncture.

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

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

This recommendation places a high value on the potential for CINV control using interventions that are recommended for the treatment of breakthrough CINV and 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.

Addition of acupressure or acupuncture to acute CINV prophylaxis

Adult Patients

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

Pediatric patients

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

This recommendation places a high value on the possibility that acupressure or 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 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/acupuncture in children with refractory CINV.

Research Gaps

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

Conclusions

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

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Conflict of Interest Statement

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

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Legends

Figure 1: Interventions to treat breakthrough chemotherapy-induced nausea and vomiting (CINV) or prevent CINV in refractory patients: flowchart of literature identification process

Supplementary Table I: Guideline Search Strategy

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

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

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

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

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

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

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[9,10]
Health Question #1: What interventions are recommended to treat breakthrough CINV in children? *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.	
Recommendation 1.1: For children receiving acute CINV prophylaxis recommended for minimally, low, or moderately emetogenic chemotherapy, clinicians should upgrade or escalate the acute CINV prophylaxis provided to that recommended for chemotherapy of the next higher level of emetogenic risk.	Strong Recommendation Very Low Quality Evidence
Recommendation 1.2: For children receiving acute CINV prophylaxis recommended for highly emetogenic chemotherapy, we suggest that olanzapine be added to guideline-consistent CINV prophylaxis**.**	Weak Recommendation Low Quality Evidence
Recommendation 1.3: For children receiving acute CINV prophylaxis recommended for highly emetogenic chemotherapy and who cannot receive olanzapine, we suggest that one of the following antiemetic agents be added to guideline-consistent CINV prophylaxis: • methotrimeprazine (also known as levomepromazine) or • 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.**	Weak Recommendation Very Low Quality Evidence

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-HT3 antagonist given for CINV prophylaxis be changed from ondansetron or granisetron to palonosetron. In jurisdictions where palonosetron is not available, we suggest that granisetron be substituted 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	Weak Recommendation Very Low Quality Evidence
• stimulation of Nei Gaun (P6) by means of acupressure or electro-acupuncture.	Weak Recommendation Very Low Quality Evidence

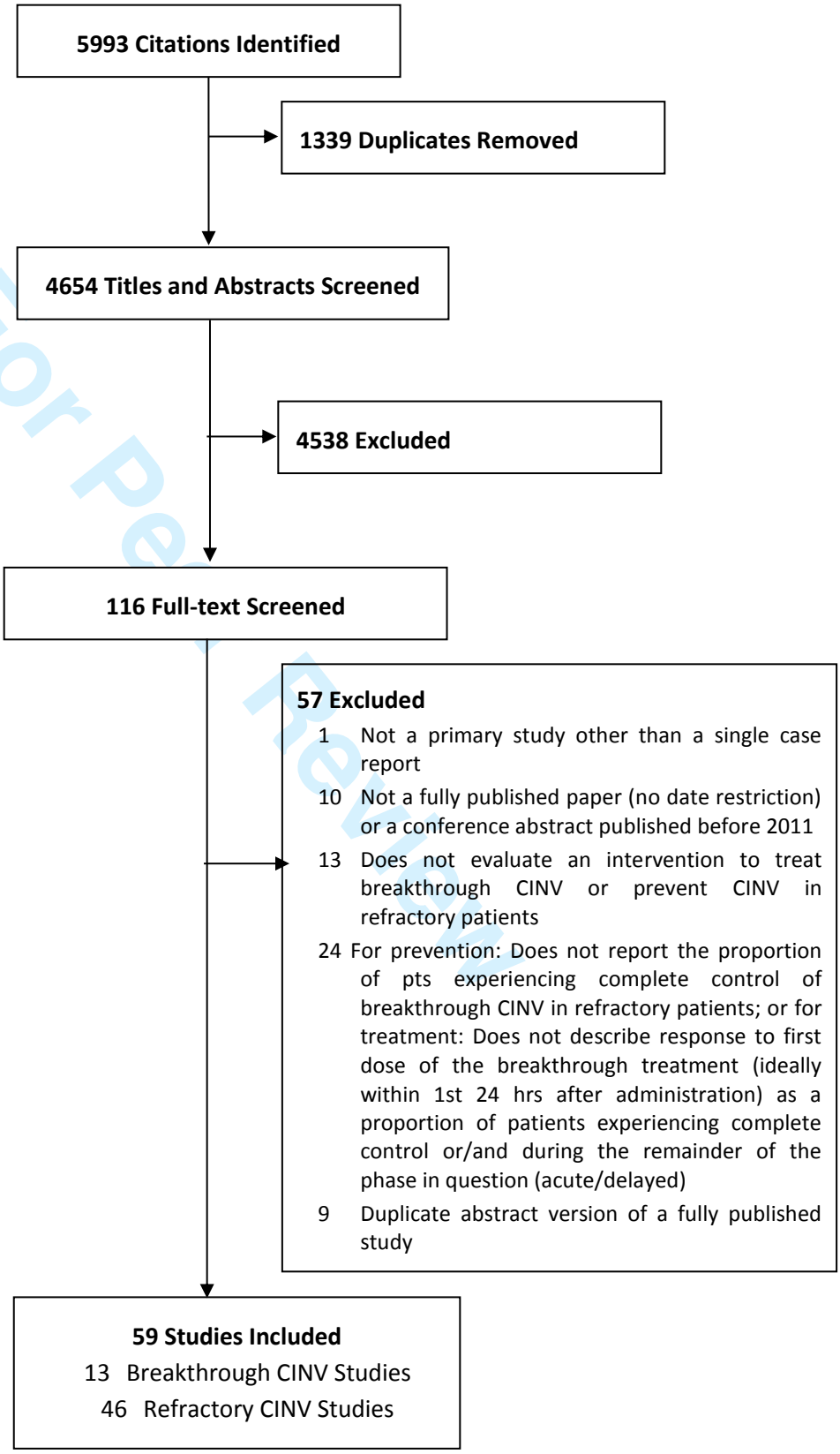
TABLE II: Study inclusion criteria for three systematic reviews undertaken

Guidelines	
(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.
Treatment of breakthrough CINV and prevention of CINV in patients who have experienced refractory CINV	
(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).
Safety of methotrimeprazine in children	
(i)	published in English in a journal in full text or a letter to the editor reporting primary data;
(ii)	included patients ≤18 years of age and either results were reported separately for patients ≤18 years of age or the mean or median age pf participants was ≤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	• efficacy of CINV prophylaxis escalation
	• optimal dose, efficacy and safety of olanzapine and methotrimeprazine
	• optimal dose, efficacy of metoclopramide and risk factors for toxicity
Refractory CINV	• optimal palonosetron dose in children receiving multiple day chemotherapy
	• extent and clinical significance of interactions between aprepitant and chemotherapy

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")

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 tisercin 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 tisercin 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 tisercin 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 tisercin or veractil).mp.
2	limit 1 to (100 childhood <birth to age 12 yrs> or 120 neonatal <birth to age 1 mo> or 140 infancy <2 to 23 mo> or 160 preschool age <age 2 to 5 yrs> or 180 school age <age 6 to 12 yrs> or 200 adolescence <age 13 to 17 yrs>)
3	(infan* or neonat* or child* or adolescen* or teen* or girl* or boy* or youth* or tot or tots or toddler* or paediatric* or pediatric*).mp.
4	1 and 3
5	2 or 4

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

First Author (Year)	Study Design, Objective and Population	Definition of Breakthrough CINV	Antiemetic Prophylaxis and Interventions	Proportion with Complete Control of Breakthrough Nausea and/or Vomiting
Pediatric Studies				
No studies identified				
Adult Studies				
5HT-3 Antagonist - Granisetron				
Jones (2011) [1]	▪ Prospective observational trial ▪ Aim: Describe the response to antiemetic therapy taken for breakthrough CINV ▪ N = 27 ▪ Adults with cancer receiving chemotherapy ▪ Median age: 57 yrs; range: 30-72 yrs ▪ CINV assessment: patient report ▪ Emetogenicity classification: moderately or highly emetogenic	Nausea and/or vomiting requiring antiemetic rescue medication occurring any time during the first 3 days post-chemotherapy	Prophylactic regimen: Dexamethasone: 25/27 (93%) Granisetron: 20/27 (74%) Palonosetron: 7/27 (26%) Aprepitant: 1/27 (4%) *Guideline consistent antiemetic prophylaxis: unable to determine (authors report prophylactic regimens were based on antiemetic guidelines) Breakthrough intervention: G1: **Prochlorperazine** 10mg PO (n=24) G2: **5-HT antagonist** (granisetron 1mg PO (n=1), ondansetron 8mg IV (n=1), ondansetron 8mg sublingually (n=1)	Proportion with complete control of breakthrough vomiting: G1: 23/24 (96%) G2: 3/3 (100%) Proportion with complete control of breakthrough nausea: G1: 2/24 (8.3%) G2: 1/3 (33.3%) Proportion with complete control of breakthrough CINV: not reported Time of occurrence of breakthrough CINV: acute and delayed phases (over 3 days) Timeframe of assessments: Acute phase (baseline (when breakthrough treatment initiated) then every half hour x 4hrs)
Marty (1990)[2]	▪ Prospective trial ▪ Aim: Compare the efficacy and safety of granisetron vs chlorpromazine + dexamethasone for CINV, evaluation of rescue with a second dose of granisetron was evaluated secondarily in the granisetron arm ▪ N = 23 ▪ Adults with cancer receiving chemotherapy ▪ Median age: Not reported for breakthrough cohort ▪ CINV assessment: patient and clinician report ▪ Emetogenicity classification: moderately or highly emetogenic	Moderate or severe nausea	Prophylactic regimen: Granisetron 40mcg/kg IV (5 min pre-chemo) *Guideline consistent antiemetic prophylaxis: **no** Breakthrough intervention: Additional **Granisetron** 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]	▪ Prospective open-label study ▪ Aim: Compare the efficacy and safety of 3 different doses of granisetron, evaluation of rescue with a second dose of granisetron was evaluated secondarily ▪ N = 64 ▪ Adult patients receiving cisplatin-containing chemotherapy ▪ Median age: Not reported for breakthrough cohort ▪ CINV assessment: patient and clinician report ▪ Emetogenicity classification: highly emetogenic	Moderate or severe nausea (more than mild nausea or vomiting occurred)	Prophylactic regimen for all patients (5 min pre-chemo): G1: Granisetron 2mcg/kg IV G2: Granisetron 10mcg/kg IV G3: Granisetron 40mcg/kg IV *Guideline consistent antiemetic prophylaxis: **no** Breakthrough intervention: **Granisetron** 3mg IV up to 2 x's, administered at least 10min apart	Proportion with complete control of breakthrough CINV after 1 additional granisetron dose: G1: 26/30 (86.7%) G2: 12/19 (63.2%) G3: 9/15 (60%) Proportion with complete control of breakthrough CINV after 2 additional granisetron doses: G1: 5/12 (41.7%) G2: 9/11 (81.8%) G3: 2/7 (28.6%) Time of occurrence of breakthrough CINV: not reported Timeframe of assessments: acute phase (baseline, 6hrs, 12hrs, 18hrs, and 24hrs)
Takigawa (1996)[4]	▪ Prospective observational trial ▪ Aim: Determine the usefulness of granisetron rescue therapy for CINV ▪ N = 20 ▪ Adults with urogenital malignant tumors receiving chemotherapy (including cisplatin) ▪ Mean age: 61.9 ± 15 yrs; range: 25-76 yrs ▪ CINV assessment: Not reported, patients examined by a healthcare professional q6h for 24hrs ▪ Emetogenicity classification: highly emetogenic	No response to antiemetics or emesis	**Prophylactic regimen:** Not reported *Guideline consistent antiemetic prophylaxis: unable to determine/not reported Breakthrough intervention: **Granisetron** 3mg IV administered 30min after the onset of nausea or vomiting	Proportion with complete control of breakthrough vomiting: 5/20 (25%) Proportion with complete control of breakthrough nausea: 15/20 (75%) Proportion with complete control of breakthrough CINV: not reported Time of occurrence of breakthrough CINV: not reported Timeframe of assessments: acute phase (q6h x 24hrs)
5HT-3 Antagonist - Ondansetron				
Ariyoshi (1992)[5]	▪ Double-blind randomized comparison with placebo ▪ Aim: Determine the antiemetic efficacy and safety of ondansetron tablets ▪ N = 12 ▪ Adults with cancer receiving a single dose of cisplatin 50mg/m^2 or higher ▪ Median Age: Not reported for breakthrough cohort ▪ CINV assessment: Not reported, patients examined by a healthcare professional q6h for 24hrs ▪ Emetogenicity classification: highly emetogenic	"Satisfactory" anti-emetic effects not obtained	**Prophylactic regimen:** Ondansetron 4mg PO once (2hrs pre-chemo) *Guideline consistent antiemetic prophylaxis: **no** Breakthrough intervention: **Ondansetron** 4mg IV once	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: not reported, 5/12 (41.7%) achieved a "satisfactory response" Timeframe of assessments: acute phase (q6h x 24hrs after administration of cisplatin)

