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PEDIATRIC ONCOLOGY GROUP OF ONTARIO

COLLABORATING FOR KIDS WITH CANCER SINCE 1983

Guideline for the Prevention of Acute Nausea and Vomiting due to Antineoplastic Medication in Pediatric Cancer Patients

The POGO Antineoplastic–induced Nausea and Vomiting Guideline Development Panel:

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The Pediatric Oncology Group of Ontario (POGO) Guideline for the Prevention of Acute Nausea and Vomiting due to Antineoplastic Medication in Pediatric Cancer Patients was developed by health care professionals using evidence-based or best practice references available at the time of its creation. The content of the guideline will change since it will be reviewed and revised on a periodic basis. Care has been taken to ensure accuracy of the information. However, every health care professional using this guideline is responsible for providing care according to their best professional judgement and the policies and standards in place at their own institution.

OVERVIEW OF MATERIAL

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SUMMARY OF RECOMMENDATIONS

Table 1: Summary of Recommendations

Recommendation	Strength of Recommendation & Level of Evidence*
1. How is optimal control of acute AINV defined?	
We recommend that optimal control of acute AINV be defined as no vomiting, no retching, no nausea, no use of antiemetic agents other than those given for AINV prevention and no nausea-related change in the child's usual appetite and diet. This level of AINV control is to be achieved on each day that antineoplastic therapy is administered and for 24 hours after administration of the last antineoplastic agent of the antineoplastic therapy block.	Strong recommendation Very low quality evidence
2a. What pharmacological interventions provide optimal control of acute AINV in children receiving antineoplastic agents of high emetic risk?	
We recommend that: ▪ Children ≥ 12 years old and receiving antineoplastic agents of high emetic risk which are not known or suspected to interact with aprepitant receive: *ondansetron or granisetron + dexamethasone + aprepitant*	Strong recommendation Very low quality evidence
▪ Children ≥ 12 years old and receiving antineoplastic agents of high emetic risk which are known or suspected to interact with aprepitant receive: *ondansetron or granisetron + dexamethasone*	Strong recommendation Moderate quality evidence
▪ Children < 12 years old and receiving antineoplastic agents of high emetic risk receive: *ondansetron or granisetron + dexamethasone*	Strong recommendation Moderate quality evidence
2b. What pharmacological interventions provide optimal control of acute AINV in children receiving antineoplastic agents of moderate emetic risk?	
We recommend that children receiving antineoplastic agents of moderate emetogenicity receive: *ondansetron or granisetron + dexamethasone*	Strong recommendation Moderate quality evidence
2c. What pharmacological interventions provide optimal control of acute AINV in children receiving antineoplastic agents of low emetic risk?	
We recommend that children receiving antineoplastic agents of low emetic risk receive: *ondansetron or granisetron*	Strong recommendation Moderate quality evidence
2d. What pharmacological interventions provide optimal control of acute AINV in children receiving antineoplastic agents of minimal emetic risk?	
We recommend that children receiving antineoplastic agents of low emetic risk receive: *no routine prophylaxis*	Strong recommendation Very low quality evidence

Recommendation	Strength of Recommendation & Level of Evidence*
3. What adjunctive non-pharmacological interventions provide control of acute AINV in children receiving antineoplastic agents of any emetic risk?	
We suggest that acupuncture, acupressure, guided imagery, music therapy, progressive muscle relaxation and psycho-educational support and information may be effective in children receiving antineoplastic agents. Virtual reality may convey benefit. We suggest that the following dietary interventions may be effective: ▪ eat smaller, more frequent meals; ▪ reduce food aromas and other stimuli with strong odours; ▪ avoid foods that are spicy, fatty or highly salty; ▪ take antiemetics prior to meals so that the effect is present during and after meals; and ▪ measures and foods (e.g. "comfort foods") that helped to minimize nausea in the past	Weak recommendation Very low quality evidence
4. What is the role of aprepitant in children receiving antineoplastic therapy?	
We recommend that the use of aprepitant be restricted to children 12 years of age and older who are about to receive highly emetogenic antineoplastic therapy which is not known or suspected to interact with aprepitant. There is no evidence to support the safe and effective use of aprepitant in younger children.	Strong recommendation Very low quality evidence
5. What pharmacological interventions provide optimal control of acute AINV in children receiving highly or moderately emetogenic antineoplastic agents in whom corticosteroids are contra-indicated?	
We suggest that children receiving highly emetogenic antineoplastic therapy who cannot receive corticosteroids receive: *ondansetron or granisetron* + *chlorpromazine* *or* *nabilone*	Weak recommendation Low quality evidence
We suggest that children receiving moderately emetogenic antineoplastic therapy who cannot receive corticosteroids receive: *ondansetron or granisetron* + *chlorpromazine* *or* *metoclopramide* *or* *nabilone*	Weak recommendation Low quality evidence

Recommendation	Strength of Recommendation & Level of Evidence*
6. What doses of antiemetic agents are known to be effective in children receiving antineoplastic agents?	
We recommend the following **aprepitant** dose for children 12 years of age and older: *Day 1: 125mg PO x 1; Days 2 and 3: 80mg PO once daily*	Strong recommendation Moderate quality evidence
We recommend the following **chlorpromazine** dose: *0.5mg/kg/dose IV q6h*	Strong recommendation Low quality evidence
We suggest the following **dexamethasone** for children receiving highly emetogenic antineoplastic therapy: *6 mg/m^2/dose IV/PO q6h* If given concurrently with aprepitant, reduce dexamethasone dose by half.	Weak recommendation Low quality evidence
We recommend the following **dexamethasone** for children receiving moderately emetogenic antineoplastic therapy: *≤ 0.6m^2: 2mg/dose IV/PO q12h* *> 0.6m^2: 4mg/dose IV/PO q12h* If given concurrently with aprepitant, reduce dexamethasone dose by half	Strong recommendation Low quality evidence
We recommend the following **IV granisetron** dose for children receiving highly emetogenic antineoplastic therapy: *40 mcg/kg/dose IV as a single daily dose*	Strong recommendation Low quality evidence
We recommend the following **IV granisetron** dose for children receiving moderately emetogenic antineoplastic therapy: *40 mcg/kg/dose IV as a single daily dose*	Strong recommendation Moderate quality evidence
We suggest the following **oral granisetron** dose for children receiving moderately emetogenic antineoplastic therapy: *40 mcg/kg/dose PO q12h*	Weak recommendation Low quality evidence
We recommend the following **IV granisetron** dose for children receiving antineoplastic therapy of low emetogenicity: *40 mcg/kg/dose IV as a single daily dose*	Strong recommendation Low quality evidence
We suggest the following **oral granisetron** dose for children receiving antineoplastic therapy of low emetogenicity: *40 mcg/kg/dose PO q12h*	Weak recommendation Low quality evidence
We recommend the following **metoclopramide** dose for children receiving moderately emetogenic antineoplastic therapy: *1 mg/kg/dose IV pre-therapy x 1 then 0.0375 mg/kg/dose PO q6h* Give diphenhydramine or benztropine concurrently	Strong recommendation Low quality evidence

Recommendation	Strength of Recommendation & Level of Evidence*
We suggest the following **nabilone** dose: *< 18 kg: 0.5 mg/dose PO twice daily* *18 to 30 kg: 1 mg/dose PO twice daily* *> 30 kg: 1 mg/dose PO three times daily* *Maximum: 0.06 mg/kg/day*	Weak recommendation Low quality evidence
We recommend the following **ondansetron** dose for children receiving highly emetogenic antineoplastic therapy: *5 mg/m^2/dose (0.15 mg/kg/dose) IV/PO pre-therapy x 1 and then q8h*	Strong recommendation Moderate quality evidence
We recommend the following **ondansetron** dose for children receiving moderately emetogenic antineoplastic therapy: *5 mg/m^2/dose (0.15 mg/kg/dose; maximum 8 mg/dose) IV/PO pre-therapy x 1 and then q12h*	Strong recommendation Moderate quality evidence
We recommend the following **ondansetron** dose for children receiving therapy of low emetogenicity: *10 mg/m^2/dose (0.3 mg/kg/dose; maximum 16 mg/dose IV or 24 mg/dose PO) pre-therapy x 1*	Strong recommendation Low quality evidence

*See Appendix E for key to strength of recommendations and quality of evidence descriptions.

GLOSSARY

Acute antineoplastic-induced nausea and vomiting: nausea, vomiting, and/or retching that occurs within 24 hours following the administration of an antineoplastic therapy.

Anticipatory antineoplastic-induced nausea and vomiting: nausea, vomiting, and/or retching that occurs within 24 hours prior to administration of antineoplastic therapy.

Delayed antineoplastic-induced nausea and vomiting: nausea, vomiting, and/or retching that occur more than 24 hours after and usually within 7 days of administration of an antineoplastic therapy.

Chemotherapy/antineoplastic therapy block: series of consecutive days that antineoplastic agents are given within a treatment plan or protocol

Emetogenicity: the propensity of an agent to cause nausea, vomiting or retching. Please refer to the POGO Guideline classification of the acute emetogenic potential of antineoplastic medication in pediatric cancer patients for information regarding the emetogenicity of specific agents. [1, 2]

- **High emetic potential:** greater than 90% frequency of emesis in the absence of effective prophylaxis
- **Moderate emetic potential:** 30 to 90% frequency of emesis in the absence of effective prophylaxis
- **Low emetic potential:** 10 to less than 30% frequency of emesis in the absence of effective prophylaxis
- **Minimal emetic potential:** less than 10% frequency of emesis in the absence of effective prophylaxis

INTRODUCTION

Nausea and vomiting as a result of antineoplastic medication continue to be a negative influence on the lives of children with cancer.[3] Although acute antineoplastic-induced vomiting may improve over the course of treatment, antineoplastic-induced nausea may actually become more problematic.[4] The use of evidence-based or consensus-based guidelines for antiemetic selection has been shown to improve control of acute antineoplastic-induced nausea and vomiting (AINV) in adults.[5] The lack of a rigorously developed guideline for antiemetic selection for children receiving antineoplastic therapy has likely been an impediment to optimizing AINV control in children with cancer.

Appropriate antiemetic selection for acute AINV prophylaxis begins with an assessment of the intrinsic emetogenicity of the antineoplastic therapy to be given. The POGO Guideline for the Classification of the Acute Emetogenic Potential of Antineoplastic Medication in Pediatric Cancer Patients provides evidence-based recommendations on which to base the assessment of a regimen's emetogenicity.[1] With this information, it is now possible to evaluate current evidence and develop a guideline for the prevention of acute AINV specifically for children.

SCOPE AND PURPOSE

The purpose of this guideline is to provide physicians, nurses, pharmacists and other health care providers who care for children aged 1 month to 18 years who are receiving antineoplastic medication with an approach to the prevention of acute AINV. The scope of this guideline is limited to the prevention of AINV in the acute phase (within 24 hours of administration of an antineoplastic agent). Its scope does not include anticipatory, breakthrough or delayed phase AINV, or nausea and vomiting that is related to radiation therapy, disease, co-incident conditions or end-of-life care. Management of anticipatory, breakthrough and delayed AINV will be addressed in a future POGO guideline. Although the evidence review and appraisal was comprehensive, the antiemetic strategies recommended are limited to those available in Canada at the time of guideline development. In addition, this guideline is most applicable to children who are naïve to antineoplastic therapy and who are about to receive their first course of antineoplastic therapy.

The objectives of this guideline are:

1. To facilitate the selection of interventions, including pharmacological, non-pharmacological and complementary interventions (e.g. homeopathy, herbal, acupressure), which will provide optimal control of acute AINV in children with cancer receiving antineoplastic therapy including those undergoing conditioning for hematopoietic stem cell transplant (HSCT).
2. To reduce the impact of inconsistent antiemetic prophylaxis on patients and families, especially those who receive care at more than one facility.

This guideline represents the second of a series of guidelines to address the need for, and the selection of, antiemetic prophylaxis and intervention in children with cancer receiving antineoplastic therapy. The first of

the series, Guideline for the Classification of the Acute Emetogenic Potential of Antineoplastic Medication in Pediatric Cancer Patients, can be accessed at: http://www.pogo.ca/_media/File/guidelines/AINV1-Full.pdf.

These guidelines will lead to improvements in the supportive care of children with cancer by offering a standardized, evidence-based approach to the prophylaxis of AINV, optimization of AINV control and provision of cost-effective antiemetic prophylaxis.

HEALTH QUESTIONS ADDRESSED BY THE GUIDELINE

1. How is optimal control of acute AINV defined?
2. What pharmacological interventions provide optimal control of acute AINV in children receiving antineoplastic agents of high, moderate, low and minimal emetic risk?
3. What adjunctive non-pharmacological interventions provide control of acute AINV in children receiving antineoplastic agents of any emetic risk?
4. What is the role of aprepitant in children receiving antineoplastic therapy?
5. What pharmacological interventions provide optimal control of acute AINV in children receiving highly or moderately emetogenic antineoplastic agents in whom corticosteroids are contra-indicated?
6. What doses of antiemetic agents are known to be effective in children receiving antineoplastic agents?

TARGET AUDIENCE

The target users of this guideline are all health care providers who care for children and adolescents with cancer who are receiving antineoplastic medication and who are at risk of experiencing AINV. This guideline is aimed particularly at physicians, nurse practitioners, nurses, and pharmacists working in pediatric oncology centers and satellites in Ontario where pediatric oncology patients receive care.

METHODS

Guideline Development Panel

POGO identified AINV as a key supportive care initiative in 2008 and the POGO AINV Guideline Development Group was formed in December 2008. Members were selected with a view to obtain inter-disciplinary representation from several POGO institutions as well as content expertise. Experts who had published in the area of AINV in children or who had a current research interest in AINV or supportive care in cancer were invited to join the guideline development group. After the completion of the POGO Guideline for the Classification of the Acute Emetogenic Potential of Antineoplastic Medication in Pediatric Cancer Patients[1, 2] in July 2010, panel members were asked to confirm their willingness to continue as members of the panel tasked with the adaptation of a second guideline in this series. One member resigned while a new member was recruited.

Identification and Appraisal of Existing Guidelines

A guideline was sought which could be adapted to the POGO context for acute AINV prevention.

(a) Guideline Search Strategy: In February 2010, the POGO AINV Guideline Development Group conducted a comprehensive literature search and environmental scan to identify existing practice guidelines for the management of acute antineoplastic induced nausea and vomiting for children and youth with cancer. Computerized searches were performed with the assistance of a library scientist using the OVID search platform in the following databases: Medline, Embase, Cochrane Central Register of Controlled Trials (CCTR), Allied and Complementary Medicine (AMED), Health Technology Assessment (HTA) and NHS Economic Evaluation Database (NHSEED) as well as the EBSCOhost information provider in the CINHAL database. The search engine Google was utilized for identification of grey literature including local, provincial, national and international databases. Personal files of panel members were also reviewed for papers that merited inclusion in our results. In addition, panel members identified guidelines for prevention of AINV for pediatric patients with cancer from their institutions as well as from other agencies and associations with which they had affiliations. The guideline search strategy is provided in Appendix A.

(b) Guideline Selection Criteria and Appraisal: Guidelines were selected for inclusion that were: (i) focused on antiemetic use for the prevention of acute AINV; (ii) based on a systematic review of the literature and (iii) published in English or French. Guidelines were excluded if it was not clear that the guideline statements or recommendations were based on a review of evidence from the literature and/or were not based on a source that used evidence to support the guideline development process.

Each guideline identified through the search (Appendix A) was independently reviewed and scored by 3 to 4 members of the POGO AINV Guideline Development Panel using the Appraisal of Guidelines for Research & Evaluation (AGREE) instrument[6]. The domains assessed by this instrument include: scope and purpose; stakeholder involvement; rigor; clarity and presentation; applicability, and editorial independence. The domain scores and overall assessments of each reviewer were aggregated and presented for discussion at a panel meeting held by teleconference. The AGREE scores are presented in Appendix B. The suitability of each guideline for adaptation using the ADAPTE[7] process was discussed by the panel. Reasons to support or refute adaptation of each guideline were provided. Rigor and applicability scores were emphasized in the selection of a source guideline.

Primary Literature Search for Pediatric Studies

As none of the guidelines identified specifically addressed antiemetic use for the prevention of acute AINV in children with cancer, a systematic review of primary pediatric oncology studies addressing this topic was conducted.

(a) Search Strategy: The following electronic databases were searched: Medline, Embase, CCTR, AMED, HTA, NHSEED and CINHAL. The search strategy including search terms and limits for these searches are provided in Appendix C. In addition to the results of the electronic database search, studies identified from the personal files of panel members and unpublished supplementary data from the research of panel members were evaluated for inclusion.

(b) Selection Criteria and Appraisal: Studies were included if: (i) they were published in full text (i.e. abstracts were excluded), (ii) they were published in English or French (iii) they reported pediatric data separately, (iv) it was possible to determine the emetogenicity of the antineoplastic therapy administered using the POGO classification guideline or an assessment provided by the study's author(s); (v) they provided an explicit or implicit definition of complete acute AINV response; and (vi) they reported the complete acute AINV response rate as a proportion or percentage. Citations were divided among panel members for screening for inclusion/exclusion. Full-text screening was performed for those citations identified as potentially relevant. Evidence summary tables were compiled and reviewed by two panel members before consideration by the panel.

(c) Meta-Analysis: A meta-analysis was undertaken to evaluate the contribution of each antiemetic agent or antiemetic regimen to complete AINV control. All outcomes were described as proportions; for example, the proportion of patients with complete control among a particular group. Each study was weighted by the inverse variance. Given the anticipation of heterogeneity between studies, a random effects model [8] was used for all analyses. The meta-analysis was performed using Review Manager (RevMan) (Version 5.1.0, The Cochrane Collaboration, Oxford, England). Sub-groups were compared by evaluating heterogeneity across sub-group results.

Decision-Making Process for Formulation of the Recommendations

Therapeutic efficacy and safety were the primary determinants of recommendations made by the guideline development panel regarding antiemetic choice. In the event of contradictory information regarding therapeutic efficacy, the panel members took a conservative approach; that is, the more aggressive, comprehensive antiemetic prophylaxis would be recommended. This approach would be less likely to lead to breakthrough AINV and would perhaps allow reduction of antiemetic prophylaxis, if desired, in a patient in whom AINV was well-controlled.

The authors of several studies categorized the emetic risk of the antineoplastic regimens they studied as high or moderate without providing sufficient detail to determine the emetic risk as per the POGO Guideline for the Classification of the Acute Emetic Risk of Antineoplastic Medications in Paediatric Oncology Patients.[1,2] The emetogenicity classification of several single and combination antineoplastic therapies differs between the

POGO and adult guidelines. Many study authors relied upon emetogenicity classification guidelines employed in adult practice at the time of their study. Less weight was placed on the results of these studies than those where the emetic risk of the antineoplastic regimens studied was able to be verified against the POGO classification.

In the case of studies which describe groups of children each receiving antineoplastic therapy of varied emetogenicity and did not report AINV control results separately for these groups, the study results were reported in the lowest emetogenic risk category included. For example, when a study included children receiving antineoplastic agents of both high and moderate emetic risk and reported the incidence of AINV control only of the group as a whole, the study results would be interpreted as relevant to agents of moderate emetic risk. This conservative approach may increase the extent of antiemetic prophylaxis provided for some children but may increase the likelihood that adequate prophylaxis would be provided to all. In children who experience complete control of AINV during the initial antineoplastic block, it is possible to step down the extent of prophylaxis in subsequent blocks if so desired.

In the case of studies which describe AINV control in children receiving multiple day antineoplastic regimens where the emetogenicity varied between treatment days and where AINV control is reported for the entire acute phase, the study results were reported according to the individual agents of highest emetogenicity given during the antineoplastic block.

All studies that met inclusion criteria were appraised. Evidence regarding the use of 5-HT3 antagonists in children was included in the evidence summary and synthesis since first generation agents have been deemed to be equivalent in efficacy in adults. Evidence regarding the use of other antiemetic agents which are not marketed in Canada was included in the evidence summary and synthesis. However, recommendations for this guideline were limited to antiemetic agents safe for use and marketed in Canada. Specifically, dolasetron is not included in the recommendations due to its potential to cause serious and potentially fatal arrhythmia[9] while tropisetron was not included because it was not marketed in Canada at the time of guideline development.

Decisions were taken through panel discussions and any differences in opinion were resolved by consensus. The quality of evidence and strength of recommendations were assessed using the system developed by Guyatt et al[10] by one author (LLD) and confirmed through discussion by the remaining panel members. If consensus was unable to be reached on any matter, a decision was made by the majority of panel members by a vote.

EVIDENCE SYNTHESIS AND RECOMMENDATIONS

Identification and Appraisal of Existing Guidelines

The guideline search yielded 60 citations that were screened for inclusion. Thirteen guidelines that were either developed for use in adults and/or for use in children using were identified (Appendix A) and assessed using the AGREE Instrument. The assessments are summarized in Appendix B. Two guidelines were selected as the source guideline for adaptation of this guideline:

(1) The American Society of Clinical Oncology Guidelines for Antiemetics in Oncology: Update 2006[11]

(2) Putting Evidence into Practice: Evidence-Based Interventions to Prevent, Manage, and Treat Chemotherapy-Induced Nausea and Vomiting (2007) by Tipton et al.[12]

Using ADAPTE methods, the American Society of Clinical Oncology (ASCO) guideline was the primary document utilized as the framework for the development of guidelines for AINV prevention in pediatric cancer patients for pharmacological therapies. While the ASCO guideline does provide a general recommendation for prophylaxis in the pediatric setting, the focus of the guideline is on antiemetic use for adult cancer patients and it is in this capacity that the guideline is referenced as a source document. Tipton et al. was used as the framework for non-pharmacological interventions. Although the recommendations of the source guidelines are based on adult data, the advantages of these guidelines include the rigorous methodologies used in their development and their structure. When it became available, the 2011 update to the ASCO guideline[13] was compared to the previous version. Since the 2011 recommendations did not differ substantially from those provided in the 2006 version with respect to the health questions of interest, the 2011 update was cited as the source guideline.

Primary Literature Review of Pediatric Oncology Studies

A total of 1660 references were retrieved from 7 electronic databases. An updated search was performed through November 1, 2011 and panel members also reviewed their personal files for papers that met inclusion criteria. There were a total of 574 duplicates, 704 were excluded based on the title/abstract screen and 321 excluded after full text screening. There were 72 papers that met inclusion criteria (refer to flowchart in Appendix C).

Due to the lack of evidence identified with respect to pediatric experience with dronabinol, levomepromazine or methotrimeprazine in the initial search for primary literature, separate computerized literature searches were performed for these agents. No relevant papers were identified (Appendix D).

Health Question #1: How is Optimal Control of Acute AINV Defined?

Recommendation	Strength of Recommendation & Level of Evidence*
We recommend that optimal control of acute AINV be defined as no vomiting, no retching, no nausea, no use of antiemetic agents other than those given for AINV prevention and no nausea-related change in the child's usual appetite and diet. This level of AINV control is to be achieved on each day that antineoplastic therapy is administered and for 24 hours after administration of the last antineoplastic agent of the antineoplastic therapy block.	Strong recommendation Very low quality evidence

* See Appendix E for key to strength of recommendations and quality of evidence descriptions.

Changes from the Source Guideline[11-13]:

- This question was not addressed by the source guidelines.

Evidence Summary and Discussion:

The source guidelines[11-13] did not explicitly address the question of how to define optimal AINV control. No evidence was identified that would inform this recommendation. Even in adults, where validated nausea assessment instruments have been available for some time, the endpoints of studies of antiemetic efficacy are heavily focused on prevention of vomiting. Recent adult antiemetic trials have defined complete AINV control as: no vomiting, no retching, no rescue therapy and no premature discontinuation from the study[14] or no vomiting, no retching, no rescue therapy.[15, 16] Nausea assessment may be included as a secondary study endpoint. Nausea assessment is rarely incorporated into pediatric antiemetic studies. This is changing, however, now that validated instruments are available.[17, 18] The fact that current guidelines and antiemetic literature do not always consider nausea control in defining response indicates that nausea, a symptom that is considered to be quite bothersome by patients, has not been adequately addressed by clinicians.[3, 19, 20] Similar to pain, another subjective experience, nausea is prone to under-treatment. Appetite or diet is rarely incorporated into adult or pediatric antiemetic study endpoints.

This recommendation was developed through discussion with the guideline panel members and was unanimously supported. Though the antiemetic agents in common use today are not likely to achieve optimal AINV control as defined here, the recognition of this definition by the pediatric oncology community will increase the probability that it will become a goal of future antiemetic trials making its future achievement more likely.

Research Gaps:

Information regarding the impact of each component of the definition of optimal AINV control (vomiting, retching, nausea, appetite and use of breakthrough antiemetic agents) on quality of life is needed to inform their individual importance from the patient's point of view. Research is warranted to determine the optimal methods of measuring appetite and to describe its relationship with nausea.

Health Question #2a: What Pharmacological Interventions Provide Optimal Control of Acute AINV in Children Receiving Antineoplastic Agents of High Emetic Risk?

Recommendation	Strength of Recommendation & Level of Evidence*
We recommend that: ▪ Children ≥ 12 years old and receiving antineoplastic agents of high emetic risk which are not known or suspected to interact with aprepitant receive: *ondansetron or granisetron + dexamethasone + aprepitant*	Strong recommendation Very low quality evidence
▪ Children ≥ 12 years old and receiving antineoplastic agents of high emetic risk which are known or suspected to interact with aprepitant receive: *ondansetron or granisetron + dexamethasone*	Strong recommendation Moderate quality evidence
▪ Children < 12 years old and receiving antineoplastic agents of high emetic risk receive: *ondansetron or granisetron + dexamethasone*	Strong recommendation Moderate quality evidence

* See Appendix E for key to strength of recommendations and quality of evidence descriptions.

Changes from the Source Guidelines[11, 13]

- the limitation of the use of aprepitant to children aged 12 years and older (see recommendation 3) and
- the addition of a statement regarding antineoplastic agent interactions with aprepitant.

Evidence Summary and Discussion:

Overall, the rates of complete control reported in studies of antiemetic efficacy in children receiving highly emetogenic antineoplastic therapy are low. The rate of complete AINV control was consistent regardless of whether the emetogenicity of the antineoplastic regimens included in studies was defined as per the POGO guideline (43%; 95% CI: 29, 56) or by the investigators (47%; 95% CI: 22, 72). Furthermore, the rate of AINV control was also similar between studies that did (52%; 95% CI: 42, 61) and did not (50%; 95%: 34, 67) include nausea in their definition of complete AINV control. The reasons for this are unclear although the variable methodologies for the evaluation of endpoints and the common use of non-validated instruments to determine nausea severity may have contributed.

A summary of the evidence used to support this recommendation can be found in Appendix F. The results of meta-analysis of these data are summarized in Table 2. Forest plots are presented in Appendix G.

Table 2: Summary of results of meta-analysis of studies evaluating AINV response in children receiving highly emetogenic antineoplastic therapy

	Number of Studies or Study Arms	Number of Patients or Antineoplastic Blocks	% with Complete Control (95% CI)
All Studies	26	1229	49 (37, 60)
Prophylaxis with 5-HT3 antagonist + corticosteroid: all studies	4	188	50 (43, 57)
Prophylaxis with 5-HT3 Antagonist Alone: All Studies	17	958	56 (43, 69)
Prophylaxis with 5-HT3 antagonist alone: emetogenicity determined using POGO guideline AND definition of complete AINV control included nausea control	8	539	66 (60, 72)

CI: confidence interval

5-HT3 Antagonist, Corticosteroid Plus Aprepitant

The source guideline[11] recommends administration of a 5-HT3 antagonist, dexamethasone plus aprepitant to adults receiving highly emetogenic antineoplastic therapy. Aprepitant appears to be both a safe and effective antiemetic in adult cancer patients. Its attractive safety record and ability to substantially improve AINV control in both the acute and delayed phases in adults receiving highly emetogenic antineoplastic therapy led to its swift adoption as a standard of care in adult oncology. Pediatric data has been minimal and, anecdotally, pediatric clinicians have been eager for their patients to enjoy the same benefits of aprepitant as adult cancer patients.

Published pediatric experience regarding the efficacy in preventing acute AINV of the combination of this 3-drug regimen in the setting of highly emetogenic antineoplastic therapy is limited to 6 adolescents who were enrolled in a predominantly adult study at a single centre.[21] Of these, 3 received aprepitant. The experience of the adolescents was similar to that of adults enrolled in the trial both in terms of AINV control and adverse effects. (personal communication, Pregent E. Merck Frosst Canada Ltd., March 14, 2007)

Aprepitant is a cytochrome P-450 isoenzyme 3A4 (CYP3A4) substrate and inhibitor and an inhibitor of CYP2C9/8 and CYP2C19. It therefore has the potential for increasing the dose intensity of other CYP3A4, CYP2C substrates given concurrently including several antineoplastic agents. (see Appendix H)

The pediatric dose of aprepitant and its safety in children, especially in younger children, is unknown. The extent of its impact on many antineoplastic agents that rely on the cytochrome P450 system for bioactivation or metabolism has not yet been determined. Health Question #4 specifically addresses the use of aprepitant in children.