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]	▪ Open-label randomized trial ▪ Aim: evaluate the efficacy and safety of two different schedules of ondansetron as rescue antiemetic treatment ▪ N = 44 ▪ Adults with cancer receiving chemotherapy ▪ Median age: Not reported for breakthrough cohorts ▪ CINV assessment: patient report ▪ Emetogenicity classification: moderately emetogenic	At least 1 episode of nausea and/or vomiting occurring from days 2-6 of cycle 1 of chemotherapy	Prophylactic regimen for all patients: Day 1: Dexamethasone 8mg IV + ondansetron 8mg IV Days 2-5: Dexamethasone 8mg PO once daily *Guideline consistent antiemetic prophylaxis: **yes** Breakthrough intervention: G1: **Ondansetron** 8mg IM (n=22) G2: ODT **ondansetron** 16mg PO (n=22)	Proportion with complete control of breakthrough vomiting: G1: 7/22 (31.8%) G2: 18/22 (81.8%) p=0.001 Proportion with complete control of breakthrough nausea: G1: 9/22 (40.9%) G2: 17/22 (77.3%) p=0.01 Proportion with complete control of breakthrough CINV: not reported Time of occurrence of breakthrough CINV: delayed phase (days 2-6) Timeframe of assessments: acute and delayed phases (patients followed for 6 days following chemo)
Jones (2011)[1]	▪ Prospective observational trial ▪ Aim: Describe the response to antiemetic therapy taken for breakthrough CINV ▪ N = 27 ▪ Adults with cancer receiving chemotherapy ▪ Median age: 57 yrs; range: 30-72 yrs ▪ CINV assessment: patient report ▪ Emetogenicity classification: moderately or highly emetogenic	Nausea and/or vomiting requiring antiemetic rescue medication occurring any time during the first 3 days post-chemotherapy	Prophylactic regimen: Dexamethasone: 25/27 (93%) Granisetron: 20/27 (74%) Palonosetron: 7/27 (26%) Aprepitant: 1/27 (4%) *Guideline consistent antiemetic prophylaxis: unable to determine (authors report prophylactic regimens were based on antiemetic guidelines) Breakthrough intervention: G1: **Prochlorperazine** 10mg PO (n=24) G2: **5-HT antagonist** (granisetron 1mg PO (n=1), ondansetron 8mg IV (n=1), ondansetron 8mg sublingually (n=1)	Proportion with complete control of breakthrough vomiting: G1: 23/24 (96%) G2: 3/3 (100%) Proportion with complete control of breakthrough nausea: G1: 2/24 (8.3%) G2: 1/3 (33.3%) Proportion with complete control of breakthrough CINV: not reported Time of occurrence of breakthrough CINV: acute and delayed phases (over 3 days) Timeframe of assessments: Acute phase (baseline (when breakthrough treatment initiated) then every half hour x 4hrs)
Ohta (1992)[7]	▪ Double-blind randomized comparison with placebo ▪ Aim: Determine the antiemetic efficacy and safety of IV ondansetron ▪ N = 7 ▪ Adults with cancer receiving a single dose of cisplatin 50mg/m^2 or higher ▪ Median age: Not reported for breakthrough cohort ▪ CINV assessment: Not reported, patients examined by a healthcare professional q6h for 24hrs ▪ Emetogenicity classification: highly emetogenic	Insufficient anti-emetic effect after initial dose of IV ondansetron	**Prophylactic regimen:** Ondansetron 4mg IV (15 min pre-chemo) *Guideline consistent antiemetic prophylaxis: **no** Breakthrough intervention: **Ondansetron** 4mg IV once	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: not reported, 1/7 (14.3%) achieved an "inhibitory effect" from the rescue ondansetron dose Timeframe of assessments: acute phase (q6h for the first 24hrs after administration of cisplatin)

First Author (Year)	Study Design, Objective and Population	Definition of Breakthrough CINV	Antiemetic Prophylaxis and Interventions	Proportion with Complete Control of Breakthrough Nausea and/or Vomiting
5HT-3 Antagonist - Palonosetron				
Musso (2009)[8]	▪ Prospective observational trial ▪ Aim: Evaluate the efficacy of a single dose of palonosetron for CINV control, evaluation of rescue with a second dose of palonosetron was evaluated secondarily ▪ N =27 ▪ Adolescents and adults with haematological malignancies receiving multiple day chemotherapy (2-7 days) ▪ Median age: Not reported for breakthrough cohorts ▪ CINV assessment: patient report ▪ Emetogenicity classification: moderately or highly emetogenic	Not reported	Prophylactic regimen: 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 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 Dexamethasone excluded for patients receiving DHAP (dexamethasone + cisplatin + cytarabine) *Guideline consistent antiemetic prophylaxis: **yes** for MEC, **no** for HEC Breakthrough intervention: G1: **Palonosetron** 0.25mg IV 72 hrs after administration of the first dose G2: **Metoclopramide** 20mg IV q6h or q12h	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: G1: 6/9 (67%) G2: 4/18 (22%) p=0.039 Time of occurrence of breakthrough CINV: acute and delayed phases (over 5 days) Timeframe of assessments: not reported
Musso (2010)[9]	▪ Prospective open-label trial ▪ Aim: Evaluate the efficacy of a single dose of palonosetron for CINV control, evaluation of rescue with a second dose of palonosetron was evaluated secondarily ▪ N = 51 ▪ Adolescents and adults with haematological malignancies receiving conditioning for autologous stem cell transplant ▪ Median age: Not reported for breakthrough cohorts ▪ CINV assessment: patient reported ▪ Emetogenicity classification: moderately or highly emetogenic	Not reported	Prophylactic regimen for all patients: 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 *Guideline consistent antiemetic prophylaxis: **no** Breakthrough intervention: **Palonosetron** 0.25mg IV 48 or 72 hrs after administration of the first dose	Proportion with complete control of breakthrough vomiting when palonosetron administered 72hrs after initial dose: 25/51 (50%) Proportion with complete control of breakthrough vomiting when palonosetron administered 48hrs after initial dose: 9/20 (45%) Proportion with complete control of breakthrough nausea: Not reported Proportion with complete control of breakthrough CINV: not reported Time of occurrence of breakthrough AINV: delayed phase Timeframe of assessments: not reported

First Author (Year)	Study Design, Objective and Population	Definition of Breakthrough CINV	Antiemetic Prophylaxis and Interventions	Proportion with Complete Control of Breakthrough Nausea and/or Vomiting
Methotrimeprazine				
McCabe (2003)[10]	▪ Prospective observational study ▪ Aim: Evaluate the efficacy of levomepromazine for management of breakthrough CINV ▪ N = 32 ▪ Adult patients with high grade delayed chemotherapy-induced emesis requiring hospital admission to control this ▪ Median age: 58 yrs; range: 35-76 yrs ▪ CINV assessment: patient report ▪ Emetogenicity classification: highly emetogenic	Delayed chemotherapy-induced emesis Grade II and above (graded using the NCI-CTC)	Prophylactic regimen for all patients: various potential regimens described (not reported which regimens actually received by patients included in the analysis) *Guideline consistent antiemetic prophylaxis: unable to determine/not reported Breakthrough intervention: **Levomepromazine** 25mg SC over 24-48 hrs	Proportion with complete control of breakthrough vomiting in 24 hours: 28/32 (88%) Proportion with complete control of breakthrough vomiting in 48 hours: 30/32 (94%) Proportion with complete control of breakthrough nausea in 24 hours: 24/32 (75%) Proportion with complete control of breakthrough nausea in 48 hours: 30/32 (94%) Time of occurrence of breakthrough CINV: acute and delayed phase (within 24 and 48 hours) Timeframe of assessments: acute and delayed phases (baseline, 24hrs , and 48hrs)
Metoclopramide				
Musso (2009)[8]	▪ Prospective observational trial ▪ Aim: Evaluate the efficacy of a single dose of palonosetron for CINV control, evaluation of rescue with a second dose of palonosetron was evaluated secondarily ▪ N =27 ▪ Adolescents and adults with haematological malignancies receiving multiple day chemotherapy (2-7 days) ▪ Median age: Not reported for breakthrough cohorts ▪ CINV assessment: patient report ▪ Emetogenicity classification: moderately or highly emetogenic	Not reported	Prophylactic regimen: 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 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 Dexamethasone excluded for patients receiving DHAP (dexamethasone + cisplatin + cytarabine) *Guideline consistent antiemetic prophylaxis: **yes** for MEC, **no** for HEC Breakthrough intervention: G1: **Palonosetron** 0.25mg IV 72 hrs after administration of the first dose G2: **Metoclopramide** 20mg IV q6h or q12h	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: G1: 6/9 (67%) G2: 4/18 (22%) p=0.039 Time of occurrence of breakthrough CINV: acute and delayed phases (over 5 days) Timeframe of assessments: not reported