5-HT3 Antagonist Plus Corticosteroid

Evaluations of the efficacy of a 5-HT3 antagonist plus dexamethasone in children receiving highly emetogenic chemotherapy are limited to 4 studies.[17, 21-23] Specific 5-HT3 antagonists evaluated were: ondansetron and

tropisetron. The emetogenicity of the antineoplastic agents administered in all 4 studies was able to be determined using the POGO classification guideline. A meta-analysis of these studies observed a complete AINV control rate of 50% (95% CI: 43%, 57%; Table 2 and Appendix G). Nausea assessment was included in the definition of complete control in 2 of these studies.[17, 23] The observed complete AINV control rate in these studies was similar (48%; 95% CI: 41%, 56%).

In the only pediatric randomized controlled trial, the use of both ondansetron plus dexamethasone resulted in a higher rate of complete vomiting control than did the use of ondansetron alone (61 vs. 23%; no p value provided).[22] The recommendation for the use of a 5-HT3 antagonist plus a corticosteroid for prevention of acute AINV in children receiving highly emetogenic antineoplastic therapy is also confirmed by the meta-analysis conducted by Phillips et al which concluded that the addition of a corticosteroid to a 5-HT3 antagonist resulted in a relative risk (RR) of complete control of vomiting of 2.03 (95% CI 1.35, 3.04).[24] The 2 randomized controlled trials included in this meta-analysis evaluated antiemetic response in a total of 45 children,[22, 25] most of whom received highly emetogenic antineoplastic therapy as per the POGO Guideline for the Classification of the Acute Emetogenic Potential of Antineoplastic Medication in Pediatric Oncology Patients.[1] The findings of one of these studies[25] are presented in the evidence summary for recommendation 2c since it included children receiving antineoplastic therapy of moderate to low emetogenicity.

5-HT3 Antagonist Alone

Studies evaluating the efficacy of ondansetron (5 studies), granisetron (2 studies), and tropisetron (8 studies) met the criteria for inclusion. The majority of studies are prospective, non-comparative, and observational in nature. Two randomized trials reported a complete AINV control rate of 56% and 23% in children receiving granisetron or ondansetron, respectively.[22, 26] The remaining 3 non-comparative studies reported complete vomiting control rates of 12, 70 and 71%.[27-29] Notably, the study reporting the lowest rate of complete control exclusively enrolled children receiving cisplatin.[27]

Meta-analysis of the 8 studies which evaluated the efficacy of 5-HT3 antagonists in the setting of highly emetogenic antineoplastic therapy determined using the POGO classification and that incorporated nausea control in their definition of complete AINV control observed a complete AINV control rate of 66% (95% CI: 60, 72).(Appendix G)

Other Antiemetic Agents

Metoclopramide has been evaluated in 2 randomized trials with disparate findings. Koseoglu et al administered metoclopramide plus diphenhydramine to 9 children receiving cisplatin-containing therapy and observed no vomiting and no nausea in 11%.[26] Using a less stringent definition of complete AINV control (no vomiting only), Marshall et al observed a higher rate of complete control (46%) in a larger group of children receiving a variety of antineoplastic agents.[30] Metoclopramide was ineffective in controlling AINV in an open study in 22 children.[31] The variability in the metoclopramide dose administered in each of these studies may account for some of variability in reported AINV control.

Chlorpromazine has been evaluated in a single randomized trial and reported to have only moderate success in providing complete vomiting control in children receiving highly emetogenic antineoplastic therapy.[30]
Given the limited information regarding the use of metoclopramide and chlorpromazine in the setting of highly emetogenic antineoplastic therapy and the limited ability of these agents to achieve complete AINV control, neither agent can be recommended for administration as first line AINV prophylaxis.

Summary:

Despite the lack of evidence to support the pediatric use of aprepitant as a standard of care, the panel members agreed that the desirable effects offered by its use in adolescents receiving highly emetogenic antineoplastic therapy were likely to outweigh its potential adverse effects. However, since the pediatric dose of aprepitant and its safety in younger children is unknown and the extent of its impact on many antineoplastic agents that rely on the cytochrome P450 system for bioactivation or metabolism is not yet determined, the use of aprepitant at the present should be limited to adolescents receiving antineoplastic therapy not known or suspected to interact with aprepitant. Health Question #4 provides further information regarding the use of aprepitant in children.

A cursory assessment of the meta-analysis of studies evaluating a 5-HT3 antagonist with and without dexamethasone in children may lead to the conclusion that administration of a 5-HT3 antagonist alone provides sufficient AINV control. However, the majority of studies included in this meta-analysis were of low quality. Conversely, the results of randomized controlled trials in children and the source guideline support the recommendation to administer both a 5-HT3 antagonist and dexamethasone to optimize AINV control in children receiving highly emetogenic antineoplastic therapy. This recommendation is further supported by Phillips et al.[24]

Research Gaps:

The body of literature upon which to base recommendations for the prevention of AINV in children who are about to receive antineoplastic therapy of high emetic risk is extremely limited. Existing studies are mainly non-randomized, comparative or non-comparative studies with small sample sizes and tend to be of very low quality. AINV control reported in children receiving highly emetogenic antineoplastic therapy and given a 5-HT3 antagonist plus a corticosteroid varies widely and at 38% is lower than that reported in adult cancer patients. Prospective evaluation of the efficacy of the antiemetic prophylaxis strategy recommended here is required.

Palonosetron, a second generation 5-HT-3 antagonist, provides improved AINV control in adults[32] receiving highly emetic antineoplastic agents compared to first generation agents such as ondansetron. Published pediatric experience with this agent is scant.[33-38] None met criteria for inclusion in the evidence summary and synthesis in the setting of highly emetogenic antineoplastic therapy. The possible benefits of palonosetron to children receiving highly emetogenic antineoplastic agents should be explored.

In addition, the lack of information required to administer aprepitant safely and confidently to pre-adolescent children is worrisome, particularly since the use of a 5-HT3 antagonist and dexamethasone in this setting is known to confer sub-optimal AINV protection in adults. More information must be sought regarding the effectiveness, safety, pharmacokinetics, and propensity to interact with antineoplastic agents via cytochrome P450 enzyme system (see health question #4) of aprepitant and fosaprepitant in children. Indeed, safe and effective antiemetic agents other than aprepitant and fosaprepitant need to be identified and specifically studied in children as adjuncts to a 5-HT3 antagonist and dexamethasone. Ginger,[39] metopimazine[40] and olanzapine[41] may have promise in this regard.

Health Question #2b: What Pharmacological Interventions Provide Optimal Control of Acute AINV in Children Receiving Antineoplastic Agents of Moderate Emetic Risk?

Recommendation	Strength of Recommendation & Level of Evidence*
We recommend that children receiving antineoplastic agents of moderate emetogenicity receive: *ondansetron or granisetron + dexamethasone*	Strong recommendation Moderate quality evidence

* See Appendix E for key to strength of recommendations and quality of evidence descriptions.

Changes from the Source Guideline[11, 13]:

- Palonosetron was not included in the recommendation since the pediatric evidence is not sufficiently robust to support its recommendation

Evidence Summary and Discussion:

A meta-analysis of all studies evaluating antiemetic efficacy in children receiving moderately emetogenic antineoplastic therapy observed a complete AINV control rate of 45% (95% CI: 31%, 58%); Table 3 and Appendix G). Interpretation of study results is hampered by the wide possible risk of AINV in this group of antineoplastic agents (30 to 90%) since the success of prophylaxis will likely be influenced by the proportion of patients receiving antineoplastic agents of emetogenicity at the extremes of the moderate range.

Note that although dolasetron is included in the evidence summary, its use for the prevention of AINV is not recommended due to its potential to cause serious and potentially fatal arrhythmia when given IV.[9] Dolasetron injection was withdrawn from the Canadian market on May 10, 2011. Similarly, tropisetron is included in the evidence summary but is not included in the recommendation since it is not marketed in Canada.

A summary of the evidence used to support this recommendation can be found in Appendix F. The results of meta-analysis of these data are summarized in Table 3. Forest plots are available in Appendix G.

Table 3: Summary of results of synthesis of studies evaluating AINV response in children receiving moderately emetogenic antineoplastic therapy

	Number of Studies or Study Arms	Number of Patients or Chemotherapy Blocks	Percentage with Complete Control (95% CI)
All Studies	28	1874	46 (33, 60)
Prophylaxis with 5-HT3 antagonist + corticosteroid: All Studies	1	428	79
Prophylaxis with 5-HT3 antagonist + corticosteroid: emetogenicity determined using POGO guideline AND definition of complete AINV control included nausea control	0	0	NA
Prophylaxis with 5-HT3 Antagonist Alone: All Studies	20	1274	54 (38, 69)
Prophylaxis with 5-HT3 antagonist alone: emetogenicity determined using POGO guideline AND definition of complete AINV control included nausea control	9	727	33 (17, 48)

CI: confidence interval

5-HT3 Antagonist Plus Corticosteroid

No studies which defined the emetogenicity of the antineoplastic agents administered using the POGO guideline or which defined complete AINV control as the control of both vomiting and nausea were identified. White et al evaluated the efficacy of dexamethasone plus either oral or IV ondansetron in a randomized controlled study in 428 children about to receive what the authors described as moderately/highly emetogenic antineoplastic therapy.[42] On the first day of the antineoplastic block, complete control of vomiting and retching was achieved in 78-81% of children whereas control of nausea was achieved in 70-73%. These results may underestimate the degree of AINV control that may be possible in children receiving moderately emetogenic antineoplastic agents since some received highly emetogenic therapy. Nevertheless, this large study confirms the recommendation of a 5-HT3 antagonist plus dexamethasone for patients about to receive moderately emetogenic antineoplastic therapy made by the source guideline.

5-HT3 Antagonist Alone

Single agent prophylaxis with a 5-HT3 antagonist is the most studied option in the setting of moderately emetogenic antineoplastic therapy. AINV control rates observed in children receiving moderately emetogenic antineoplastic therapy as defined by the investigators and given a 5-HT3 antagonist for prophylaxis tended to be higher than reported in studies where the antineoplastic therapy administered was known to be of moderate emetogenicity as defined by POGO.

Overall, synthesis of the data from studies which evaluated the performance of 5-HT3 antagonists alone in the setting of moderately emetogenic antineoplastic therapy observed a complete AINV control rate of 54% (95%

CI: 38%, 69%). One prospective, observational study evaluated AINV control after administration of a single dose of palonosetron to children receiving methotrexate 5g/m^2. When the results of this study were excluded from the evidence synthesis of single agent 5-HT3 antagonist prophylaxis, a complete AINV control rate of 52% (95% CI: 37%, 66%) was observed. Of the 7 studies (9 study arms) which evaluated AINV control in children receiving moderately emetogenic antineoplastic therapy as defined by POGO and which included nausea control when defining complete AINV control, 2 were randomized trials.[43, 44] Synthesis of the findings of the studies, all of which evaluated first generation 5-HT3 antagonists, observed a complete AINV control rate of 33% (95% CI: 17%, 48%).(Appendix G)

Summary:

The findings of a large pediatric trial of dexamethasone plus either intravenous or oral ondansetron supports the recommendation of the source guideline that a 5HT3 antagonist plus dexamethasone be given to patients receiving moderately emetogenic antineoplastic therapy. Based on the meta-analysis, administration of a 5HT3 antagonist alone in this setting is much less likely to completely control AINV.

Research Gaps:

Ideally, the findings of White et al[42] that support the recommendation that a 5HT3 antagonist plus dexamethasone be given to prevent AINV due to moderately emetogenic therapyshould be substantiated by other investigators.. The efficacy of this regimen in children receiving antineoplastic agents known to be moderate emetogens in rigorously designed prospective studies is needed to determine whether antiemetic prophylaxis can be less aggressive.

The role of novel antiemetic agents such as palonosetron in preventing AINV in children receiving moderately emetogenic antineoplastic therapy merits further investigation.[33, 34, 36, 37] Recent published experience in adults receiving moderately emetogenic antineoplastic therapy indicates that aprepitant, when added to ondansetron and dexamethasone, provides improved AINV control compared with ondansetron, dexamethasone plus placebo.[45, 46] This regimen requires evaluation in children.

Health Question #2c: What Pharmacological Interventions Provide Optimal Control of Acute AINV in Children Receiving Antineoplastic Agents of Low Emetic Risk?

Recommendation	Strength of Recommendation & Level of Evidence*
We recommend that children receiving antineoplastic agents of low emetic risk receive: *ondansetron or granisetron*	Strong recommendation Moderate quality evidence

* See Appendix E for key to strength of recommendations and quality of evidence descriptions.

Changes from the Source Guideline[11, 13]:

- inclusion of 5-HT3 antagonists as an option for prophylaxis.
- omission of dexamethasone as an option for prophylaxis

Evidence Summary and Discussion:

There are no pediatric studies which evaluated the efficacy of the antiemetic strategy recommended in the source guideline (i.e. dexamethasone alone) for patients about to receive antineoplastic agents of low emetic risk and which met our inclusion criteria. In the complete absence of supporting evidence for its application to pediatrics, the panel did not adopt the source guideline's recommendation. A meta-analysis of all studies that evaluated an antiemetic intervention in children receiving antineoplastic agents of low emetic risk observed an overall complete control rate of 75% (95% CI: 66%, 85%). A summary of the evidence used to support this recommendation can be found in Appendix F. The results of meta-analysis of these data are summarized in Table 4. Forest plots are available in Appendix G.

Table 4 Summary of results of synthesis of studies evaluating AINV response in children receiving antineoplastic therapy of low emetogenicity

	Number of Studies or Study Arms	Number of Patients or Chemotherapy Blocks	Percentage with Complete Control (95% CI)
All Studies	9	162	75 (66, 85)
Prophylaxis with 5-HT3 Antagonist Alone: All Studies	7	119	74 (62, 87)

CI: confidence interval

5-HT3 Antagonist Plus Corticosteroid

Pediatric experience with the use of a 5-HT3 antagonist plus corticosteroid as prophylaxis for antineoplastic therapy of low emetogenicity is limited to a single randomized cross-over trial.[25] The results of this trial are presented in the low emetogenicity category but the antineoplastic therapy administered actually ranged from low to high. Thus, the reported complete control rates likely underestimate the performance of this antiemetic strategy in the setting of antineoplastic agents of low emetic risk. Furthermore, the definition of complete control used in this study is unique in that it permits up to 2 emetic episodes. The number of children who did not vomit during the acute phase is not reported. However, 70% of children were free from vomiting in the first 6 hours after antineoplastic administration.