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]	▪ Double-blinded randomized trial ▪ Aim: Compare the use of olanzapine vs metoclopramide for the treatment of breakthrough CINV ▪ N = 108 ▪ Chemotherapy-naïve adults with cancer receiving chemotherapy (cisplatin ≥ 70mg/m^2 or doxorubicin ≥ 50mg/m^2 + cyclophosphamide ≥ 600mg/m^2) ▪ Median age: G1: 61 yrs; range: 38-75 yrs G2: 63 yrs; range: 42-79 yrs ▪ CINV assessment: patient report ▪ Emetogenicity classification: highly emetogenic	Any emesis and/or any moderate to severe nausea (>3 on visual analogue scale of 0 to 10)	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 *Guideline consistent antiemetic prophylaxis: **yes** Breakthrough intervention: G1: **Olanzapine** 10mg PO once daily x 3 days (n=56) G2: **Metoclopramide** 10mg PO q8h x 3 days (n=52) Oral dexamethasone discontinued immediately once breakthrough treatment with olanzapine initiated	Proportion with complete control of breakthrough vomiting: G1: 39/56 (70%) G2: 16/52 (31%) p<0.01 Proportion with complete control of breakthrough nausea: G1: 38/56 (68%) G2: 12/52 (23%) p<0.01 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 and delayed phases (at least once daily x 72hrs)
Olanzapine				
Chanthawong (2014)[12]	▪ Phase II open label pilot study ▪ Aim: Evaluate the efficacy and safety of olanzapine for breakthrough CINV ▪ N = 46 ▪ Adults with cancer receiving chemotherapy ▪ Median age: 33.5 yrs (males; 18 yrs (females) ▪ Emetogenicity classification: highly emetogenic	Any vomiting episode during days 1 to 4	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 *Guideline consistent antiemetic prophylaxis: **no** Breakthrough intervention: **Olanzapine** 5 mg PO q12h x 2 doses Lorazepam 0.5 to 2mg/dose PO q4 – 6h PRN added if olanzapine not effective	Proportion with complete control of breakthrough vomiting: 28/46 (60.8%) Proportion with complete control of breakthrough nausea: 23/46 (50.0%) Proportion with complete control of breakthrough CINV: not reported Time of occurrence of breakthrough CINV: not reported Timeframe of assessments: q6h x 24 hrs after receipt of olanzapine
Navari (2013)[11]	▪ Double-blinded randomized trial ▪ Aim: Compare the use of olanzapine vs metoclopramide for the treatment of breakthrough CINV ▪ N = 108 ▪ Chemotherapy-naïve adults with cancer receiving chemotherapy (cisplatin ≥ 70mg/m^2 or doxorubicin ≥ 50mg/m^2 + cyclophosphamide ≥ 600mg/m^2) ▪ Median age: G1: 61 yrs; range: 38-75 yrs G2: 63 yrs; range: 42-79 yrs ▪ CINV assessment: patient report ▪ Emetogenicity classification: highly emetogenic	Any emesis and/or any moderate to severe nausea (>3 on visual analogue scale of 0 to 10)	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 *Guideline consistent antiemetic prophylaxis: **yes** Breakthrough intervention: G1: **Olanzapine** 10mg PO once daily x 3 days (n=56) G2: **Metoclopramide** 10mg PO q8h x 3 days (n=52) Oral dexamethasone discontinued immediately once breakthrough treatment with olanzapine initiated	Proportion with complete control of breakthrough vomiting: G1: 39/56 (70%) G2: 16/52 (31%) p<0.01 Proportion with complete control of breakthrough nausea: G1: 38/56 (68%) G2: 12/52 (23%) p<0.01 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 and delayed phases (at least once daily x 72hrs)

First Author (Year)	Study Design, Objective and Population	Definition of Breakthrough CINV	Antiemetic Prophylaxis and Interventions	Proportion with Complete Control of Breakthrough Nausea and/or Vomiting
Prochlorperazine				
Jones (2011)[1]	▪ Prospective observational trial ▪ Aim: Describe the response to antiemetic therapy taken for breakthrough CINV ▪ N = 27 ▪ Adults with cancer receiving chemotherapy ▪ Median age: 57 yrs; range: 30-72 yrs ▪ CINV assessment: patient report ▪ Emetogenicity classification: moderately or highly emetogenic	Nausea and/or vomiting requiring antiemetic rescue medication occurring any time during the first 3 days post-chemotherapy	Prophylactic regimen: Dexamethasone: 25/27 (93%) Granisetron: 20/27 (74%) Palonosetron: 7/27 (26%) Aprepitant: 1/27 (4%) *Guideline consistent antiemetic prophylaxis: unable to determine (authors report prophylactic regimens were based on antiemetic guidelines) Breakthrough intervention: G1: **Prochlorperazine** 10mg PO (n=24) G2: **5-HT antagonist** (granisetron 1mg PO (n=1), ondansetron 8mg IV (n=1), ondansetron 8mg sublingually (n=1)	Proportion with complete control of breakthrough vomiting: G1: 23/24 (96%) G2: 3/3 (100%) Proportion with complete control of breakthrough nausea: G1: 2/24 (8.3%) G2: 1/3 (33.3%) Proportion with complete control of breakthrough CINV: not reported Time of occurrence of breakthrough CINV: acute and delayed phases (over 3 days) Timeframe of assessments: Acute phase (baseline (when breakthrough treatment initiated) then every half hour x 4hrs)
Other				
Bleicher (2008)[13]	▪ 2 prospective open-label trials ▪ Aim: Describe the efficacy of ABH gel in reducing breakthrough CINV ▪ N =33 ▪ Adults with cancer receiving chemotherapy ▪ Median age: Not reported ▪ CINV assessment: patient report ▪ Emetogenicity classification: highly emetogenic	Significant nausea and/or vomiting in the days following chemotherapy	Prophylactic regimen for all patients: not reported *Guideline consistent antiemetic prophylaxis: unable to determine (authors report patients were given standard antiemetic prophylaxis similar to those recommended in established guidelines with ASCO guidelines referenced) Breakthrough intervention: 0.5mL of **ABH gel** applied topically to the wrists q6h prn ABH 0.5 mL contains: lorazepam 2 mg, diphenhydramine 25 mg, haloperidol 2mg ABH gel ingredients: 120mg lorazepam, 1500mg diphenhydramine, 120mg haloperidol, 12mL lecithin organogel, 5mL ethoxydiglycol, 1mL water, and 60mL pluronic gel 20% qs	Proportion with complete control of breakthrough vomiting: not reported Proportion with complete control of breakthrough nausea: not reported Proportion with complete control of breakthrough CINV: 10/33 (30.3%) Time of occurrence of breakthrough CINV: not reported Timeframe of assessments: variable (within 1 month for 23 patients; at baseline and every half hour x 4hrs in 10 patients)

Emetogenicity classified according to the MASCC and ASCO guidelines

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

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

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

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

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

First Author (Year)	Study Design, Objective and Population	Definition of Refractory CINV and CINV Prophylaxis Provided During Previous Chemo Blocks	Antiemetic Interventions	Proportion with Complete Control of Refractory Nausea and/or Vomiting
Pediatric Studies				
5HT-3 Antagonist – Tropisetron				
Hachimi-Idrissi (1993)[18]	▪ Prospective open-label trial ▪ Aim: Determine the efficacy and tolerability of ICS 205-930 (tropisetron) in children with refractory CINV ▪ N = 19 (169 chemotherapy courses) ▪ Children with cancer receiving chemotherapy over 1-5 days ▪ Median age: 9 yrs; range: 2-16yrs ▪ CINV assessment: parent report ▪ Emetogenicity classification: moderately or highly emetogenic	Grade 3 emesis (> 4 episodes of vomiting/day) **Previous prophylactic regimen:** Alizapride 4-6mg/kg/day or metoclopramide 5mg/kg day Guideline consistent antiemetic prophylaxis: no	**Tropisetron** 0.2mg/kg IV (max 5mg) once daily on each day prior to chemo and then PO for 5 days after chemo if patients received cisplatin	Proportion of courses with complete control of vomiting: 131/169 (77.5%) Proportion with complete control of nausea: not reported Proportion with complete control of CINV: not reported Timeframe of assessments: not reported
Aprepitant				
Bauters (2013)[19]	▪ Retrospective, observational study ▪ Aim: Determine the efficacy of aprepitant in children and adolescents with refractory CINV ▪ N = 20 (104 chemotherapy cycles) ▪ Children with cancer receiving chemotherapy ▪ Mean age: 14 yrs; range: 8-16yrs ▪ CINV assessment: Only vomiting evaluated ▪ Emetogenicity classification: moderately or highly emetogenic	Intolerable and uncontrollable emesis in the preceding chemo cycle **Previous prophylactic regimen:** Tropisetron 0.2mg/kg IV once daily (max 5mg) or ondansetron 5-8mg/m^2 bid (max 8mg/dose) or granisetron 0.04mg/kg once daily (max 9mg) + dexamethasone 3mg/m^2 once-twice daily given at least 30 minutes prior to chemo Guideline consistent antiemetic prophylaxis: **yes** (no for patients receiving HEC > 12yrs where aprepitant use permitted)	Day 1: **Aprepitant** 125mg PO once Days 2-3: Aprepitant 80mg po once daily Plus Tropisetron 0.2mg/kg IV once daily (max 5mg) or ondansetron 5-8mg/m^2 bid (max 8mg/dose) or granisetron 0.04mg/kg once daily (max 9mg) + dexamethasone 1.5mg/m^2 once-twice daily given at least 30 minutes prior to chemo	Proportion with complete control of vomiting: patients: 10/20 (50%) courses: 89/104 (85.6%) Proportion with complete control of nausea: not reported Proportion with complete control of CINV: not reported Timeframe of assessments: not reported

First Author (Year)	Study Design, Objective and Population	Definition of Refractory CINV and CINV Prophylaxis Provided During Previous Chemo Blocks	Antiemetic Interventions	Proportion with Complete Control of Refractory Nausea and/or Vomiting
Adult Studies				
5HT-3 Antagonists – Granisetron				
Arevalo-Araujo (2013)[20] [abstract]	▪ Prospective trial (abstract) ▪ Aim: Determine the antiemetic efficacy of APF530 (sustained formulation of granisetron) in refractory patients ▪ N = 72 ▪ Adults with cancer receiving chemotherapy ▪ Median age: not reported ▪ CINV assessment: not reported ▪ Emetogenicity classification: moderately or highly emetogenic	Failure to achieve a complete response (no emesis or rescue medication) with palonosetron during cycle 1 **Previous Prophylactic regimen:** Palonosetron 0.25mg IV Guideline consistent antiemetic prophylaxis: no	**APF530** (sustained formulation of granisetron) 500mg SC	Proportion with complete control of vomiting: not reported Proportion with complete control of nausea: not reported 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%) Timeframe of assessments: not reported/unable to determine
Carmichael (1998)[21]	▪ Prospective open-label trial ▪ Aim: evaluate the tolerability and antiemetic efficacy of granisetron in refractory patients ▪ N = 456 ▪ Adults with cancer receiving chemotherapy ▪ Median age: not reported for refractory cohort ▪ CINV assessment: patient report and direct observation for a minimum of 2hrs from the onset of chemotherapy administration ▪ Emetogenicity classification: unable to determine/not reported	Failed antiemetic therapy during the previous cycle **Previous prophylactic regimens:** One or more of the following: metoclopramide, Dexamethasone, alizapride, ondansetron, chlorpromazine, "other" Guideline consistent antiemetic prophylaxis: unable to determine/not reported	**Granisetron** 3mg IV once 5min prior to chemo + up to 2 additional doses of granisetron 3mg IV with at least 10min between doses	Proportion with complete control of vomiting: not reported Proportion with complete control of nausea: not reported Overall proportion with complete CINV response (defined as no vomiting, mild or absent nausea, and no rescue medications): 237/456 (52%) Timeframe of assessments: acute phase (first 24hrs following chemo)

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]	▪ Randomized, double-blind trial ▪ Aim: evaluate the efficacy of crossing over to granisetron after CINV failure while receiving ondansetron ▪ N = 40 ▪ Adults with cancer receiving cisplatin-or cyclophosphamide-based chemotherapy ▪ Median age: G1: 46yrs; range: 29-71yrs G2: 46yrs; range: 30-73yrs ▪ CINV assessment: patient report ▪ Emetogenicity classification: highly emetogenic	≥ 2 vomits and/or severe nausea (no significant intake possible) or nausea lasting > 4hrs **Previous prophylactic regimen:** Day 1: Ondansetron 8mg IV + dexamethasone 10mg IV Guideline consistent antiemetic prophylaxis: no	G1: **Granisetron** 3mg IV + dexamethasone 10mg IV (n=19) G2: Ondansetron 8mg IV + dexamethasone 10mg IV (n=21)	Proportion with complete control of vomiting: not reported Proportion with complete control of nausea: not reported 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 Timeframe of assessments: acute phase (first 24hrs following chemo)
Sigsgaard (2000)[23]	▪ Prospective open-label trial ▪ Aim: Determine the antiemetic efficacy of granisetron + prednisolone + metopimazine in refractory patients ▪ N = 25 ▪ Adults with breast cancer receiving cyclophosphamide + fluorouracil + either methotrexate or epirubicin ▪ Median age: 45yrs; range: 29-66yrs ▪ CINV assessment: patient report ▪ Emetogenicity classification: moderately emetogenic	≥ 5 emetic episodes during any of days 1-5 following chemo or patients not satisfied with the antiemetic treatment during a previous chemotherapy cycle **Previous prophylactic regimen:** Either granisetron 3mg IV once OR prednisolone 25mg PO once a day x 3 days + metopimazine 30mg PO qid x 3 days Guideline consistent antiemetic prophylaxis: no	**Granisetron** 3mg IV once + **prednisolone** 25mg PO once a day x 3 days + **metopimazine** 30mg PO qid x 3 days	Proportion of cycles with complete control of vomiting: acute phase: 100/113 (88.5%) delayed phase: 107/113 (94.7%) Proportion of cycles with complete control of nausea: acute phase: 49/113 (43.4%) delayed phase: 56/113 (49.6%) 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%) Timeframe of assessments: acute and delayed phases (q24h x 5 days)

First Author (Year)	Study Design, Objective and Population	Definition of Refractory CINV and CINV Prophylaxis Provided During Previous Chemo Blocks	Antiemetic Interventions	Proportion with Complete Control of Refractory Nausea and/or Vomiting
5HT-3 Antagonists – Ondansetron				
Campora (1991)[24]	▪ Prospective open-label trial ▪ Aim: Evaluate the efficacy of ondansetron for antiemetic prophylaxis in refractory patients ▪ N = 24 ▪ Adults with cancer receiving chemotherapy ▪ Median age: 53yrs; range: 21-70yrs ▪ CINV assessment: patient report ▪ Emetogenicity classification: moderately or highly emetogenic	> 15 emetic episodes within 24hrs of therapy while receiving combination antiemetics **Previous prophylactic regimen:** Metoclopramide 0.5-1mg/kg IV + methylprednisolone 40-125mg IV prior to chemo and repeated after 2hrs: 24/24 pts Lorazepam 2mg IV prior to chemo: 7/24 pts Guideline consistent antiemetic prophylaxis: no	**Ondansetron** 8mg PO prior to chemo and repeated after 6 and 12hrs on day 1, then 8mg PO tid on days 2-5	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%) Proportion with complete control of nausea: not reported Proportion with complete control of CINV: not reported Timeframe of assessments: acute and delayed phases (q24h x 5 days)
De Wit (2001) [22]	▪ Randomized, double-blind trial ▪ Aim: evaluate the efficacy of crossing over to granisetron after CINV failure while receiving ondansetron ▪ N = 40 ▪ Adults with cancer receiving cisplatin-or cyclophosphamide-based chemotherapy ▪ Median age: G1: 46yrs; range: 29-71yrs G2: 46yrs; range: 30-73yrs ▪ CINV assessment: patient report ▪ Emetogenicity classification: highly emetogenic	≥ 2 vomits and/or severe nausea (no significant intake possible) or nausea lasting > 4hrs **Previous prophylactic regimen:** Day 1: Ondansetron 8mg IV + dexamethasone 10mg IV Guideline consistent antiemetic prophylaxis: no	G1: **Granisetron** 3mg IV + dexamethasone 10mg IV (n=19) G2: Ondansetron 8mg IV + dexamethasone 10mg IV (n=21)	Proportion with complete control of vomiting: not reported Proportion with complete control of nausea: not reported 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 Timeframe of assessments: acute phase (first 24hrs following chemo)
Du Bois (1990)[25]	▪ Prospective open-label trial ▪ Aim: Determine the antiemetic efficacy of ondansetron ▪ N = 17 (34 chemotherapy cycles) ▪ Adults with cancer receiving platinum based chemotherapy ▪ Median age: 63.5yrs; range 41-75yrs ▪ CINV assessment: Patient report ▪ Emetogenicity classification: highly emetogenic	Severe emesis refractory to standard antiemetic regimen **Previous prophylactic regimen:** Metoclopramide (2-3mg/kg) ± additional antiemetics Guideline consistent antiemetic prophylaxis: no	Day 1: **Ondansetron** 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	Proportion of cycles with complete control of vomiting: 7/34 (20.6%) Proportion with complete control of nausea: not reported Proportion with complete control of CINV: not reported Timeframe of assessments: acute and delayed phases (q24h x 8 days)

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]	▪ Prospective open-label trial ▪ Aim: Report on experience with ondansetron for antiemetic prophylaxis in refractory patients ▪ N = 25 ▪ Adults with ovarian cancer or testicular germ cell tumors receiving carboplatin + etoposide ▪ Median age: 52yrs; range: 24-68yrs ▪ CINV assessment: patient report ▪ Emetogenicity classification: highly emetogenic	Multiple episodes of vomiting (≥ 3) during the first 24hrs of the previous course of chemo **Previous prophylactic regimens:** Metoclopramide 2mg/kg q2h x 3-5 doses: 22 pts Metoclopramide 0.5mg-1/kg IV q2h x 4 doses: 3 pts Lorazepam 1-2mg PO pre-chemo: 16 pts Dexamethasone 8mg IV q6h x 2 doses: 13 pts Haloperidol 2.5mg IV q4h prn: 8 pts Scopaderm patch: 15 pts Guideline consistent antiemetic prophylaxis: no	**Ondansetron** 4mg IV and 4mg PO prior to chemo, then 8mg PO 6 and 12hrs later, and 8mg PO tid for an additional 4 days	Proportion with complete control of vomiting: acute phase: 17/25 (68%) delayed phase: 14/25 (56%) Proportion with complete control of nausea acute phase: 14/25 (56%) delayed phase: 12/25 (48%) Proportion with complete control of CINV: not reported Timeframe of assessments: acute and delayed phases (q24h x 5 days)
Mitchell (1992)[27]	▪ Prospective open-label trial ▪ Aim: Report on experience with ondansetron in refractory patients ▪ N = 91 ▪ Adults with cancer receiving chemotherapy ▪ Median age: G1 (non-cisplatin chemotherapy): 47 yrs; range: 19-72yrs G2 (cisplatin-based chemotherapy): 33yrs; range: 18-44yrs ▪ CINV assessment: patient report (daily) and nurse report (first 24hrs) ▪ Emetogenicity classification: minimal, low, moderate and highly emetogenic agents	At least 3 (non-cisplatin chemo) or 5 (cisplatin-based chemo) episodes of vomiting in the first 24hrs following previous chemo **Previous prophylactic regimen:** G1: Metoclopramide <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 Guideline consistent antiemetic prophylaxis: unable to determine/not reported	G1: **Ondansetron** 4mg IV and 4mg PO prior to chemo, then 8mg PO after 6 and 12hrs, then 8mg PO q8h on days 2-5 (n=75) G2: Ondansetron 8mg IV prior to chemo, then 1mg/hr infusion for 8hrs and 8mg PO at the end of the infusion, then 8mg PO q8h on days 2-6 (n=16)	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%) 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%) Proportion with complete control of CINV: not reported Timeframe of assessments: acute and delayed phases (q24h x 5-6 days)

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]	▪ Prospective open-label trial ▪ Aim: Evaluate the efficacy of 2 dosage regimens of ondansetron for antiemetic prophylaxis in refractory patients ▪ N = 35 ▪ Adults with cancer receiving chemotherapy ▪ Median age: G1: 45yrs; range: 20-66yrs G2: 3yrs; range: 37-72yrs (Note: median age likely publication error based on the range reported by the authors) ▪ CINV assessment: patient report ▪ Emetogenicity classification: moderately or highly emetogenic	> 5 emetic episodes while receiving previous standard antiemetics **Previous prophylactic regimen:** Alizapride or metoclopramide 5-6mg/kg/day Guideline consistent antiemetic prophylaxis: no	G1: **Ondansetron** 4mg IV and 4mg PO prior to chemo, then 4mg PO qid for an additional 4 days (n=19) G2: **Ondansetron** 8mg IV prior to chemo, then 8mg PO tid for an additional 4 days (n=16)	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%) Proportion with complete control of nausea: acute phase: G1: 5/19 (26%) G2: 7/16 (43.75%) Proportion with complete control of CINV: not reported Timeframe of assessments: acute and delayed phases (q24h x 5 days)
Smith (1991)[29]	▪ Prospective open-label trial ▪ Aim: Assess the efficacy of ondansetron for antiemetic prophylaxis in patients receiving carboplatin ▪ N = 16 ▪ Adults with ovarian cancer receiving carboplatin ▪ Median age: 58yrs; range: 23-73yrs ▪ CINV assessment: patient report ▪ Emetogenicity classification: highly emetogenic	>2 emetic episodes in the 24hrs following carboplatin **Previous prophylactic regimen:** Days 1: dexamethasone 8mg PO tid + metoclopramide 20mg PO qid beginning prior to chemo Guideline consistent antiemetic prophylaxis: no	**Ondansetron** 4mg IV and 4mg PO prior to chemo, then 8mg PO tid x 5 days	Proportion with complete control of vomiting: acute phase: 11/16 (69%) acute and delayed phases (days 1-5): 6/16 (46%) Proportion with complete control of nausea: not reported Proportion with complete control of CINV: not reported Timeframe of assessments: acute and delayed phases (q24hr x 5 days)