The very sparse and difficult to interpret information regarding the use of a 5-HT3 antagonist plus a corticosteroid in children receiving antineoplastic therapy of low emetogenic risk makes it difficult to appreciate the actual benefit that dual agent prophylaxis would provide.

5-HT3 Antagonist Alone

Synthesis of the studies which evaluated the AINV control provided by 5-HT3 antagonists alone observed a rate of complete AINV control of 74% (95% CI: 62%, 87%). (Appendix G) All identified studies evaluated the use of 5-HT3 antagonists alone in the setting of antineoplastic agents of low emetogenicity as defined by the POGO guideline and included nausea control in their definition of complete AINV control. Three studies were

randomized trials.[25, 26, 47] Reported complete control rates ranged from 50% to 91%. The concerns previously raised regarding the interpretation of the results of Hirota et al[25] also apply here.

Other antiemetic agents

A single randomized trial evaluated the AINV control provided by metoclopramide plus diphenhydramine over 23 antineoplastic blocks of low to high emetogenicity.[26] The reported rate of complete nausea and vomiting control was 74% and compares favourably with the rates reported for 5-HT3 antagonists alone. Due to the limited information regarding the use of metoclopramide in this setting, it was not recommended for first line AINV prophylaxis.

Summary:

The recommendation of the source guideline regarding the use of dexamethasone for the prevention of AINV in patients receiving antineoplastic agents of low emetic potential was not adopted since there is no published pediatric experience to support it. The panel was reluctant to recommend its use without specific pediatric evidence due to its adverse effect profile. However, it seems that the use of a 5-HT3 antagonist alone in this setting conveys reasonable AINV prophylaxis as it compares favourably with the rates of control achieved in adults. Implementation of this recommendation may lead to administration of ondansetron or granisetron to many children who may not require them to experience complete AINV control. However, since AINV is a known risk factor for uncontrolled AINV with future antineoplastic therapy, the panel believed that the cost/benefit of giving 5-HT3 antagonists, at least with the first course of antineoplastic therapy of low emetogenicity, was acceptable. If AINV is controlled, AINV prevention strategies can be re-evaluated with subsequent antineoplastic blocks of low emetogenicity.

Research Gaps:

Corroboration of the adult experience with the use of dexamethasone for the prevention of AINV due to antineoplastic therapy of low emetic risk is necessary to determine the risk:benefit of its use in children. Ideally, such investigations would include assessments of the possible short and long term adverse effects of corticosteroid use such as mood changes, sleep disturbance, fatigue and osteopenia. However, given the rate of AINV control observed after administration of a 5HT-antagonist and the general desire to limit corticosteroid use in children, it is unlikely that these studies will be undertaken.

Health Question #2d: What Pharmacological Interventions Provide Optimal Control of Acute AINV in Children Receiving Antineoplastic Agents of Minimal Emetic Risk?

Recommendation	Strength of Recommendation & Level of Evidence*
We recommend that children receiving antineoplastic agents of low emetic risk receive: *no routine prophylaxis*	Strong recommendation Very low quality evidence

* See Appendix E for key to strength of recommendations and quality of evidence descriptions.

Changes from the Source Guidelines[11, 13]:

- None.

Evidence Summary and Discussion:

No pediatric studies which evaluate AINV control in children receiving antineoplastic agents of minimal emetic risk without antiemetic prophylaxis and which met our exclusion criteria were identified. The recommendation of the source guidelines[11, 13] to give no routine antiemetic prophylaxis was therefore adopted. A summary of the evidence used to support this recommendation can be found in Appendix F.

5-HT3 Antagonist Alone

A single prospective observational study evaluated the complete AINV control rate in 16 children receiving antineoplastic agents of minimal to high emetogenicity with tropisetron prophylaxis.[23] It is not possible to discern the complete control rate in children receiving only antineoplastic agents of minimal emetic risk. This information is not sufficiently robust to alter the recommendation of the source guideline.

Research Gaps:

More information is required regarding the AINV experienced by children who receive antineoplastic agents of minimal emetic risk and who receive no antiemetic prophylaxis.

Health Question #3: What Adjunctive, Non-Pharmacological Interventions Provide Control Of Acute AINV in Children Receiving Antineoplastic Agents of Any Emetic Risk?

Recommendation	Strength of Recommendation & Level of Evidence*
We suggest that acupuncture, acupressure, guided imagery, music therapy, progressive muscle relaxation and psycho-educational support and information may be effective in children receiving antineoplastic agents. Virtual reality may convey benefit. We suggest that the following dietary interventions may be effective: ▪ eat smaller, more frequent meals; ▪ reduce food aromas and other stimuli with strong odours; ▪ avoid foods that are spicy, fatty or highly salty; ▪ take antiemetics prior to meals so that the effect is present during and after meals; and ▪ measures and foods (e.g. "comfort foods") that helped to minimize nausea in the past	Weak recommendation Very low quality evidence

* See Appendix E for key to strength of recommendations and quality of evidence descriptions.

The source guideline[12] assigned a level of "likely to be effective" to non-dietary measures other than virtual reality; "benefits balanced with harms" to virtual reality, and "expert opinion" to dietary measures.

Changes from the Source Guideline[12]:

- None

Evidence Summary and Discussion:

No pediatric evidence to support the source guideline's recommendation that met inclusion criteria was identified.

In the opinion of the panel, the measures included in the source guideline's recommendation are unlikely to result in undesirable effects or adversely affect quality of life. The recommendations of the source guideline were therefore adopted by the guideline panel despite the lack of pediatric supporting information.

Research Gaps:

Rigorous evaluations of the efficacy of complementary interventions such as acupuncture[48], acupressure[49], guided imagery, music therapy, progressive muscle relaxation, psycho-educational support and virtual reality are required to understand their role in AINV control. Although little is known regarding the role of food composition and presentation on AINV control, it is unlikely that trials will be undertaken to determine their contribution. Careful consideration of the control arms of these investigations will be required.

Health Question #4: What is the Role of Aprepitant in Children Receiving Antineoplastic Therapy?

Recommendation	Strength of Recommendation & Level of Evidence*
We recommend that the use of aprepitant be restricted to children 12 years of age and older who are about to receive highly emetogenic antineoplastic therapy which is not known or suspected to interact with aprepitant. There is no evidence to support the safe and effective use of aprepitant in younger children.	Strong recommendation Very low quality evidence

* See Appendix E for key to strength of recommendations and quality of evidence descriptions.

Changes from the Source Guideline[11, 13]:

- Recommendation of aprepitant to children who meet specific criteria

Evidence Summary and Discussion:

A summary of the evidence used to support this recommendation can be found in Appendix F. The source guideline[11, 13] recommends the use of aprepitant for adults receiving highly emetogenic antineoplastic agents and suggests consideration of its use in adults receiving moderately emetogenic antineoplastic agents. However, the source guideline does not recommend the administration of aprepitant to children receiving antineoplastic therapy.

Efficacy

The existing publications that describe the administration of aprepitant to children receiving antineoplastic therapy are presented in Appendix F, Table F.5. There are no published reports of the use of fosaprepitant, the IV pro-drug of aprepitant, or other neurokinin-1 receptor antagonists in children. The published pediatric experience with aprepitant is exceedingly sparse and of poor quality. A single prospective trial has been published to date but the primary aim of this study was to describe the pharmacokinetics of aprepitant. Any assessment of the efficacy of aprepitant in this study is hampered by the lack of information regarding the emetogenicity of the antineoplastic therapy administered and by the omission of nausea in the outcome assessment.

Given that the pediatric aprepitant dose has not been determined (refer to Health Question #6) and that the rate of complete AINV control has not been described in children receiving highly emetogenic antineoplastic therapy, the potential contribution of aprepitant to AINV control in children is as yet unknown.

Safety

The most common adverse effects attributed to aprepitant in adults are fatigue and hiccups.[50] Gore et al observed a higher incidence of febrile neutropenia in children receiving aprepitant compared to the control arm (25% vs 11.1%). Choi et al describe hyperglycemia in 2 of 32 children included in a retrospective review.[51]

The available published pediatric descriptions of the use of aprepitant in children are insufficient to judge its safety in this age group.

Pediatric experience with aprepitant remains so limited that it is not possible to administer aprepitant with the confidence that it is both safe and effective; this is most especially relevant to its use in infants and young children.

Interactions with Antineoplastic Agents

As a cytochrome P-450 isoenzyme 3A4 (CYP3A4) substrate and inhibitor and an inhibitor of CYP2C9/8 and CYP2C19, aprepitant has the potential for increasing the dose intensity of other CYP3A4 substrates given concurrently. For example, it is recommended that half the usual dose of dexamethasone (a CYP3A4 substrate) be given in conjunction with aprepitant. Aprepitant may also induce CYP3A4 – an effect which will manifest once aprepitant administration has ended.[52] Other modulators of CYP3A4 function may furthermore alter the dose intensity of aprepitant. Many agents commonly used in pediatric oncology have the potential to interact with aprepitant including: azole antifungal agents, and lansoprazole.

However, potential interactions between aprepitant and antineoplastic agents are of the utmost concern due to their potential impact on toxicity and long-term outcomes. Of the antineoplastic agents classified as highly emetogenic when given alone or with other antineoplastic agents, the following rely on CYP3A4 for their metabolism or bioactivation: cyclophosphamide,[53] cytarabine, daunorubicin, doxorubicin, etoposide,[54] ifosfamide, teniposide,[54] and thiotepa.[53] Thus, it is possible that the concurrent use of aprepitant with these agents may lead to increased dose-related toxicity or, in some cases, decreased therapeutic effect. That being said, predicted theoretical interactions between aprepitant and antineoplastic agents have not always been observed when specifically evaluated. For example, the dose intensity of neither docetaxel nor vinorelbine, both of which are CYP3A4 substrates, is significantly influenced by aprepitant co-administration.[55, 56]

De Jonge et al evaluated the effect of aprepitant on thiotepa and cyclophosphamide pharmacokinetic disposition in 8 adults.[53] Mean clearance of thiotepa to its active metabolite, tepa, was 33% lower in the presence of aprepitant, resulting in a 15% higher total thiotepa exposure and a 20% lower tepa exposure, on average. Similarly, aprepitant was found to inhibit the autoinduction of cyclophosphamide to an active metabolite, 4-hydroxycyclophosphamide, by CYP3A4. A mean increase of total cyclophosphamide exposure of 7% and a mean decrease of 5% in the exposure of 4-hydroxycyclophosphamide was observed. Interpretation of these results has been controversial with some authors considering the interaction between aprepitant and either thiotepa or cyclophosphamide to be clinically insignificant[52, 57] and others being more wary.[58-60]

The active and toxic metabolites of ifosfamide are produced via CYP3A4. Cases of ifosfamide-induced encephalopathy have been associated with aprepitant co-administration.[61-64] In one of these cases, concentrations of neurotoxic metabolites (2-dechloroethyl-ifosfamide and 3-dechloroethyl-ifosfamide) and ifosfamide clearance were observed to be higher in the presence of aprepitant.[64]

In a case series reporting the use of aprepitant in 33 children, 2 cases of peripheral neuropathy were attributed to an interaction between aprepitant and the antineoplastic agents.[65] No details regarding the antineoplastic agents given or the nature of the peripheral neuropathy were provided.

Potential interactions between aprepitant and other antineoplastic agents which rely on CYP3A4 (e.g. cytarabine, doxorubicin, daunorubicin, etoposide and teniposide), CYP2C9 (e.g. bortezomib, cyclophosphamide, ifosfamide, imatinib, paclitaxel, tamoxifen and tretinoin) and CYP2C19 (e.g. bortezomib, cyclophosphamide, ifosfamide, imatinib) have not yet been evaluated.

Aprepitant has the potential to both increase and decrease the dose intensity of certain antineoplastic agents. The impact of most potential aprepitant- antineoplastic agent interactions will not be realized until weeks or months after aprepitant administration. A prudent approach would therefore be to avoid the concurrent administration of aprepitant and those antineoplastic agents known or suspected to interact with aprepitant. A list of antineoplastic agents known or suspected to interact with aprepitant and fosaprepitant can be found in Appendix H.

Summary

Aprepitant appears to be both a safe and effective antiemetic in adult cancer patients. It attractive safety record and ability to substantially improve AINV control in both the acute and delayed phases in adults receiving highly emetogenic antineoplastic therapy led to its swift adoption as a standard of care in adult oncology. Pediatric data are limited. To balance the desire to better control AINV against the large gaps in our knowledge about how best to dose and administer aprepitant to children, the panel recommends that the routine use of aprepitant be reserved for patients in the age group for which there is information to support a dosing guideline (12 years of age and older) and who are about to receive highly emetogenic antineoplastic therapy whose dose intensity will not be altered by concurrent administration with aprepitant. However, the panel acknowledges that there may be cases when all other antiemetics have failed to achieve the AINV control desired where aprepitant may be offered to younger children. In these cases, the panel recommends that the lack of data to support the choice of aprepitant dose, the extent of therapeutic benefit and safety in children be disclosed to the patient and their guardians.

Research Gaps:

An aprepitant formulation of known stability and bioavailability should be developed for use in children who cannot swallow oral solid dosage forms. Dose-finding studies are required in children less than 12 years of age and additional information to corroborate the pharmacokinetic disposition of aprepitant in older children would be helpful. Dose-finding studies of fosaprepitant are required in all pediatric age groups. The effectiveness of a single dose aprepitant/fosaprepitant regimen or regimens which extend beyond 3 days needs to be evaluated in children receiving single day or multiple day antineoplastic therapy.

Information regarding the contribution of aprepitant and fosaprepitant to AINV control in children is required as is information regarding its safety. Information that describes the impact of aprepitant/fosaprepitant on the dose intensity of antineoplastic therapy metabolized via CYP3A4, CYP2C9/8 or CYP2C19 and which are commonly used in pediatric cancer is needed. Doxorubicin, daunorubicin, etoposide and cyclophosphamide are priorities in this regard.

Similar information is required for other neurokinin-1 receptor antagonists currently in development.