First Author (Year)	Study Design, Objective and Population	Definition of Refractory CINV and CINV Prophylaxis Provided During Previous Chemo Blocks	Antiemetic Interventions	Proportion with Complete Control of Refractory Nausea and/or Vomiting
5HT-3 Antagonists – Palonosetron				
Hesketh (2012)[30]	▪ Prospective open-label trial ▪ Aim: Determine the efficacy and safety of a single IV dose of palonosetron for prevention of CINV ▪ N = 34 ▪ Adults with cancer receiving chemotherapy who experienced refractory CINV ▪ Mean age: 64.6 ± 13.77yrs ▪ CINV assessment: patient report ▪ Emetogenicity classification: low emetogenicity	Vomiting and/or at least moderate nausea during cycle 1 **Previous prophylactic regimen:** not reported Guideline consistent antiemetic prophylaxis: unable to determine/not reported	Day 1: **Palonosetron** 0.25mg IV 30min prior to chemo	Proportion with complete control of vomiting: acute phase: 31/34 (91.2%) delayed phase: 27/34 (79.4%) Proportion with complete control of nausea: acute phase: 25/34 (73.5%) delayed phase: 18/34 (52.9%) 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%) Timeframe of assessments: acute and delayed phases (q24h x 5 days)
Massa (2009)[31]	▪ Prospective open label trial ▪ Aim: Determine if palonosetron is able to prevent CINV in refractory patients ▪ N = 47 ▪ Adults with cancer receiving chemotherapy ▪ Mean age: 60.7 ± 3yrs; range: 32-89yrs ▪ CINV assessment: patient report ▪ Emetogenicity classification: moderately or highly emetogenic	Grade 3-4 CINV during the first course of chemo that failed to respond to a different 5-HT3 antagonist **Previous prophylactic regimen:** D1: 5-HT3 antagonist (granisetron 1mg IV or ondansetron 8mg IV) + dexamethasone 8mg or 12mg IV D2-3 or 4: Dexamethasone 8mg PO Guideline consistent antiemetic prophylaxis: **yes for MEC**, no for HEC	D1: **Palonosetron** 0.25mg IV + dexamethasone 16mg IV D2-3: Dexamethasone 8mg IV q12h D4: Dexamethasone 4mg IV q12h ± metoclopramide IM prn	Proportion with complete control of vomiting: not reported Proportion with complete control of nausea: not reported 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%) Timeframe of assessments: acute and delayed phases (q24h x 5 days)

First Author (Year)	Study Design, Objective and Population	Definition of Refractory CINV and CINV Prophylaxis Provided During Previous Chemo Blocks	Antiemetic Interventions	Proportion with Complete Control of Refractory Nausea and/or Vomiting
5HT-3 Antagonists – Tropisetron				
Bruntsch (1993)[32]	▪ Prospective, randomized, open-label trial ▪ Aim: Determine the efficacy of tropisetron in refractory patients compared to conventional antiemetic treatment ▪ N = 115 ▪ Adults with cancer receiving chemotherapy ▪ Mean age: 49 yrs ▪ CINV assessment: patient report plus report by an additional individual for the first 24hrs ▪ Emetogenicity classification: low, moderate and highly emetogenic agents	≥ 3 vomiting episodes within 24hrs during previous chemo cycles **Previous prophylactic regimen: i**ndividually prescribed for each patient by investigator Guideline consistent antiemetic prophylaxis: unable to determine/not reported	**Tropisetron** 5mg IV/PO beginning the day before chemo and continuing for at least 5 days (duration dependent on duration of chemo)	Proportion with complete control of vomiting: acute phase: 60/115 (52%) Proportion with complete control of nausea: acute phase: 37/115 (32%) Proportion with complete control of CINV: not reported Timeframe of assessments: acute and delayed phases (q24h x 6 days)
Falkson (1995)[33]	▪ Prospective open-label trial ▪ Aim: Determine the antiemetic efficacy and safety of tropisetron in refractory patients ▪ N = 164 ▪ **Adolescents** and adults with cancer receiving chemotherapy ▪ Median age: 48yrs; range: 14-88yrs ▪ CINV assessment: patient report ▪ Emetogenicity classification: moderately emetogenic	≥ 5 nausea and vomiting episodes despite antiemetic treatment during previous courses of chemo **Previous prophylactic regimens:** 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 Guideline consistent antiemetic prophylaxis: unable to determine/not reported	Day 1: **Tropisetron** 5mg IV Days 2-5: Tropisetron 5mg PO once daily	Proportion with complete control of vomiting: acute phase: 29/81 (36%) delayed phase: 33/81 (41%) Proportion with complete control of nausea: not reported Proportion with complete control of CINV: acute phase: 69/164 (42%) Timeframe of assessments: acute and delayed phases (q24h x 5 days)

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
Fosaprepitant				
Covens [abstract] (2014)[34]	▪ Prospective open-label study ▪ Aim: Demonstrate that fosaprepitant improves vomiting control ▪ N= 106 ▪ Adults with breast or gynaecological cancer with refractory CINV in the first cycle ▪ Median age: 45 yrs (breast cancer); 55 yrs (gynaecological cancer) ▪ CINV assessment: not reported ▪ Emetogenicity: moderately or highly emetogenic	Vomiting or retching during the first 5 days in cycle 1. Previous prophylactic regimen: not reported Guideline consistent antiemetic prophylaxis: unable to determine	Not reported	Proportion with complete control of vomiting and retching: 58% Timeframe of assessments: within first 120 hours after initiation of chemotherapy
Aprepitant				
Abbrederis (2009)[35]	▪ Prospective open-label trial ▪ Aim: evaluate the incidence of CINV during treatment of gastrointestinal tumors with chemotherapy and assess the effect of aprepitant after failure of first line antiemetic prophylaxis ▪ N = 7 ▪ Adults with gastrointestinal tumors ▪ Median age: not reported for refractory cohort ▪ CINV assessment: patient report ▪ Emetogenicity classification: moderately or highly emetogenic	CINV ≥ grade 2 (NCI definition) during the first course of chemo **Previous prophylactic regimen:** Day 1: Granisetron 1.5mg IV + dexamethasone 12mg IV Days 2-3: Dexamethasone 8mg PO once daily Guideline consistent antiemetic prophylaxis: **yes for MEC**, no for HEC	Day 1: **Aprepitant** 125mg PO Days 2-3: Aprepitant 80mg PO + previous prophylactic regimen described	Proportion with complete control of vomiting: not reported Proportion with complete control of nausea: not reported Proportion with "complete relief" from CINV (assumed to be complete control): 5/7 (71%) p=0.096 Timeframe of assessments: not reported

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]	▪ Prospective open-label trial ▪ Aim: Evaluate efficacy of aprepitant in addition to standard antiemetic prophylaxis ▪ N = 24 ▪ Adults with breast cancer receiving docetaxel 75mg/m^2 + cyclophosphamide 600mg/m^2 IV with refractory CINV in the first cycle ▪ Median age: not reported for refractory cohort ▪ CINV assessment: patient diary and Functional Living Index-Emesis questionnaire ▪ Emetogenicity classification: moderately emetogenic	Vomiting or receipt of rescue antiemetic therapy despite prophylaxis with a 5-HT3 antagonist and dexamethasone in cycle 1 **Previous prophylactic regimen:** Day 0: dexamethasone 8mg PO at night Day 1: dexamethasone 8mg TID PO + 5-HT3 antagonist Day 2 and 3: dexamethasone 8mg BID PO Guideline consistent antiemetic prophylaxis: no	Day 1: **Aprepitant** 125mg PO Days 2-3: **Aprepitant** 80mg PO once daily + previous prophylactic regimen described Previous dexamethasone dose was reduced by 50%.	Proportion with complete control of vomiting and no use of rescue antiemetic treatment: 14/24 (56%) Proportion with complete control of nausea: not reported Proportion with complete control of CINV: not reported Timeframe of assessments: within first 120 hours after initiation of chemotherapy
Fukazawa (2011)[37]	▪ Trial design: Prospective, open-label trial ▪ Aim: evaluate the effect of aprepitant on acute and delayed nausea and vomiting ▪ N = 13 ▪ Adults with colorectal cancer receiving chemotherapy ▪ Mean age: 65±11yrs ▪ CINV assessment: Patient report (diary) ▪ Emetogenicity classification: moderately emetogenic	Definition: Delayed CINV occurring in the previous chemotherapy block **Previous prophylactic regimen:** Granisetron 3mg IV + dexamethasone 8mg IV 30-60min pre-chemo Guideline consistent antiemetic prophylaxis: **yes**	Day 1: **Aprepitant** 125mg PO + granisetron 3mg IV + dexamethasone 4mg IV 30-60min pre-chemo Days 2-3: **Aprepitant** 80mg PO 1 hr pre-chemo	Proportion with complete control of vomiting: acute phase: 13/13 (100%) delayed phase: 13/13 (100%) Proportion with complete control of nausea: acute phase: 10/13 (76.9%) delayed phase: 6/13 (46.2%), p<0.05 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%) Timeframe of assessments: acute and delayed phases (q24h x 5 days)