Health Question #5: What Pharmacological Interventions Provide Optimal Control of Acute AINV in Children Receiving Highly or Moderately Emetogenic Antineoplastic Agents in whom Corticosteroids are Contra-Indicated?

Recommendation	Strength of Recommendation & Level of Evidence*
We suggest that children receiving highly emetogenic antineoplastic therapy who cannot receive corticosteroids receive: *ondansetron or granisetron* + *chlorpromazine* *or* *nabilone*	Weak recommendation Low quality evidence
We suggest that children receiving moderately emetogenic antineoplastic therapy who cannot receive corticosteroids receive: *ondansetron or granisetron* + *chlorpromazine* *or* *metoclopramide* *or* *nabilone*	Weak recommendation Low quality evidence

* See Appendix E for key to strength of recommendations and quality of evidence descriptions.

Changes from the Source Guideline[11, 13]:

- Not applicable

Evidence Summary and Discussion:

The source guidelines[11, 12] did not address the question of AINV control in patients who cannot receive corticosteroids. Several contemporary pediatric treatment protocols, brain tumor and acute myelogenous leukemia (AML) protocols for example, discourage or prohibit corticosteroids as antiemetic agents. In brain tumor patients, it is felt that corticosteroids may prevent adequate distribution of antineoplastic agents into the central nervous system while corticosteroids are a risk factor for fungal infection in AML patients. Other treatment protocols prohibit the use of corticosteroids as antiemetic agents since corticosteroids are already a component of the anti-tumor treatment regimen. Still others may not allow the use of corticosteroids simply so that both treatment groups remain uniform and one is not 'contaminated' by the use of corticosteroids for AINV

control. Occasionally, families or patients refuse corticosteroid prophylaxis due to adverse effects such as aggressive behaviour or moodiness.

It is clear that AINV prophylaxis with a 5-HT3 antagonist alone leads to poor AINV control in patients receiving moderately and highly emetogenic antineoplastic therapy (see recommendations 2a and 2b). It is also clear that published experience with antiemetics other than 5-HT3 antagonists and dexamethasone indicate little activity. Synthesis of the 3 studies which evaluated alternative antiemetic agents (chlorpromazine, metoclopramide) observed a complete AINV control rate of 9% (95% CI: -3, 20) (Appendix G)

Ideally, every patient receiving emetogenic antineoplastic therapy will be offered and will receive the best known antiemetic prophylaxis from the outset. The anti-emetic regimen of an individual patient should consider the impact of sub-optimal AINV control on the patient's well-being, risk of corticosteroids in the patient's particular context, whether clinical trial enrolment would be jeopardized by administration of corticosteroids and how discontinuation from a clinical trial would impact the patient. A similar issue, that of adult oncology patients receiving less than the standard of care even in antiemetic trials, has been discussed elsewhere.[66,67]

Studies which evaluated individual antiemetic agents or combination of agents which did not include a corticosteroid or 5-HT3 antagonist agent, presented the pediatric data separately, where an explicit or implicit definition of complete AINV control was provided and the complete acute AINV response rate was reported as a proportion were identified. Information regarding studies of the contribution of delta-9-tetrahydrocannabinol to AINV control was not included in the evidence summary since this pharmaceutical is not readily available in Canada. Experience with delta-8-tetrahydrocannabinol[68] or delta-9-tetrahydrocannabinol[69] was not considered to be applicable to the evidence summary for nabilone or dronabinol.

A summary of the evidence used to support this recommendation can be found in Appendix F. The results of this data synthesis are summarized in Table 5. Forest plots are available in Appendix G.

Table 5: Summary of results of synthesis of studies evaluating AINV response in children receiving antiemetic agents other than corticosteroids

	Number of Studies or Study arms	Number of Patients or Antineoplastic Blocks	Percentage with complete control (95% CI)
Highly emetogenic antineoplastic therapy: All studies	3	57	9 (-3, 20)
Moderately emetogenic antineoplastic therapy: All studies	3	70	11 (4, 19)

CI: confidence interval

Chlorpromazine

Two randomized controlled trials which met the criteria for inclusion in the evidence summary were identified. The first observed a 19% complete AINV control rate in children receiving highly emetogenic antineoplastic therapy with chlorpromazine prophylaxis.[30] Sedation was observed in 9 of the 26 children enrolled; no patient experienced dystonia. Mehta et al compared the safety and efficacy of methylprednisolone and chlorpromazine in 20 children.[70] Nausea, duration and number of vomiting episodes, sedation and adverse events were recorded. No difference was detected in the antiemetic efficacy between the study arms (no p value provided) though the study was not powered to be able to detect a difference if one did exist. Seven of 10 patients who received chlorpromazine experienced mild to marked sedation to the extent that they required assistance to leave the clinic.

Two other studies evaluated the activity of chlorpromazine in preventing AINV in children but did not meet the criteria for inclusion in the evidence summary.[71, 72] However, their report of chlorpromazine-associated toxicity is of interest. Of 73 blocks of antineoplastic therapy given to 25 children aged 1.7 to 17.5 years) where chlorpromazine (31 courses) or chlorpromazine plus lorazepam (42 blocks) were given in a randomized controlled trial, dystonia and akathisia were observed in 8 (11%) and 23 blocks (32%), respectively.[71] No significant hypotension was observed. Increased nausea and vomiting were reported in a cross-over study of 23 children receiving phenothiazines or no antiemetic agents for AINV prophylaxis.[72] Three children received chlorpromazine. Parents and children evaluated AINV 3 to 5 days after administration of antineoplastic therapy using a Likert scale. The number of emetic episodes was not recorded and nausea severity was not assessed using a validated instrument.

Published experience with chlorpromazine for AINV prophylaxis is slim yet general pediatric experience with it is extensive. The antiemetic activity of chlorpromazine has not been evaluated in combination with a 5-HT3 antagonist. Given the lack of evidence-based alternatives, the use of chlorpromazine for AINV prophylaxis in combination with either ondansetron or granisetron for children who truly cannot or will not receive dexamethasone may be considered. Its use strictly in the in-patient setting seems prudent based on its sedating and hypotensive properties.

Dronabinol and Nabilone

A meta-analysis of experience with cannabinoids for the prevention of AINV concluded that cannabinoids were slightly better at controlling AIV (RR: 1.28, 95% CI: 1.08 to 1.51) and AIN (RR: 1.38; 95% CI: 1.18 to 1.62) than antiemetics such as prochlorperazine, metoclopramide, domperidone, haloperidol.[73] Patients also preferred cannabinoids over the other antiemetic agents studied (RR: 2.39; 95% CI: 2.05 to 2.78). However, adverse effects were more commonly associated with cannabinoids administration. Two of the studies of nabilone and 1 of the studies of dronabinol included in this meta-analysis included children. The former studies met the criteria for inclusion in the evidence summary for this guideline and are summarized below. No study of dronabinol in preventing AINV in children, including the study included in the above-mentioned meta-analysis, met the criteria for inclusion in the evidence summary.

A single randomized cross-over trial of the antiemetic activity of nabilone was identified that met the criteria for inclusion in the evidence summary. This trial compared the antiemetic activities of nabilone and prochlorperazine.[74] A higher proportion of children experienced an improvement in emesis (21 vs 9 of 30; p=0.003) during the nabilone phase of the study and more patients preferred nabilone to prochlorperazine (20 vs 5 of 30; p=0.015). The most common adverse effects experienced by children in the nabilone phase were dizziness and drowsiness; dose reduction improved these symptoms without reducing the therapeutic benefit.

Dalzell et al conducted a randomized controlled crossover trial of nabilone versus domperidone in 23 children aged 0.8 to 17 years old receiving antineoplastic therapy.[75] This study did not meet the criteria for inclusion in the evidence summary. However, the toxicities described in this study are of interest. Drowsiness (55%) and dizziness (36%) were the most common adverse effects attributed to nabilone. One patient receiving nabilone withdrew from the study due to a disturbing hallucination.

Despite the lack of robust supporting pediatric evidence, the use of a 5-HT3 antagonist in combination with nabilone is recommended as a consideration in patients who cannot or will not receive dexamethasone. Nabilone is available only as an oral capsule; thus its utility may be restricted to older children.

Metoclopramide

There are 2 randomized trials that describe the use of metoclopramide to control AINV in children and which met the inclusion criteria described above.[26, 31] In the setting of highly emetogenic antineoplastic therapy, the ability of metoclopramide to control AINV is marginal. Reported rates of complete AINV control were 0 and 11%. Metoclopramide is therefore not recommended for use in the setting of highly emetogenic antineoplastic therapy. However, a substantially higher rate of complete AINV control (74%) was reported by Koseoglu in children receiving antineoplastic therapy of low to moderate emetogenic potential.[26]

Metoclopramide may have a role in preventing AINV in children receiving moderately emetogenic antineoplastic therapy for whom dexamethasone is not an option.

Prochlorperazine

One randomized controlled trial evaluating the efficacy of prochlorperazine was identified.[74] This study compared nabilone and prochlorperazine and has been described above. Drowsiness was the most common adverse effect observed in the prochlorperazine arm. As stated previously, families and children preferred nabilone to prochlorperazine.

Nahata evaluated the safety of prochlorperazine in 11 children aged 0.9 to 9 years who were receiving antineoplastic therapy.[76] No sedation, dystonia, akathisia or restlessness was observed.

Prochlorperazine is not recommended for consideration as an alternative antiemetic agent to dexamethasone for children.

Summary:

Withholding corticosteroids for the purpose of antiemetic prophylaxis in patients about to receive highly or moderately emetogenic antineoplastic therapy should not be undertaken lightly. Administration of highly emetogenic antineoplastic therapy with only a 5-HT3 antagonist as antiemetic prophylaxis is likely to lead to AINV in at least half of children. A meta-analysis of the results of studies that evaluated antiemetic agents other than 5-HT3 antagonists and corticosteroids observed a complete AINV control rate of 21% (95% CI: -3%, 46%) and 11% (95% CI: 4%, 19%) in children receiving highly and moderately emetogenic antineoplastic agents, respectively. The performance of these antiemetic agents when given in combination with a 5-HT3 antagonist is unknown. Given the scarcity of evidence-based options, the panel believed it to be reasonable to recommend that nabilone, chlorpromazine or metoclopramide (moderately emetogenic antineoplastic therapy) be administered together with ondansetron or granisetron to children in whom corticosteroids are contra-indicated.

Research Gaps:

There are exceedingly few evidence-based choices when selecting antiemetic agents for the patient for whom the use of corticosteroids as antiemetics is contra-indicated or refused. Until an oral liquid dosage form for nabilone is developed, nabilone will not be a feasible option for young children. The benefits of the recommended agents in combination of a 5-HT3 antagonist should be prospectively verified. In addition, the impact of giving other antiemetic agents and interventions such as metopimazine,[40] acupressure,[49] aprepitant, fosaprepitant, olanzapine,[77] diphenhydramine-lorazepam-dexamethasone (BAD)[78] or ginger[39, 79] together with 5-HT3 antagonists or palonosetron,[36] alone merit rigorous evaluation in this setting.

Health Question #6: What Doses of Antiemetic Agents Are Known to be Effective in Children Receiving Antineoplastic Agents?

Antiemetic agents included in this recommendation are limited to those which appear in recommendations 2, 4 and 5 of this guideline. Studies evaluating each antiemetic agent alone or with other antiemetic agents which included children, presented the pediatric data separately, where an explicit or implicit definition of complete acute AINV control was provided and the complete acute AINV control rate was reported as a proportion were identified. Studies which describe pediatric experience with antiemetic agents but which do not indicate the emetogenicity of the administered antineoplastic therapy are included in the summary of included studies for the sake of completeness.

With the exception of aprepitant and dexamethasone for moderately emetogenic antineoplastic therapy, the antiemetic agents recommended in this guideline are dosed according to actual body weight or body surface area, without a maximum dose. It is not possible to identify a pediatric population for whom the use of the adult doses is appropriate nor is there specific pediatric evidence to support the recommendation of maximum doses; thus, the panel has not recommended maximum doses for these agents. However, the panel recognizes that clinicians may have reservations about using a body weight- or body surface area-based dosing strategy when prescribing antiemetic agents for adolescents. Therefore, Appendix I presents the doses

of antiemetic agents recommended in the source guideline for adults to guide clinicians as they make dosing decisions for individual patients.

Aprepitant Dose Recommendation:

Recommendation	Strength of Recommendation & Level of Evidence*
We recommend the following **aprepitant** dose for children 12 years of age and older: *Day 1: 125mg PO x 1; Days 2 and 3: 80mg PO once daily*	Strong recommendation Moderate quality evidence

* See Appendix E for key to strength of recommendations and quality of evidence descriptions.

Evidence Summary and Discussion:

A summary of the evidence used to support this recommendation can be found in Appendix F. In all but two publications, children were given the recommended adult dose of aprepitant; that is, 125mg on day 1 followed by 80mg on day 2 and 3.[21, 80-83] Choi et al gave the recommended adult dose to children whose weight was greater than 20kg but gave a lower dose (80mg/day for 3 days) to children who weighed less than 20kg.[51] Dexamethasone was given to 20 of the 32 patients included in this descriptive report at a dose of 0.15mg/kg (maximum 20mg) as a single IV dose. The extent of AINV control afforded by each dosing scheme was not provided. Coppola et al briefly reviewed the use of aprepitant in 33 children less than 18 years old.[65] Children weighing less than 40kg were most often given aprepitant 80mg on Day 1 and then 40mg per day on Days 2 and 3. Details regarding the antineoplastic therapy given and the other antiemetic agents given concurrently are not provided.

Children receiving antineoplastic blocks that are shorter than 3 days will technically receive aprepitant during the delayed phase of AINV. The focus of this guideline is on the control of AINV during the acute phase. Nevertheless, aprepitant is recommended for administration for 3 days since the prescription for aprepitant is initiated on the first day of the acute phase.

The pharmacokinetic disposition of aprepitant in adolescents has been shown to be similar to that observed in adults.[80] It is therefore reasonable to administer the adult dose to adolescents. However, the pharmacokinetic disposition of aprepitant in infants and pre-adolescent children is unknown and no dose-finding studies have been conducted in this age group.

Research Gaps:

Rigorous pediatric dose-finding studies are required to determine the optimal aprepitant dose for use in children. Information regarding dosing of aprepitant in obese children is lacking.

Chlorpromazine Dose Recommendation:

Recommendation	Strength of Recommendation & Level of Evidence*
We recommend the following **chlorpromazine** dose: *0.5mg/kg/dose IV q6h*	Strong recommendation Low quality evidence

* See Appendix E for key to strength of recommendations and quality of evidence descriptions.

Evidence Summary and Discussion:

A summary of the evidence used to support this recommendation can be found in Appendix F. The use of chlorpromazine for AINV control in children has been described in 6 studies, 5 of which were randomized blinded trials.[30, 44, 70-72, 84] These studies administered chlorpromazine in doses ranging from 0.3 to 1mg/kg every 3 to 6 hours; Hahlen et al initiated their investigation using a dose of 0.5mg/kg and later reduced it to 0.3mg/kg due to excessive sedation.[44] Since higher doses were most often evaluated, the guideline development panel recommends a starting chlorpromazine dose of 0.5mg/kg/dose IV given every 6 hours with consideration of a higher dose if AINV is not controlled and sedation is not a concern. The findings of Zeltzer et al that children receiving phenothiazines (either chlorpromazine (3 children) or prochlorperazine (20 children)) had increased nausea and vomiting may be due to the doses given or the retrospective nature of the analysis.[72]

Research Gaps:

Experience with chlorpromazine use for AINV control in the setting of a modern antiemetic backbone (e.g. in addition to ondansetron or granisetron with/without dexamethasone) would allow a more full appreciation of its contribution and of its optimal dosage. Information regarding dosing of chlorpromazine in obese children is lacking.

Dexamethasone Dose Recommendation:

Recommendation	Strength of Recommendation & Level of Evidence*
We suggest the following **dexamethasone** for children receiving highly emetogenic antineoplastic therapy: *6 mg/m^2/dose IV/PO q6h* If given concurrently with aprepitant, reduce dexamethasone dose by half.	Weak recommendation Low quality evidence
We recommend the following **dexamethasone** for children receiving moderately emetogenic antineoplastic therapy: *≤ 0.6m^2: 2mg/dose IV/PO q12h* *> 0.6m^2: 4mg/dose IV/PO q12h* If given concurrently with aprepitant, reduce dexamethasone dose by half	Strong recommendation Low quality evidence

* See Appendix E for key to strength of recommendations and quality of evidence descriptions.

Evidence Summary and Discussion:

A summary of the primary evidence used to support this recommendation can be found in Appendix F. Dexamethasone doses administered to children receiving antineoplastic therapy varied widely across studies, ranging from 5mg/m^2/day[17] to 24mg/m^2/day.[22] Most studies did not apply a maximum dexamethasone dose regardless of body size. No pediatric dexamethasone dose finding studies were identified.

It is important to note that pediatric dexamethasone dosing strategies remain empiric. The pharmacokinetic disposition of a drug would normally be considered to be a reasonable guide for dosing frequency. Yet, there are good reasons to believe that this approach would be misleading in the case of dexamethasone. For instance, the biologic half-lives of the corticosteroids differ markedly from their plasma elimination half-lives. In adults, the biologic half-life of dexamethasone ranges from 36 to 54 hours, while its plasma elimination half-life is only 2 to 4 hours.[85] The elimination half-life of dexamethasone in older children is similar. A mean elimination half-life of 1.27 hours was reported in 100 children with cancer aged 5 to 18 years[86] and 4.34 hours (range: 2.33 to 9.54 hours) in 12 children without cancer aged 0.33 to 16 years.[87]

The lack of an association between dexamethasone biological half-life and pharmacokinetic disposition is further highlighted by the marked contrast between maximal plasma dexamethasone concentrations and cortisol suppression: the latter peaks approximately 8 to 10 hours after the maximal plasma dexamethasone concentration is reached, with a duration of effect that is dose-dependent.[88] The best predictors of corticosteroid biologic activity are in fact binding to transport proteins and other cellular receptors. Whether and how such biologic activity can be extrapolated to the antiemetic arena remains unclear. This is mainly due to a very incomplete understanding of the actual mechanism of action of the antiemetic activity of corticosteroids as well as the lack of an adequate surrogate marker for this type of drug activity. However, while dexamethasone antiemetic effects do not appear to be related to prostanoid synthesis or to a membrane stabilizing/blood brain barrier influence upon chemotherapy,[89] there may be some influence upon other inflammatory mediators such as cytokines that could mediate chemotherapy-induced emesis.[90]

(a) Highly emetogenic antineoplastic therapy:

In total, five studies were identified which met the above mentioned inclusion criteria and in which antineoplastic therapy was assessed as being highly emetogenic using the POGO guideline or deemed by the investigators to be highly emetogenic. Four of these were randomized trials[21, 22, 30, 91] and one was a prospective descriptive study.[17] Of the randomized trials, 3 were conducted exclusively in children.[22, 30, 91] In these studies, dexamethasone doses ranged from approximately 6 mg/m^2/day to 24 mg/m^2/day IV. In the largest of these studies, 2 dexamethasone dosing regimens (24 mg/m^2/day: 8 mg/m^2/dose given IV pre-therapy x 1 and then 16 mg/m^2/day IV either divided q6h or divided into 2 doses given q4h) were given; however, the results were provided in aggregate.[22] These studies did not evaluate AINV control using common antiemetic backbones so comparison of the performance of the dexamethasone doses used in these studies is not possible. The fourth randomized controlled trial involved too few children to permit evaluation of the outcome in this subset of the study sample.[21]

The panel's recommendation for dexamethasone dosing is based on the most robust, published evidence[22, 30, 91] in children receiving highly emetogenic antineoplastic therapy. This is limited to dexamethasone in doses of 24 mg/m^2/day. Of course, as outlined previously, the dexamethasone dose should be halved in patients receiving aprepitant concurrently.

Lower dexamethasone doses are recommended for use in adult cancer patients when normalized to body size. For adults receiving highly emetogenic antineoplastic therapy, the source guideline[11,13] recommend a dexamethasone dose of 12mg (estimated 7 mg/m^2) as a single oral dose prior to antineoplastic therapy. A higher dose requirement for children, particularly younger children, is reasonable since dexamethasone clearance increases with decreasing age.[86] The use of lower dexamethasone doses in children receiving highly emetogenic antineoplastic agents, similar to that administered by Holdsworth et al[17] (i.e. 10mg/m^2/dose once or twice daily IV) is intriguing but this approach requires more rigorous and controlled evaluation before it can be recommended with confidence.

The question of the maximum dexamethasone dose regardless of body weight or surface area led to considerable discussion between the guideline development panel members. Most panel members felt some unease with a recommendation that did not include a maximum dose. However, dexamethasone doses administered in the studies[22, 30, 91] which support the dexamethasone dose recommendation did not cap dexamethasone doses at an upper limit regardless of weight or body surface area. Direct application of the dexamethasone dose recommended for adult cancer patients would lead to the administration of the maximum dose in all children of body surface area of 0.5m^2 or more. This would represent an approach to dexamethasone dosing which is unsubstantiated by pediatric literature. Because assignment of a maximum dose would be arbitrary, no maximum dexamethasone dose is recommended in this guideline.

Similarly, the majority of published pediatric experience with dexamethasone in children receiving highly emetogenic antineoplastic therapy has been with the administration of multiple divided doses rather than a single daily dose. For this reason, it is recommended that patients who are receiving highly emetogenic chemotherapy receive dexamethasone doses divided every 6 hourly though it may be more convenient to administer doses in ambulatory clinics on a 3-dose, q4h schedule.

Dexamethasone-associated hyperglycemia may be more common in children receiving higher dexamethasone doses. When this does occur, guideline panel members recommend elimination of dextrose from intravenous fluid and judicious dietary restriction. Short term use of insulin may be initiated to control hyperglycemia while optimizing AINV control. A decision may also be taken to reduce the total daily dexamethasone dose or the number of dexamethasone doses administered per day. A reasonable first step to dexamethasone dose reduction would be to cap the dexamethasone dose at the doses currently recommended for adults: 20 mg or 12 mg if given concurrently with aprepitant.[13] In this case, the degree of AINV control being experienced by the patient and the expected duration of dexamethasone administration should be factored into the decision regarding the extent of dexamethasone dose reduction. The patient's AINV control should be closely monitored and additional antiemetic agents be added if necessary.

(b) Moderately emetogenic antineoplastic therapy:

Three studies were identified which met the above mentioned inclusion criteria and in which antineoplastic therapy was assessed as being moderately emetogenic using the POGO guideline or deemed by the investigators to be moderately emetogenic.[42, 44, 92] All were randomized comparisons of varying antiemetic regimens, at least arm of which included dexamethasone. A single randomized controlled trial evaluated AINV control provided by dexamethasone plus either oral or IV ondansetron in children receiving moderately to highly emetogenic antineoplastic therapy.[42] Dexamethasone was given by mouth in a dose based on body surface area ($\leq 0.6m^2$: 2mg BID; $> 0.6m^2$: 4mg BID). This dosing regimen is approximately equivalent to 5 to $20mg/m^2$/day depending on the child's size. The complete CIV control rate observed in this study was relatively high (approximately 80%). No other study has evaluated the combination of dexamethasone plus a 5-HT3 antagonist in children receiving moderately emetogenic antineoplastic therapy. The other 2 studies identified compared dexamethasone doses ranging from 6 to 10 mg/m^2/day combined with either chlorpromazine or metoclopramide.[42, 44]

The panel's recommendation regarding the dexamethasone dose to be given to children receiving moderately emetogenic antineoplastic therapy stems from the observations of White et al. Given the highly variable apparent clearance of dexamethasone in children[93] and the lack of specific information regarding bioavailability of dexamethasone in children, it is reasonable to recommend the same dose IV in cases where the oral route of administration is not appropriate.

For adults receiving moderately emetogenic antineoplastic therapy, the source guideline[11] and its recent update[13] recommend a dexamethasone dose of 8 mg (estimated 4.6 mg/m^2) as a single oral dose prior to antineoplastic therapy. As stated above, children may have a higher dexamethasone dose requirement compared to adults due to the inverse relationship between dexamethasone clearance and age. As outlined previously, the dexamethasone dose should be halved in patients receiving aprepitant concurrently.

Research Gaps:

It is likely that the dexamethasone dose recommended in this guideline for children receiving highly emetogenic antineoplastic agents is effective; but, it is unclear if this dose is necessary. That is, lower doses given less frequently may be equally effective. A dexamethasone dose-finding study must be conducted in all pediatric age groups to determine the optimal pediatric dose and administration frequency. Studies of the duration of the biological activity of dexamethasone indicate that the recommended dosing interval of dexamethasone requires additional thought and further investigation. A maximum dexamethasone dose regardless of body surface area or body weight requires evaluation in the setting of highly emetogenic antineoplastic therapy. Children, adolescents in particular, may achieve good acute AINV control with the lower dexamethasone doses given on a single daily dosing schedule recommended for adults. Information regarding dosing of dexamethasone in obese children is lacking.

Granisetron Dose Recommendation:

Recommendation	Strength of Recommendation & Level of Evidence*
We recommend the following **IV granisetron** dose for children receiving highly emetogenic antineoplastic therapy: *40 mcg/kg/dose IV as a single daily dose*	Strong recommendation Low quality evidence
We recommend the following **IV granisetron** dose for children receiving moderately emetogenic antineoplastic therapy: *40 mcg/kg/dose IV as a single daily dose*	Strong recommendation Moderate quality evidence
We suggest the following **oral granisetron** dose for children receiving moderately emetogenic antineoplastic therapy: *40 mcg/kg/dose PO q12h*	Weak recommendation Low quality evidence
We recommend the following **IV granisetron** dose for children receiving antineoplastic therapy of low emetogenicity: *40 mcg/kg/dose IV as a single daily dose*	Strong recommendation Low quality evidence
We suggest the following **oral granisetron** dose for children receiving antineoplastic therapy of low emetogenicity: *40 mcg/kg/dose PO q12h*	Weak recommendation Low quality evidence

* See Appendix E for key to strength of recommendations and quality of evidence descriptions.

Evidence Summary and Conclusions:

Six randomized trials and 3 prospective open studies that met the criteria for inclusion in the evidence summary were identified. Three studies compared the rates of complete AINV control provided by 2 or more granisetron doses.[43, 94, 95] One described the use of oral granisetron.[43] A summary of the evidence used to support this recommendation is presented in Appendix E.

Significant or serious adverse effects attributable to granisetron were not reported in any of the studies which met criteria for inclusion in the evidence summary or in which the emetogenicity of the antineoplastic therapy administered was not able to be determined. Headache[44, 96, 97] and constipation[96] were often reported to be the most common adverse effects. Abnormal liver function tests were reported in 4 of 22 children in one study.[31] Two studies prospectively evaluated cardiovascular toxicity including continuous electrocardiographic monitoring for 24 hours after receipt of granisetron.[95, 98] No dysrhythmias were observed in 64 children enrolled in these 2 studies. Clinically insignificant, isolated ventricular arrhythmias were reported infrequently in one study.[95]

(a) Highly emetogenic antineoplastic therapy:

One randomized trial was identified that evaluated granisetron in children receiving highly emetogenic antineoplastic therapy.[94] This crossover trial compared 2 granisetron doses in 13 children receiving cytarabine 3g/m^2/dose. Administration of granisetron either 20 or 40 mcg/kg/dose once daily before antineoplastic therapy plus dexamethasone resulted in complete AINV control in all patients regardless of the granisetron dose administered (13/13 in each arm). No patient required rescue antiemetic agents.

In an open prospective study Miyajima et al gave granisetron as a single daily dose of 40 mcg/kg and observed complete AINV control in approximately 60% of children receiving highly emetogenic antineoplastic therapy. Although the study protocol allowed for the administration of a second granisetron dose in patients in whom AINV control was not ideal, no patient receiving granisetron required a second dose. This level of control is similar to that reported in children receiving highly emetogenic antineoplastic therapy and single agent 5-HT3 antagonists for AINV prevention as reported in recommendation 2; that is, 66% (95% CI: 60, 72).

Granisetron 40 mcg/kg/day IV as a single daily dose is recommended for children receiving highly emetogenic antineoplastic therapy. The very small number of patients included in the dose comparison trial by Komada et al limits the confidence that giving a granisetron dose of 20 mcg/kg/dose will achieve the same degree of AINV control as seen following a larger dose.[94] A maximum granisetron dose is not recommended since neither of the identified studies capped the dose of granisetron.

(b) Moderately emetogenic antineoplastic therapy:

Five randomized trials were identified that evaluated AINV control in children receiving moderately emetogenic antineoplastic therapy with granisetron prophylaxis.[43, 44, 94, 96, 99] Three evaluated IV granisetron, 1 evaluated different IV doses of granisetron and another evaluated oral granisetron.