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]	▪ Prospective open-label trial ▪ Aim: Determine the antiemetic activity of aprepitant when used as salvage antiemetic therapy ▪ N = 44 ▪ Adults with breast cancer receiving anthracycline +cyclophosphamide ▪ Median age: not reported for refractory cohort ▪ CINV assessment: patient report ▪ Emetogenicity classification: moderately emetogenic	Any vomiting, nausea, or use of rescue antiemetic medications during cycle 1 **Previous Prophylactic regimen:** Day 1: A 5-HT3 antagonist (ondansetron 8mg IV or 24mg PO, dolasetron 100mg IV or PO, or granisetron 1mg IV or 2mg PO) + dexamethasone 8-10mg IV or PO Days 2-3: Dexamethasone 4mg PO bid Guideline consistent antiemetic prophylaxis: **yes**	Day 1: **Aprepitant** 125mg PO + a 5-HT3 antagonist + dexamethasone 8-10mg IV or PO Days 2-3: Aprepitant 80mg PO + dexamethasone 4mg PO once daily	Proportion with complete control of vomiting (acute and delayed phases): 36/44 (82%) Proportion with complete control of nausea (acute and delayed phases): 8/44 (18%) Proportion with complete control of CINV (including no use of rescue antiemetics): acute phase: 13/44 (30%) delayed phase: 10/44 (23%) Timeframe of assessments: acute and delayed phases (q24h x 5 days)
Hu (2014) [39]	▪ Prospective open-label study ▪ Aim: Evaluate effectiveness of aprepitant in addition to standard antiemetic prophylaxis ▪ N = 25 ▪ Adults with cancer receiving cisplatin 75mg/m2/dose with refractory CIV in the first cycle ▪ Median age: 61 yrs (range: 32 to 72 yrs) ▪ CINV assessment: patient diary ▪ Emetogenicity: highly emetogenic	Vomiting greater than or equal to NCI-CTCAEv3.0 and receipt of rescue antiemetic therapy despite prophylaxis with granisetron and dexamethasone in cycle 1 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 Guideline consistent antiemetic prophylaxis: no	Day 1: **Aprepitant** 125mg PO Days 2-3: **Aprepitant** 80mg PO once daily + previous prophylactic regimen described Dexamethasone dose was not reduced.	Proportion with complete control of vomiting and no use of rescue antiemetic treatment: 16/25 (64%) Proportion with complete control of nausea: acute phase: 6/8 (75%) delayed phase: 7/25 (28%) Proportion with complete control of CINV: 7/25 (28%) Timeframe of assessments: within first 120 hours after initiation of chemotherapy
Oechsle (2006)[40]	▪ Prospective open-label trial ▪ Aim: evaluate the efficacy of the addition of aprepitant in refractory patients ▪ N = 34 ▪ Adults with cancer receiving chemotherapy ▪ Median age: 51yrs; range: 23-77yrs ▪ CINV assessment: patient report ▪ Emetogenicity classification: moderately or highly emetogenic	At least 2 days of nausea and/or emesis considered intolerable by the patient despite the use of guideline-based antiemetic standard prophylaxis **Previous prophylactic regimen:** Acute: Granisetron 1-3mg IV once daily + dexamethasone 4-8mg IV at least twice daily or 20mg IV once daily on the days of chemo Delayed: Dexamethasone 4mg IV/PO bid + metoclopramide 10mg PO tid x 3 days after completion of chemo Guideline consistent antiemetic prophylaxis: **yes For MEC**, no for HEC	Day 1: **Aprepitant** 125mg PO + granisetron 1-3mg IV + dexamethasone 4-8mg IV/PO x 2 doses All further days of chemo: Aprepitant 80mg PO + granisetron 1-3mg IV + dexamethasone 4-8mg IV/PO bid Days 2-3 after chemo: Aprepitant 80mg PO + dexamethasone 4mg PO bid + metoclopramide 20mg PO tid	Proportion with complete control of vomiting (acute and delayed phases): 26/34 (76.5%) Proportion with complete control of nausea: not reported Proportion with complete control of CINV: not reported Timeframe of assessments: acute and delayed phases (q24h x 5 days after the last dose of chemo)

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]	▪ Prospective open-label trial ▪ Aim: Evaluate aprepitant as secondary antiemetic prophylaxis ▪ N = 40 ▪ Adults with cancer receiving cisplatin + 5-fluorouracil ± other chemotherapy with refractory CINV ▪ Median age: not reported for refractory cohort ▪ CINV assessment: investigator (physicians and nurses) and patient report ▪ Emetogenicity classification: highly emetogenic	Failure to achieve complete protection from vomiting with a 5-HT3 antagonist and dexamethasone in cycle 1 **Previous prophylactic regimen:** Day 1: Granisetron 3mg IV + dexamethasone 20mg IV ± diphenhydramine 30mg IM q6h prn Additional days chemo was administered: Dexamethasone 5mg IV q12h ± diphenhydramine 30mg IM q6h prn Guideline consistent antiemetic prophylaxis: no	Day 1: **Aprepitant** 125mg PO Days 2-3: **Aprepitant** 80mg PO once daily + previous prophylactic regimen described	Proportion with complete control of vomiting: acute phase: 39/40 (97.5%) delayed phase: 26/40 (65%) Proportion with complete control of nausea: acute phase: 37/40 (92.5%) delayed phase: 24/40 (60%) Proportion with complete control of CINV: not reported Timeframe of assessments: acute and delayed phases (q24h x 6 days)
Benzodiazepines (Clonazepam, Lorazepam, and Midazolam)				
Hayashi (2010)[42]	▪ Prospective open-label trial ▪ Aim: Evaluate the efficacy of clonazepam in preventing CINV in refractory patients ▪ N = 7 (10 chemotherapy courses) ▪ Adults with cancer receiving cisplatin-based chemotherapy ▪ Median age: 61yrs; range: 43-73yrs ▪ CINV assessment: patient report ▪ Emetogenicity classification: highly emetogenic	Vomiting despite conventional antiemetic therapy **Previous prophylactic regimen:** Day 1: Granisetron 3mg IV + dexamethasone 12mg IV 60min prior to chemo Days 2-4: Dexamethasone 4mg IV once daily Guideline consistent antiemetic prophylaxis: no	Day -1: **Clonazepam** 0.5mg or 1mg PO beginning 12hrs prior to chemo Days 1-4: Clonazepam 0.5mg or 1mg PO once daily + previous prophylactic regimen described	Proportion of cycles with complete control of vomiting: acute phase: 8/10 (80%) delayed phase: 6/10 (60%) Proportion with complete control of nausea: not reported Proportion with complete control of CINV: not reported Timeframe of assessments: acute and delayed phases (q24h x 5 days)
Mandala (2005)[43]	▪ Prospective open-label trial ▪ Aim: evaluate the efficacy of the addition of midazolam to dexamethasone and granisetron for refractory acute CINV ▪ N = 26 ▪ Adults with cancer receiving cisplatin-based chemotherapy ▪ Median age: 58yrs; range: 30-70yrs ▪ CINV assessment: patient report and physician assessment ▪ Emetogenicity classification: highly emetogenic	Grade 2 acute nausea (oral intake significantly reduced) and/or vomiting (2-5 emetic episodes in 24hrs) **Previous prophylactic regimen:** Day 1: Granisetron 3mg IV + dexamethasone 20mg IV Days 2-5: Dexamethasone 4mg PO once daily + metoclopramide 20mg PO tid Guideline consistent antiemetic prophylaxis: no	**Midazolam** 0.04mg/kg continuous infusion during administration of chemo + previous prophylactic regimen described	Proportion with complete control of vomiting: acute phase: 6/26 (23%) delayed phase: 9/26 (34.6%) Proportion with complete control of nausea: acute phase: 5/26 (19.2%) delayed phase: 6/26 (23%) Proportion with complete control of CINV: not reported Timeframe of assessments: acute and delayed phases (q24h, duration not reported)

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]	▪ Prospective open-label trial ▪ Aim: Evaluate the antiemetic efficacy of lorazepam in patients who failed to benefit from standard antiemetics ▪ N = 24 ▪ **Adolescents** and adults with lymphoma receiving chemotherapy ▪ Age range: 14-60yrs ▪ CINV assessment: patient report ▪ Emetogenicity classification: moderately or highly emetogenic	Severe vomiting for several hrs after chemo ± anticipatory vomiting **Previous prophylactic regimen:** Prochlorperazine 10-15mg/m2 IV ± metoclopramide 10-15mg/m^2 IV Guideline consistent antiemetic prophylaxis: no	**Lorazepam** 3mg/m^2 PO 30min prior to chemo + prochlorperazine 10mg IV	Proportion with complete control of vomiting: 17/24 (71%) Proportion with complete control of nausea: not reported Proportion with complete control of CINV: not reported Timeframe of assessments: acute phase (1-2hrs after chemo)
Dexamethasone				
Aapro (1981)[45]	▪ Prospective open-label trial ▪ Aim: Evaluate high-dose dexamethasone for CIV ▪ N = 10 ▪ Adults with cancer receiving chemotherapy ▪ Median age: not reported for refractory cohort ▪ CINV assessment: patient report ▪ Emetogenicity classification: unable to determine/not reported (28 patients received highly emetogenic chemotherapy)	Previous failure to respond to other antiemetics **Previous prophylactic regimen:** not reported Guideline consistent antiemetic prophylaxis: unable to determine/not reported	**Dexamethasone** 8mg PO the night before chemo, then dexamethasone 4mg PO q4-6h on the day of treatment + dexamethasone 10mg IV prior to chemo ± droperdiol or haloperidol 2-2.5mg IV	Proportion with complete control of vomiting: not reported Proportion with complete control of nausea: not reported Proportion with complete control of CINV (defined as no symptoms or slight nausea): 3/10 (30%) Timeframe of assessments: not reported/unable to determine

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]	▪ Randomized, double-blind trial ▪ Aim: Assess whether the addition of dexamethasone leads to improved control of CINV ▪ N = 96 ▪ Adults with cancer receiving chemotherapy ▪ Median age: G1: 44yrs; range: 17-79yrs G2: 52yrs; range: 17-69yrs ▪ CINV assessment: patient report (daily) and nursing assessment (first 24 hrs) ▪ Emetogenicity classification: unable to determine/not reported	> 5 vomiting episodes over 24hrs **Previous prophylactic regimen:** Day 1: Ondansetron 8mg IV x 3 doses Days 2-5: Ondansetron 8mg PO once daily Guideline consistent antiemetic prophylaxis: unable to determine/not reported	G1: Placebo G2: Day 1: **Dexamethasone** 20mg IV once Days 2-5: Dexamethasone 4mg PO tid + previous prophylactic regimen described Patients receiving multiple-days of chemo received IV antiemetics on the days of chemo and PO treatment as described afterward	Proportion with complete control of vomiting: acute phase: G1: 25/52 (48.1%) G2: 31/44 (70.5%) (p = 0.03) Proportion with complete control of nausea: acute phase: G1: 22/52 (42.3%) G2: 27/44 (61.3%) (p = 0.06) Proportion with complete control of CINV: acute phase: G1: 18/52 (34.6%) G2: 24/44 (54.5%) (p = 0.05) Timeframe of assessments: acute and delayed phases (q24h x 5 days)
Prochlorperazine				
Johansson (1982)[47]	▪ Randomized, double-blind, cross-over trial ▪ Aim: Compare the antiemetic efficacy of nabilone to prochlorperazine ▪ N = 18 ▪ Adults with cancer receiving chemotherapy ▪ Median age: not reported ▪ CINV assessment: patient report ▪ Emetogenicity classification: highly emetogenic	Uncontrolled nausea and vomiting despite use of standard antiemetic drugs **Previous prophylactic regimen:** not reported Guideline consistent antiemetic prophylaxis: unable to determine/not reported	G1: **Nabilone** 2mg PO bid x 4 doses G2: **Prochlorperazine** 10mg PO bid x 4 doses	Proportion with complete control of vomiting: G1: 3/18 (17%) G2: 0/18 (0%) Proportion with complete control of nausea: G1: 3/18 (17%) G2: 0/18 (0%) Proportion with complete control of CINV: not reported Timeframe of assessments: acute phase (q24h x 2 days)