<u>IV Granisetron</u>: Komada et al gave granisetron 20 mcg/kg/dose or 40 mcg/kg/dose IV before antineoplastic therapy in a crossover design to 36 children about to receive methotrexate 3 g/m^2/dose and vincristine.[94] Complete AINV control rates on the first day of antineoplastic therapy were 81% (lower dose) and 94% (higher dose). This difference is not statistically significant.

Lower dose granisetron was evaluated in a second randomized trial.[44] However, multiple daily doses were permitted. The emetogenicity of the antineoplastic therapy ranged from moderate to high. Granisetron 20 mcg/kg/dose was administered IV prior to antineoplastic therapy and could be repeated once or twice to a maximum of 60 mcg/kg/day. The number of children who received more than 1 granisetron dose was not stated. However, improved AINV control was reported in 93% of children who received a second dose and in all children who received a third dose. The rate of complete control reported in children receiving granisetron was 22%, lower than one would expect in children receiving moderately emetogenic antineoplastic therapy (58%; 95% CI: 43, 73; see recommendation 2b). However, the definition of complete AINV control applied in this trial included not only vomiting control but also mild or no nausea and no administration of rescue antiemetic agents. The more stringent definition may have resulted in a comparatively lower control rate when compared to trials which defined complete control as merely the absence of vomiting.

The third randomized trial to evaluate granisetron IV gave 40 mcg/kg as a single daily dose prior to moderately to highly emetogenic antineoplastic therapy.[96] The dose was capped at a maximum of 3 mg regardless of body weight. Again, the reported complete AINV control rate (32%) was comparatively low perhaps due at least in part to the definition of complete control applied (absence of both nausea and vomiting).

Lemerle et al conducted an evaluation of AINV control in children receiving escalating granisetron doses in the setting of moderately or highly emetogenic antineoplastic therapy.[95] Three IV dose levels were evaluated: 10, 20 and 40 mcg/kg/dose. Children receiving the lowest dose were also given IV chlorpromazine for AINV prophylaxis. The number of children who participated in this study was small. However, there was no difference in the rate of AINV control achieved by the 2 higher doses.

The final study evaluated granisetron 40 mcg/kg/dose given IV once daily prior to antineoplastic therapy in an open design.[98] Using a definition of complete AINV control that included nausea control, complete AINV control was observed in 28% of children.

Dose comparison studies in small numbers of children receiving moderately emetogenic antineoplastic therapy indicate no difference in rates of complete AINV control offered by granisetron 20 mcg/kg/dose or 40 mcg/kg/dose.[44, 94] Fujimoto et al made similar observations in children receiving antineoplastic therapy of unknown emetogenicity.[100] However, Tsuchida et al observed a significant difference in the complete AINV control rates achieved in children receiving antineoplastic therapy of unknown emetogenicity depending on the granisetron dose administered (20 vs 40 mcg/kg/dose).[101] Furthermore, the findings of improved control with repeated doses of granisetron 20 mcg/kg raise questions about the reliability of gaining complete AINV control with single granisetron doses of 20 mcg/kg.[44, 97] For these reasons, the guideline development panel recommends that granisetron 40 mcg/kg be given as a single daily dose to children receiving moderately emetogenic antineoplastic therapy. No maximum dose is recommended since all but one study had no dose cap.

<u>Oral Granisetron</u>: Two randomized trials evaluated the efficacy of oral granisetron in children receiving moderately emetogenic antineoplastic therapy. Jaing et al administered granisetron in set doses based on weight that corresponded to approximately 10 to 20 mcg/kg/dose.[99] Mabro et al evaluated granisetron 20 vs 40 mcg/kg/dose given twice within a 12 hour period in a randomized, double blind trial.[43] Both dosing regimens achieved the same degree of complete AINV control. In both studies, the complete AINV control rates achieved were comparable to those achieved in the studies of IV granisetron in children receiving moderately emetogenic antineoplastic therapy described above.

The bioavailability of granisetron in adults is approximately 60%.[102] Therefore, oral granisetron doses should be almost double the IV dose to achieve the same dose intensity. Mabro et al[43] adopted this strategy while the oral dose given by Jaing et al[99] was actually lower than the recommended IV dose. Possible explanations for the unexpectedly high complete AINV control rate observed by Jaing et al include: antineoplastic therapy of

inherently lower emetogenicity and the omission of nausea assessment in the definition of complete AINV control.

Based on the findings of Mabro et al, the guideline development panel recommends that children receiving moderately emetogenic antineoplastic therapy receive granisetron 40 mcg/kg/dose every 12 hours by mouth. No maximum dose is recommended. No oral liquid formulation of granisetron is commercially available in Canada though extemporaneous formulations[103, 104] have been developed, the use of oral granisetron may be limited in some areas to children who can swallow tablets.

(c) Antineoplastic therapy of low emetogenic potential:

Two randomized trials were identified that met the inclusion criteria.[25, 96] Both administered granisetron in doses of 40 mcg/kg IV as a single daily dose prior to antineoplastic therapy of low to high emetogenicity. In one study, the maximum granisetron dose was 3 mg regardless of body weight.[96]

Based on the available pediatric evidence, the guideline development panel recommends that children receiving antineoplastic therapy of low emetogenicity receive granisetron 40 mcg/kg IV as a single daily dose. No maximum dose is recommended. Based on the evidence supporting the administration of oral granisetron to children receiving moderately emetogenic antineoplastic therapy, it seems reasonable and practical to adopt the same oral dosing strategy in the setting of antineoplastic therapy of low emetogenicity.

Research Gaps

Experience with oral granisetron in children is scant. More robust substantiation of the efficacy or oral granisetron across all levels of emetogenicity is needed. Knowledge of the performance of the adult dose (IV: 1 mg/dose or 0.01 mg/kg/dose; oral: 2 mg/dose) in controlling AINV in adolescents and older children would be very helpful from a pharmacoeconomic standpoint. Recommendation of a maximum granisetron IV and oral dose regardless of body weight or body surface area may be reasonable. In addition, an evaluation of the performance of granisetron 20 mcg/kg/dose in the setting of moderately emetogenic antineoplastic therapy as currently defined would also be worthy of study. Information regarding dosing of granisetron in obese children is lacking.

Metoclopramide Dose Recommendation:

Recommendation	Strength of Recommendation & Level of Evidence*
We recommend the following **metoclopramide** dose for children receiving moderately emetogenic antineoplastic therapy: *1 mg/kg/dose IV pre-therapy x 1 then 0.0375 mg/kg/dose PO q6h* Give diphenhydramine or benztropine concurrently	Strong recommendation Low quality evidence

* See Appendix E for key to strength of recommendations and quality of evidence descriptions.

Evidence Summary and Conclusions:

Four randomized trials that evaluated the use of metoclopramide to prevent AINV in children and that met the criteria for inclusion in the evidence summary were identified.[26, 30, 92, 105] Metoclopramide doses studied in children receiving chemotherapy have been lower than those proven to be moderately effective in adult cancer patients. For example, the doses administered to children receiving highly emetogenic antineoplastic therapy have ranged from 1.15 to 8 mg/kg/day whereas doses of metoclopramide once recommended for adults were 10 mg/kg/day given in single doses of 2 to 3 mg/kg.[106] The table of included studies is available in Appendix F, Table F.7e.

Several pediatric studies did not meet criteria for inclusion in the evidence summary for this recommendation, but reported findings regarding toxicity of metoclopramide in the setting of AINV. Terrin et al observed 12 dystonic reactions in 7 of 8 patients aged 8 to 19 years receiving metoclopramide 2 to 8 mg/kg/day for AINV prophylaxis without concurrent diphenhydramine administration.[107] Five of these patients went on to receive metoclopramide plus diphenhydramine for AINV prophylaxis during subsequent antineoplastic treatment; one of these patients had dystonic reactions on 2 occasions. A prospective, pediatric dose-finding study identified metoclopramide doses greater than 2 mg/kg/dose and receipt of metoclopramide for 2 consecutive days as risk factors for dystonic reactions, even when diphenhydramine was given concurrently.[108] Four and 10 of 48 patients experienced extrapyramidal reactions or akathisia within the first 24 hours of receipt of metoclopramide, respectively. Similarly, metoclopramide doses of 0.5 mg/kg were associated with no dystonic reactions in 5 children whereas dystonia and/or akathisia were observed in 5 of 5 and 4 of 5 children receiving doses of 1 mg/kg and 2 mg/kg, respectively.[84] Howrie et al[109] retrospectively evaluated the efficacy and toxicity of various dosing regimens of metoclopramide in 11 children (aged 6 to 20 yrs). Four patients received 5 doses of metoclopramide 2mg/kg/dose IV every 2 to 3 hours over approximately 9 hours. Three of these children experienced a dystonic reaction. Three other children received the same metoclopramide dose and schedule together with diphenhydramine prophylaxis; 1 patient had a dystonic reaction. Five children received metoclopramide 1mg/kg/dose IV every 2 to 3 hours over a 9 hour period with (2 patients) or without diphenhydramine (3 patients) prophylaxis. One of the patients who did not receive diphenhydramine experienced a dystonic reaction. A further 3 patients received 2 or 3 doses of metoclopramide 1mg/kg/day IV along with diphenhydramine prophylaxis; none of these patients had a dystonic reaction. Observations in adults and children in settings other than oncology also have observed that the metoclopramide dose, age 12 to 19 years and female sex may predispose patients to dystonic reactions.[110-113]

Two randomized trials were identified which described outcomes in children given metoclopramide to prevent AINV due to antineoplastic therapy of moderate emetogenic potential.[26, 92] One of these included children receiving antineoplastic agents of low to high emetogenicity but did not present outcomes for children receiving moderately emetogenic agents separately.[26] Since only one of the 13 possible antineoplastic agents administered in this study was of low emetogenicity, the results of this study are included in the assessment of metoclopramide dose for patients receiving moderately emetogenic antineoplastic therapy.

Each trial administered very different metoclopramide doses; the trial incorporating the lower metoclopramide dose (approximately 1.33 mg/kg/day) observed a poor rate of complete control of vomiting (20%; 3/15).[92]
The metoclopramide dose recommended for administration to children receiving moderately emetogenic antineoplastic therapy was associated with a complete rate of vomiting control of 74% (17/23).[26] Concurrent administration of diphenhydramine is recommended due to the high likelihood of dystonic reactions.

Research Gaps:

The optimal metoclopramide dose and dosing frequency to optimize its contribution to AINV control in children needs to be evaluated. Furthermore, both the need for the administration of prophylaxis of extra-pyramidal reactions and the effectiveness of diphenhydramine or benztropine in preventing metoclopramide-associated extra-pyramidal reactions deserve evaluation. Information regarding dosing of metoclopramide in obese children is lacking.

Nabilone Dose Recommendation:

Recommendation	Strength of Recommendation & Level of Evidence*
We suggest the following **nabilone** dose: *< 18 kg: 0.5 mg/dose PO twice daily* *18 to 30 kg: 1 mg/dose PO twice daily* *> 30 kg: 1 mg/dose PO three times daily* *Maximum: 0.06 mg/kg/day*	Weak recommendation Low quality evidence

* See Appendix E for key to strength of recommendations and quality of evidence descriptions.

Evidence Summary and Conclusions:

A single randomized trial was identified that describes AINV control in 30 children receiving antineoplastic therapy.[74] Nabilone doses were selected based on actual body weight. The dose used at the initiation of the trial was reduced after 13 patients had enrolled due to unacceptable toxicity mainly consisting of dizziness and drowsiness. The authors stated that adverse effects were most common when the dose exceeded 0.06 mg/kg/day though significant variability in patient tolerance was noted. The lower dose administered to the remaining 17 patients was associated with only minor adverse effects.

A second study of the effect of nabilone in children receiving antineoplastic therapy was identified.[75] Although it does not meet the criteria for inclusion in the evidence summary, its description of the adverse effects experienced by the children receiving nabilone is of interest. A similar nabilone dose as administered in the trial by Chan et al was used in this second study: < 18 kg: 0.5 mg twice daily PO; 18 to 36 kg: 1 mg twice daily PO, and > 36 kg: 1 mg three times daily PO. Drowsiness (12/22; 55%) and dizziness (8/22; 36%) were again reported as the most common adverse effects associated with nabilone therapy. Mood changes were reported in 6 patients; in 3 the change was felt to be negative while the change was positive in another 3. One patient experienced hallucination while receiving nabilone and withdrew from the study.

The guideline development panel based the recommended nabilone dose on the single randomized trial which met the criteria for inclusion in the evidence summary. A maximum dose based on body weight is recommended based on the observation of increased toxicity above this threshold. Each patient and family must be educated to understand the high probability that nabilone-associated drowsiness, dizziness and/or mood changes may occur. The lack of an oral liquid formulation of nabilone limits it usefulness in younger children.

Research Gaps:

The evidence on which to recommend an effective and safe nabilone dose is exceedingly thin. Certainly the efficacy of nabilone needs to be more widely and rigorously evaluated in order to ascertain its role in preventing AINV in children. The published experience in very young children specifically is very limited. Information regarding dosing of nabilone in obese children is lacking.

Ondansetron Dose Recommendation:

Recommendation	Strength of Recommendation & Level of Evidence*
We recommend the following **ondansetron** dose for children receiving highly emetogenic antineoplastic therapy: *5 mg/m^2/dose (0.15 mg/kg/dose) IV/PO pre-therapy x 1 and then q8h*	Strong recommendation Moderate quality evidence
We recommend the following **ondansetron** dose for children receiving moderately emetogenic antineoplastic therapy: *5 mg/m^2/dose (0.15 mg/kg/dose; maximum 8 mg/dose) IV/PO pre-therapy x 1 and then q12h*	Strong recommendation Moderate quality evidence
We recommend the following **ondansetron** dose for children receiving therapy of low emetogenicity: *10 mg/m^2/dose (0.3 mg/kg/dose; maximum 16 mg/dose IV or 24 mg/dose PO) pre-therapy x 1*	Strong recommendation Low quality evidence

* See Appendix E for key to strength of recommendations and quality of evidence descriptions.