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]	▪ Randomized, cross-over trial ▪ Aim: Compare the antiemetic activity of THC versus prochlorperazine in refractory patients ▪ N = 36 ▪ Adults with cancer receiving chemotherapy ▪ Median age: 48yrs; range: 18-69yrs ▪ CINV assessment: patient report ▪ Emetogenicity classification: moderately or highly emetogenic	Severe nausea and vomiting refractory to standard antiemetics **Previous prophylactic regimen:** Prochlorperazine: 34 pts Thiethylperazine: 2 pts Guideline consistent antiemetic prophylaxis: no	G1: **THC** 15mg/m^2 PO prior to chemo then q4h for 24hrs G2: **Prochlorperazine** 10mg PO prior to chemo then q4h for 24hrs	Proportion with complete control of vomiting: not reported Proportion with complete control of nausea: not reported Proportion with complete control of CINV: acute phase: G1: 9/36 (25%) G2: 0/36 (0%) Timeframe of assessments: acute phase (over 24hrs)
THC Compounds (Levonantradol, Nabilone, Tetrahydrocannabinol)				
Cronin (1981)[49]	▪ Prospective open-label trial ▪ Aim: Evaluate the effectiveness of IM levonantradol in refractory patients ▪ N = 28 ▪ Adults with cancer receiving chemotherapy ▪ Median age: not reported for evaluable patients (33yrs; range: 11-68yrs for all 31 patients initially enrolled) ▪ CINV assessment: patient report and investigator monitoring ▪ Emetogenicity classification: moderately or highly emetogenic	Refractory to the aggressive use of conventional antiemetic therapy **Previous prophylactic regimen:** Parenteral phenothiazines Guideline consistent antiemetic prophylaxis: no	**Levonantradol** 0.5mg, 1mg, or 1.5mg IM q4h	Proportion with complete control of vomiting: not reported Proportion with complete control of nausea: not reported Proportion with complete control of CINV: 5/28 (18%) Timeframe of assessments: acute phase (over 24hrs)
Diasio (1981)[50]	▪ Prospective open-label trial ▪ Aim: Report on the antiemetic efficacy of levonantradol in refractory patients ▪ N = 22 (26 courses of chemotherapy) ▪ Adults with cancer receiving chemotherapy ▪ Median age: not reported for refractory cohort ▪ CINV assessment: patient report and nurse monitoring ▪ Emetogenicity classification: unable to determine/not reported	Moderate to severe nausea and vomiting unrelieved by standard antiemetics **Previous prophylactic regimen:** not reported Guideline consistent antiemetic prophylaxis: unable to determine/not reported	G1: **Levonantradol** 0.5mg PO q4h x 3-27 doses (n=14) G2: Levonantradol 1mg PO q4h x 3-27 doses (n=11) G3: Levonantradol 1.5mg PO q4h x 3-27 doses (n=11)	Proportion of courses with complete control of vomiting: G1: 1/14 (7%) G2: 3/11 (27%) G3: 0/1 (0%) Proportion with complete control of nausea: not reported Proportion with complete control of CINV: not reported Timeframe of assessments: acute phase (4hrs following administration of levonantradol)

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]	▪ Prospective open-label trial ▪ Aim: Report on experience with levonantradol in refractory patients ▪ N = 20 ▪ Adults with cancer receiving chemotherapy ▪ Mean age: 43yrs; range 19-63yrs ▪ CINV assessment: patient report ▪ Emetogenicity classification: moderately or highly emetogenic	Severe CINV despite conventional antiemetic therapy **Previous prophylactic regimen:** Levomepromazine 50mg IV/PO ± metoclopramide 10mg ± triflupromazine ± dimenhydrinate pre-chemo Guideline consistent antiemetic prophylaxis: no	**Levonantradol** 0.5-1mg SC 30min prior to chemo ± additional doses 4-8hrs later	Proportion with complete control of vomiting: 8/20 (40%) Proportion with complete control of nausea: 5/20 (25%) Proportion with complete control of CINV: not reported Timeframe of assessments: unable to determine/not reported (pts reported on their experience when the experimental cycle was finished)
Heim (1982)[52]	▪ Prospective open-label trial ▪ Aim: Determine the antiemetic efficacy of levonantradol ▪ N = 20 ▪ Adults with cancer receiving chemotherapy ▪ Median age: not reported; range: 19-66yrs ▪ CINV assessment: Patient report ▪ Emetogenicity classification: moderately or highly emetogenic	"Patients treated without sufficient success of nausea and vomiting when treated with other antiemetics" **Previous prophylactic regimen:** Meclizine, metoclopramide, haloperidol, triflupromazine, flupentixol, and/or levomepromazine Guideline consistent antiemetic prophylaxis: no	**Levonantradol** 1mg (0.5mg for patients weighing less than 50kg) IM 8hrs prior to chemo, then the same dose repeated at 2hrs and 6hrs post-chemo	Proportion with complete control of vomiting: not reported Proportion with complete control of nausea: not reported Proportion with complete control of CINV: 5/20 (25%) Timeframe of assessments: acute phase (q24h x 2 days)
Herman (1977)[53]	▪ Prospective open-label trial ▪ Aim: Determine the antiemetic efficacy of nabilone and evaluate side effects ▪ N = 13 ▪ Adults with cancer receiving chemotherapy ▪ Median age: not reported ▪ CINV assessment: patient report ▪ Emetogenicity classification: moderately or highly emetogenic	Severe nausea and vomiting from chemo not controlled by standard antiemetics **Previous Prophylactic regimen:** Prochlorperazine Guideline consistent antiemetic prophylaxis: no	**Nabilone** 1-2mg PO q8h x 5 days with 2 doses administered prior to chemo	Proportion with complete control of vomiting: not reported Proportion with complete control of nausea: not reported Proportion with complete control of CINV (defined as an average daily rating of zero for nausea and vomiting): 2/13 (15%) Timeframe of assessments: acute and delayed phases (q24h x 5 days)

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]	▪ Randomized, double-blind, cross-over trial ▪ Aim: Compare the antiemetic efficacy of nabilone to prochlorperazine ▪ N = 18 ▪ Adults with cancer receiving chemotherapy ▪ Median age: not reported ▪ CINV assessment: patient report ▪ Emetogenicity classification: highly emetogenic	Uncontrolled nausea and vomiting despite use of standard antiemetic drugs **Previous prophylactic regimen:** not reported Guideline consistent antiemetic prophylaxis: unable to determine/not reported	G1: **Nabilone** 2mg PO bid x 4 doses G2: **Prochlorperazine** 10mg PO bid x 4 doses	Proportion with complete control of vomiting: G1: 3/18 (17%) G2: 0/18 (0%) Proportion with complete control of nausea: G1: 3/18 (17%) G2: 0/18 (0%) Proportion with complete control of CINV: not reported Timeframe of assessments: acute phase (q24h x 2 days)
Laszlo (1981)[54]	▪ Prospective open-label trial ▪ Aim: Evaluate the effectiveness of parenteral levonantradol in refractory patients ▪ N = 33 ▪ Adults with cancer receiving chemotherapy ▪ Median age: not reported for refractory cohort ▪ CINV assessment: patient report and investigator monitoring ▪ Emetogenicity classification: unable to determine/not reported	Persistent nausea and vomiting despite the use of standard antiemetics **Previous prophylactic regimen:** PO or parenteral phenothiazines ± additional prn antiemetics Guideline consistent antiemetic prophylaxis: no	**Levonantradol** 0.5mg, 1mg, 1.5mg, or 2mg PO q4h x 3-27 doses	Proportion with complete control of vomiting: not reported Proportion with complete control of nausea: not reported Proportion with complete control of CINV: 3/33 (9%) Timeframe of assessments: acute phase (over the course of chemo)
Lucas (1980)[55]	▪ Prospective open-label trial ▪ Aim: Determine if PO THC is an effective antiemetic for refractory patients ▪ N = 53 ▪ Adults with cancer receiving chemotherapy ▪ Median age: 51yrs; range: 18-69yrs) ▪ CINV assessment: patient report and investigator monitoring ▪ Emetogenicity classification: unable to determine/not reported	Persistent severe nausea and vomiting in spite of aggressive use of standard antiemetics **Previous Prophylactic regimen:** "Drug therapy" beginning 10-12hrs prior to chemo and continuing throughout the course of chemo, ± additional doses of antiemetics Guideline consistent antiemetic prophylaxis: no	**Δ9-tetrahydrocannabinol** 15mg/m2 PO q6h x 4 doses beginning 1hr prior to chemo OR 5mg/m2 PO q4h beginning 8-12hrs prior to chemo and continuing for 24hrs after chemo	Proportion with complete control of vomiting: not reported Proportion with complete control of nausea: not reported Proportion with complete control of CINV: 10/53 (19%) Timeframe of assessments: not reported/unable to determine (pts observed by investigators over the course of chemo)

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]	▪ Randomized, cross-over trial ▪ Aim: Compare the antiemetic activity of THC versus prochlorperazine in refractory patients ▪ N = 36 ▪ Adults with cancer receiving chemotherapy ▪ Median age: 48yrs; range: 18-69yrs ▪ CINV assessment: patient report ▪ Emetogenicity classification: moderately or highly emetogenic	Severe nausea and vomiting refractory to standard antiemetics **Previous prophylactic regimen:** Prochlorperazine: 34 pts Thiethylperazine: 2 pts Guideline consistent antiemetic prophylaxis: no	G1: **THC** 15mg/m^2 PO prior to chemo then q4h for 24hrs G2: **Prochlorperazine** 10mg PO prior to chemo then q4h for 24hrs	Proportion with complete control of vomiting: not reported Proportion with complete control of nausea: not reported Proportion with complete control of CINV: acute phase: G1: 9/36 (25%) G2: 0/36 (25%) Timeframe of assessments: acute phase (over 24hrs)
Stambaugh (1984)[56]	▪ Randomized, double-blind, placebo-controlled trial ▪ Aim: Evaluate the efficacy and toxicity of intramuscular levonantradol ▪ N = 20 ▪ Adults with cancer receiving chemotherapy ▪ Median age: not reported ▪ CINV assessment: patient and observer report ▪ Emetogenicity classification: unable to determine/not reported	Persistent nausea and vomiting from chemo refractory to maximally recommended doses of conventional antiemetics **Previous prophylactic regimen:** not reported Guideline consistent antiemetic prophylaxis: unable to determine/not reported	**Levonantrodol** 0.5mg, 1mg, 1.5mg, or 2mg IM 2hrs prior to chemo then q4h for 3 additional doses	Proportion with complete control of vomiting: not reported Proportion with complete control of nausea: not reported Proportion with complete control of CINV: acute phase: 11/20 (55%) Timeframe of assessments: acute phase (over 24hrs)
Stuart-Harris (1983)[57]	▪ Prospective open-label trial ▪ Aim: Determine the efficacy of levonantradol for CINV in refractory patients ▪ N = 22 ▪ Adults with cancer receiving chemotherapy ▪ Median age: 49yrs; range 20-70yrs ▪ CINV assessment: patient report and nurse monitoring ▪ Emetogenicity classification: unable to determine/not reported (6 patients received highly emetogenic chemotherapy)	Severe nausea and vomiting refractory to conventional antiemetic treatment **Previous prophylactic regimen:** Chlorpromazine 50-100mg IV/IM q4-6h: 13 pts Prochlorperazine 12.5-25mg IV q4-6h: 12 pts Metoclopramide 10-15mg IV q4h: 5 pts Thiethylperazine 10mg suppositories q6h: 2 pts Perphenazine 6mg PO q8h: 1 pt Guideline consistent antiemetic prophylaxis: no	**Levonantradol** 0.5mg IM 1 hour pre-chemo ± additional doses q4h prn	Proportion with complete control of vomiting: not reported Proportion with complete control of nausea: not reported Proportion with complete control of CINV: 3/22 (13.6%) Timeframe of assessments: not reported/unable to determine

First Author (Year)	Study Design, Objective and Population	Definition of Refractory CINV and CINV Prophylaxis Provided During Previous Chemo Blocks	Antiemetic Interventions	Proportion with Complete Control of Refractory Nausea and/or Vomiting
Miscellaneous (Methotrimeprazine, Medroxyprogesterone, and Propofol)				
Borgeat (1994)[58]	▪ Prospective open-label trial ▪ Aim: Determine the efficacy and safety of added low-dose propofol infusion in patients experiencing refractory CINV ▪ N = 20 ▪ Adults with breast cancer receiving non-cisplatin chemotherapy ▪ Median age: 56yrs; range: 45-72yrs ▪ CINV assessment: nurse report ▪ Emetogenicity classification: moderately emetogenic	> 5 emetic episodes in the first 24hrs despite antiemetic prophylaxis during their first cycle of chemo **Prophylactic regimen:** Ondansetron 8mg IV x 2 doses + dexamethasone 10mg IV once Guideline consistent antiemetic prophylaxis: **yes**	**Propofol** 1mg/kg/hr continuous infusion started 4 hrs prior to chemo and continuing for 24 hrs + previous prophylactic regimen described	Proportion with complete control of vomiting: not reported Proportion with complete control of nausea: not reported Proportion with complete control of CINV: acute phase: 18/20 (90%) Timeframe of assessments: acute phase (q2h starting 4hrs pre-chemo and continuing for 24 hrs after chemo)
Borgeat (1993)[59]	▪ Prospective open-label trial ▪ Aim: Determine the efficacy and safety of added low-dose propofol infusion in patients experiencing refractory CINV ▪ N = 20 ▪ Adults with cancer receiving cisplatin-based chemotherapy ▪ Median age: 52yrs; range: 30-70yrs ▪ CINV assessment: nurse report ▪ Emetogenicity classification: moderately emetogenic	> 5 emetic episodes in the first 24hrs despite antiemetic prophylaxis during their first cycle of chemo **Previous prophylactic regimen:** Ondansetron 8mg IV OR granisetron 3mg IV x 3 doses + dexamethasone 10mg IV once Guideline consistent antiemetic prophylaxis: **yes**	**Propofol** 1mg/kg/hr continuous infusion started 4 hours prior to chemo and continuing for 72hrs after + previous prophylactic regimen described	Proportion with complete control of vomiting: acute phase: 17/20 (85%) delayed phase: 15/20 (75%) Proportion with complete control of nausea: not reported Proportion with complete control of CINV: not reported Timeframe of assessments: acute and delayed phases (q2h starting 4hrs pre-chemo and continuing for 72hrs after chemo)

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]	▪ Case series ▪ Aim: Describe 3 cases where medroxyprogesterone acetate was effective for cisplatin-induced refractory emesis ▪ N = 3 ▪ Adults with cancer receiving cisplatin + gemcitabine ▪ Median age: 58 yrs; range:58-67yrs ▪ CINV assessment: not reported ▪ Emetogenicity classification: highly emetogenic	Emesis occurring despite the use of antiemetic prophylaxis during the previous cycle **Previous Prophylactic regimen:** Pt 1: Day 1: Granisetron 3mg + aprepitant 125mg + dexamethasone 12mg Days 2-3: Aprepitant 80mg + dexamethasone 8mg Day 4: Dexamethasone 8mg Pt 2: Day 1: Granisetron 1mg + aprepitant 125mg + dexamethasone 8mg Days 2-3 and 9-10: Aprepitant 80mg + dexamethasone 4mg Day 8: Dexamethasone 8mg Pt 3: Day 1: Palonosetron 0.75mg + aprepitant 125mg + dexamethasone 12mg Days 2-3: Aprepitant 80mg + dexamethasone 8mg Day 4: Dexamethasone 8mg Guideline consistent antiemetic prophylaxis: Pt 1: **yes** Pt 2: **yes** Pt 3: **yes**	Pt 1: Day 1: Granisetron 3mg + dexamethasone 12mg Days 2-4: **Medroxyprogesterone acetate** 900mg PO + dexamethasone 8mg Day 5: Medroxyprogesterone acetate 900mg PO Pt 2: Day 1: Granisetron 1mg + dexamethasone 8mg Days 2-4: **Medroxyprogesterone acetate** 900mg PO + dexamethasone 4mg Day 5: Medroxyprogesterone acetate 900mg PO Pt 3: Day 1: Palonosetron 0.75mg + aprepitant 125mg + dexamethasone 12mg + **Medroxyprogesterone acetate** 900mg PO Days 2-3: Aprepitant 80mg + dexamethasone 8mg + **Medroxyprogesterone acetate** 900mg PO Day 4: Dexamethasone 8mg + **Medroxyprogesterone acetate** 900mg PO	Proportion with complete control of vomiting: 3/3 (100%) Proportion with complete control of nausea: not reported Proportion with complete control of CINV: not reported Timeframe of assessments: not reported
Higi (1980)[61]	▪ Prospective open-label trial ▪ Aim: Determine the antiemetic efficacy of oral methotrimeprazine ▪ N = 113 ▪ Adults with cancer receiving either cisplatin, ifosfamide, or adriamycin-containing chemotherapy combinations ▪ Median age: not reported ▪ CINV assessment: clinical observation ▪ Emetogenicity classification: moderately or highly emetogenic	Refractory to conventional antiemetics **Previous prophylactic regimen:** Metoclopramide ± triflupromacine ± other phenothiazines/antihistamines Guideline consistent antiemetic prophylaxis: no	**Methotrimeprazine** 8-15mg PO x 2 doses beginning 12hrs and 60 min prior to chemo	Proportion with complete control of vomiting: not reported Proportion with complete control of nausea: not reported Proportion with complete control of CINV: 70/113 (62%) Timeframe of assessments: not reported/unable to determine

First Author (Year)	Study Design, Objective and Population	Definition of Refractory CINV and CINV Prophylaxis Provided During Previous Chemo Blocks	Antiemetic Interventions	Proportion with Complete Control of Refractory Nausea and/or Vomiting
Non-pharmacological Interventions - Acupressure/Acupuncture				
Choo (2006)[62]	▪ Prospective open-label trial ▪ Aim: evaluate the efficacy of electroacupuncture in preventing refractory CINV ▪ N = 27 ▪ Adults with cancer receiving anthracycline-based chemotherapy for breast cancer ▪ Median age: 48yrs; range: 37-60yrs ▪ CINV assessment: patient report and physician assessment ▪ Emetogenicity classification: moderately emetogenic	More than 2 episodes of emesis occurring in the first 24hrs after chemo when antiemetic prophylaxis and rescue antiemetics were given **Previous prophylactic regimen:** Day 1: A 5-HT3 antagonist (ondansetron 8mg IV or granisetron 3mg IV) + dexamethasone 8mg IV Days 2-3: A 5-HT3 antagonist PO Breakthrough medications including PO metoclopramide, lorazepam and dexamethasone permitted Guideline consistent antiemetic prophylaxis: **yes**	**Electroacupuncture** at PC6 for 30min beginning 10min prior to chemo + previous prophylactic regimen described	Proportion with complete control of vomiting: 10/27 (37%) Proportion with complete control of nausea: 3/27 (11%) Proportion with complete control of CINV: not reported Timeframe of assessments: not reported
Gardani (2007)[63]	▪ Prospective open-label trial ▪ Aim: evaluate the efficacy of PC6 stimulation by acupressure for the treatment of refractory CIV ▪ N = 100 ▪ Adults with solid tumors ▪ Median age: 59yrs ▪ CINV assessment: not reported ▪ Emetogenicity classification: moderately or highly emetogenic	Grade 3-4 vomiting and no response to "conventional antiemetics" including 5-HT3 antagonists, corticosteroids, and antidopaminergic agents **Previous prophylactic regimen:** not reported Guideline consistent antiemetic prophylaxis: unable to determine/not reported	Stimulation of the PC6 acupoint by **acupressure** for 8hrs a day starting prior to chemo and continuing for at least 3 days after chemo	Proportion with complete control of vomiting: 68/100 (68%) Proportion with complete control of nausea: not reported Proportion with complete control of CINV: not reported Timeframe of assessments: not reported

Emetogenicity classified according to the MASCC and ASCO guidelines

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

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

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

Health Questions and Recommendations	Strength of Recommendation & Level of Evidence[9,10]
Health Question #1: What interventions are recommended to treat breakthrough CINV in children? *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.	
Recommendation 1.1: For children receiving acute CINV prophylaxis recommended for minimally, low, or moderately emetogenic chemotherapy, clinicians should upgrade or escalate the acute CINV prophylaxis provided to that recommended for chemotherapy of the next higher level of emetogenic risk. Remarks: 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.	Strong Recommendation Very Low Quality Evidence
Recommendation 1.2: For children receiving acute CINV prophylaxis recommended for highly emetogenic chemotherapy, we suggest that olanzapine be added to guideline-consistent CINV prophylaxis**.** Remarks: 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.	Weak Recommendation Low Quality Evidence
Recommendation 1.3: For children receiving acute CINV prophylaxis recommended for highly emetogenic chemotherapy and who cannot receive olanzapine, we suggest that one of the following antiemetic agents be added to guideline-consistent CINV prophylaxis: • methotrimeprazine (also known as levomepromazine) or	Weak Recommendation Very Low Quality Evidence

• 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. 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.	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-HT3 antagonist given for CINV prophylaxis be changed from ondansetron or granisetron to palonosetron. In jurisdictions where palonosetron is not available, we suggest that granisetron be substituted	Weak Recommendation Very Low Quality Evidence

for ondansetron. Remarks: This recommendation places a high value on the improved CINV control seen in adult cancer patients receiving palonosetron and in adult patients receiving granisetron who have a genetic predisposition to a poor response to ondansetron at usual doses. It places less value on drug cost in the scenario where less expensive alternatives have been ineffective. It is a weak recommendation because direct evidence of the comparative efficacy of palonosetron or of using an alternative 5HT-3 antagonist for prevention of refractory CINV in children is not available.	
Recommendation 2.3: For children experiencing refractory CINV despite initiation of previous recommendations and who have not previously received aprepitant because it is known or suspected to interact with the chemotherapeutic agent(s) being given, we suggest that the addition of aprepitant to acute CINV prophylaxis be considered. 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.	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 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.	Weak Recommendation Very Low Quality Evidence
• stimulation of Nei Guan (P6) by means of acupressure or electro-acupuncture. Remarks: This recommendation places a high value on the possibility that acupressure or electro-acupuncture may increase control of	Weak Recommendation Very Low Quality Evidence

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

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