Evidence Summary and Discussion:

A summary of the studies used to support this recommendation can be found in Appendix F, Table F.7g. Ondansetron doses evaluated ranged from 5 mg/kg/m^2/dose (0.15 mg/kg/dose) to 15 mg/kg/m^2/dose (0.45 mg/kg/dose). However, in several studies, a single ondansetron dose was given to patients over a range of BSA so that smaller patients would have received a larger dose on a mg/m^2 basis that would larger patients within the BSA range. Most, but not all studies, capped 5 mg/kg/m^2 doses at 8 mg. No ondansetron dosing finding studies were identified although different ondansetron doses or schedules were compared in several studies.[17, 42, 47, 114-118]

Hasler et al conducted a retrospective review of the safety of ondansetron when given in an initial dose of 16 mg/m^2 (maximum: 24 mg/dose) pre-therapy and then 2 doses of 5 mg/m^2 (maximum: 8 mg/dose) given every 8 hours.[119] Thirty-seven patients receiving 543 ondansetron loading doses were included in this review. Rate

of complete AINV control was not reported. The findings of this study are limited by its retrospective nature. However, 5 severe adverse effects (headache (2), dizziness (2) and abdominal pain (1)) were believed to be attributable to ondansetron. The patient who experienced severe dizziness inadvertently received ondansetron 28 mg/m^2 within a 3.5 hr period. Mild hypotension was reported after administration of 31 (5.7%) ondansetron loading doses. Other than dizziness, there were no reports of dysrhythmia, dyspnea, fainting or other symptoms which may have indicated QT prolongation.

Clinicians have recently been warned about the association with ondansetron and the potential for QT prolongation.[120] The use of ondansetron and other 5-HT3 antagonist agents should be avoided in patients with congenital QT prolongation. The concomitant use of ondansetron with agents known to prolong the QT interval should be undertaken with caution; ECG monitoring may be prudent.

(a) Highly emetogenic antineoplastic therapy:

Three randomized trials evaluated acute AINV control in children receiving highly emetogenic antineoplastic agents.[22, 114] The number of children involved in one of these trials is too small to allow interpretation.[21] Brock et al compared the complete AINV rates in children receiving an ondansetron loading dose to those not receiving a loading dose. Each group continued to receive ondansetron IV on an 8-hourly basis as the sole antiemetic agent.[114] No significant difference was observed between study arms (44 vs 42%; $p > 0.05$).

Alvarez et al compared ondansetron 0.15 mg/kg/dose IV pre-therapy x 1 followed by 2 doses given every 4-hourly with and without dexamethasone.[22] The complete AINV control rate observed in the ondansetron arm was far lower (23%) than that observed by Brock et al. Possible explanations for this difference include: the inclusion of non-antineoplastic naïve patients in the Alvarez trial and potential lower emetogenicity of the antiemetic regimens administered in the Brock trial.

The remaining studies which assessed AINV control after ondansetron administration were descriptive in nature.[17, 28, 115, 121-123] The complete AINV control rates reported in these studies tend to be higher than those observed in controlled trials. Several of these studies gave ondansetron as a single daily dose[17, 115] or as a single dose based on a BSA range.[27, 28, 121] Although administration of ondansetron as a single daily dose is attractive on the basis of efficiency, the available data are not sufficiently robust to support a recommendation for once daily administration at the present time.

Based on the findings of randomized controlled trials and supported by descriptive studies, an ondansetron dose of 5 mg/m^2/dose given IV or by mouth every 8-hourly is recommended for use in the setting of highly emetogenic antineoplastic therapy. The ondansetron dose was capped at 8 mg q8h in a single open, non-comparative, prospective study of children receiving highly emetogenic antineoplastic therapy.[27] The small number of children evaluated in this study as well as the low complete control rate observed did not support the inclusion of a maximum ondansetron dose as a recommendation.

(b) Moderately emetogenic antineoplastic therapy:

Five randomized trials were identified that met the eligibility criteria described above and administered ondansetron to children receiving moderately emetogenic antineoplastic therapy.[42, 92, 99, 116, 118] Of these, 3 gave ondansetron twice daily at a dose of approximately 3 to 5 mg/m^2/dose. The ondansetron dose was capped at 8 mg in 2 of these studies. In all but 1 arm of 1 study, at least the first ondansetron dose was given IV; subsequent doses were given either IV, by mouth or a mixture of both routes. Complete AINV control rates ranged from 73 to 80% in studies where ondansetron was given as the sole antiemetic prophylaxis.[92, 116] White et al achieved similar complete AINV control rates in a group of children receiving either moderately or highly emetogenic antineoplastic therapy with ondansetron plus dexamethasone as prophylaxis.[42]

Parker et al conducted a randomized controlled trial to evaluate the extent of AINV control afforded by a high (0.45mg/kg/dose) and low (0.15mg/kg/dose) single IV dose of ondansetron (0.45mg/kg/dose) in children receiving intrathecal antineoplastic therapy, considered to be moderately emetogenic.[118] The relative risk of vomiting in the placebo group was 2.3 compared to the low dose group and 4.3 compared to the high dose group. High dose ondansetron may confer a benefit to children receiving intrathecal antineoplastic therapy.

Several descriptive studies report experience with various ondansetron doses in children receiving moderately emetogenic antineoplastic therapy.[27, 117, 123-125] Ondansetron was given three times daily in 2 studies,[27, 125] twice daily in 2 studies[117, 123] and once daily in one study.[17] Initial ondansetron doses ranged from 3 mg/m^2/dose to 10 mg/m^2/dose (0.3 mg/kg/dose). These studies generally support the use of lower and less frequent ondansetron doses in the setting of moderately emetogenic antineoplastic therapy.

Thus, the findings of randomized controlled trials and descriptive studies support the recommendation of an ondansetron dose of 5 mg/m^2/dose (maximum: 8 mg/dose) IV or by mouth every 12 hours to prevent AINV in children receiving moderately emetogenic antineoplastic therapy. The maximum single dose of 8 mg is based on the findings of good AINV control in 2 randomized controlled trials[92, 116] and one prospective study[27] where the ondansetron dose was capped at 8 mg.

(c) Antineoplastic therapy of low emetogenic potential:

Two studies were identified that met the previously mentioned eligibility criteria and which evaluated ondansetron in children receiving antineoplastic therapy of low emetogenic potential: one randomized control trial[47] and another descriptive study.[17] Both describe outcomes in a very small number of patients. Sandoval compared AINV control provided by 2 doses of ondansetron (0.6 mg/kg/dose (maximum: 32 mg/dose) IV pre-therapy versus 0.15 mg/kg/dose (maximum: 8 mg) IV pre-therapy followed by 3 doses given every 4-hourly) in children receiving antineoplastic therapy whose emetogenicity ranged from low to high.[47] The single dose regimen was associated with a higher complete AINV control rate than the multiple dose regimen but this difference did not reach clinical significance. Holdsworth et al observed a high complete AINV control rate (82%) after administration of 0.3 mg/kg/dose (no maximum dose) as a single IV dose given prior to antineoplastic therapy.[17]

Given that the patients studied by Sandoval et al did not all receive antineoplastic agents of low emetogenicity and concerns regarding the potential for dose-related adverse effects of ondansetron, the guideline development panel recommended that patients receiving antineoplastic therapy of low emetogenicity receive ondansetron in a dose of 10 mg/m^2/dose or 0.3 mg/kg/dose IV pre-therapy. Although neither of the studies identified administered a maximum ondansetron dose, the panel recommends a maximum single daily IV ondansetron dose of 16 mg due to the potential for QT interval prolongation with higher doses.[126] Based on the excellent bioavailability of ondansetron and its demonstrated efficacy in children receiving highly and moderately emetogenic antineoplastic therapy when given by mouth, the guideline development panel furthermore included the oral route in the recommendation despite the absence of specific evidence to support its efficacy in children receiving antineoplastic of low emetogenic potential. For oral administration, it may be reasonable to consider a maximum single daily ondansetron dose of 24 mg as has been recommended for adults.[11]

Research Gaps:

A full evaluation of ondansetron single vs multiple daily dose regimens would be helpful especially in light of the desire to administer more antineoplastic therapy in an ambulatory setting. Specific confirmatory evidence regarding the de-escalation of ondansetron dosing for antineoplastic regimens of decreasing emetogenic potential is required. The relevance of using the ondansetron dose recommended for adults as a dosing cap in adolescent patients merits investigation. It would be valuable to determine if a higher ondansetron dose could achieve a higher rate of complete AINV response in patients who exhibit cytochrome P450 polymorphisms which may predispose them to have rapid ondansetron clearance. Information regarding dosing of ondansetron in obese children is lacking.

EXTERNAL REVIEW AND CONSULTATION PROCESS

- **Who was asked to review the guideline?**

Content expert review: Physicians, nurses and pharmacists with an active clinical and/or research interest in antineoplastic-induced nausea and vomiting were asked to review the draft guideline. Content reviewers who submitted a review were: Drs. C. Baggott, S. Grunberg, A-M Langevin, A. Orsey, R. Phillips, M. van der Wetering and D. Woods.

External stakeholder review: Physician, nurse and pharmacist members of POGO centres and their satellites and members of the POGO Supportive Care Committee were asked to review the draft guideline.

- **What process was followed?**

The willingness of potential content expert reviewers to review the guideline was determined by contacting them by telephone or e-mail. Once agreement was obtained, the draft guideline was sent both electronically and by courier along with instructions for the reviewer to complete a survey (Appendix J).

Following the content expert review, the draft guideline and quick review summary were sent electronically to nurses, nurse practitioners, pharmacists and oncologists who practice in POGO satellites and tertiary centres together with a request to review the document using a survey (Appendix K).

Reviewers returned the completed survey by fax, mail or electronically.

- **Discussion of Feedback**

The survey results were discussed in detail by the POGO AINV Guideline Development Panel and a decision on each point was taken by consensus. When the decision of the panel was not unanimous, a revision was made if it was supported by at least 60% of the guideline development panel members. The comments of the expert reviewers led to revisions to the guideline as outlined in Table 4.

Table 4: Specific Feedback from Content Expert Reviewers and Results of the Guideline Development Panel's Discussion

Expert Reviewer Comment	Panel Action/decision
I think it's a clearly written document that summarises a vast amount of paediatric research. The missing sections on tools/pathways are clearly going to be needed to make this usable by practitioners.	- This section has been completed.
The limitation of scope to acute vomiting does exclude the need to answer the question "For how long should give ondansetron?". This is a tricky but very necessary question to answer in practice, and would be useful to either comment upon or note clearly its exclusion from this document.	- Scope statement has been strengthened. - Reference has been made to the final planned AINV POGO guideline.
Similarly, although the scope is mainly focussed upon prevention in the first episode of chemotherapy, approaches to failure of prophylaxis and modifications for the second and subsequent courses of chemotherapy are important practical issues. It may be worth highlighting that this guideline is NOT providing information for this aspect of care.	- Same response as above.
My disagreement re: the guideline search is really minor... the scope includes a search for grey stuff but I think there are a number of grey documents in the UK that have not been included. They wouldn't add much to the tome that you have	- The source guideline search was limited to those submitted/included in a guideline database or tagged on the web - Guidelines from the source identified by

collated. Perhaps express the limit to 'major' non-Canadian guidelines.	the reviewer will be included in the development of the next guideline. - Before future guidelines are developed or updated, external experts will be polled regarding possible guidelines that ought to be reviewed for adaptation. - No change was made to the guideline.
This is a very comprehensive body of work that indeed identifies significant research gaps in the use of antiemetics in children. I noticed that in the recommendation guidelines for 5-HT3 dosing, there is no maximum dose listed. Is this a purposeful omission?	- The evidence was reviewed. No maximum ondansetron dose was recommended for highly emetogenic antineoplastic therapy. A maximum dose of 8 mg was recommended for patients receiving moderately emetogenic antineoplastic therapy while the dose was capped at 24 mg for antineoplastic therapy of low emetogenicity. - The lack of a dose cap for HEC has been highlighted as a research gap.
The issues raised about aprepitant, the optimal dose for dexamethasone and the paucity of options for certain groups of patients in whom corticosteroids cannot be used are daily problems encountered in the clinical setting. In our practice, we have used the lower dosage of aprepitant (40 mg) with success in selected younger children who were vomiting despite the use of antiemetics per guidelines similar those proposed by POGO. I know that this practice is more common than we think and it would be useful to collect that data.	- This question is outside the scope of this guideline. - This is highlighted as a research gap.
Because we serve a large population of Hispanics with high incidence of obesity and family history of diabetes, the use of Dexamethasone which we topped at 5 mg/m2 max 10 mg per day, results in "fasting" glucose > 200 mg/dl in ~ 30% of patients and > 150 mg/dl in > 60% of patients despite modification of IV fluids. This has led to discontinuing dexamethasone as antiemetics in several of our patients receiving highly emetogenic chemotherapy. With the incidence of childhood obesity on the rise this is a phenomenon that is becoming more prevalent and alternatives to corticosteroids for control of AINV are needed.	- The evidence was reviewed. No maximum dexamethasone dose was recommended for patients receiving highly emetogenic antineoplastic therapy since there was insufficient evidence to support one. - Dosing in obesity will be included as a research gap - Advice regarding management of dexamethasone-associated hyperglycemia was included - A statement that all doses are based on actual body weight will be included in the introduction.
Pages 170-172 were difficult to follow (evidence for recommendation 5), perhaps some materials were repeated.	- Typographical mistakes have been corrected
Making a cross-reference to the list of potential interactions with aprepitant would improve readability. This information is listed in a single place in the lengthy document.	- This table has been added as Appendix H.
I must commend your committee, which has done an excellent job of summarizing a difficult, and at times non-existent, literature. However there are certain points of concern to bring to your attention. A majority of your recommendations are based on low quality evidence. One commonly used endpoint of guidelines work is the level of adoption and implementation of the guidelines. However it would be difficult to expect experienced clinicians to replace decisions based on personal experience and anecdotal	- Warr et al 2005 evaluated AINV control in adults receiving cyclophosphamide + doxorubicin or etoposide. This study was included in a re-evaluation of the findings of 3 trials published in 2011. - Under the POGO emetogenicity classification guideline, the combination of cyclophosphamide + etoposide or doxorubicin is considered to the highly

evidence with recommendations based on low quality evidence. In some cases, such as the evaluation of alternative remedies, you accept a recommendation based on little evidence while in other cases, such as the use of NK-1 antagonists in antiemetic regimens for moderately emetogenic chemotherapy, you have chosen not to extrapolate a large body of evidence in the adult population (In this case, the pivotal trial in moderately emetogenic chemotherapy was led by Dr. David Warr of Toronto). You seem to base this decision on the theoretical concerns of drug-drug interactions with aprepitant, even though you acknowledge that clinical trials (ie, the available evidence) have not shown any clinically significant interactions.	emetogenic. - Rappoport et al has described improved vomiting and complete CINV control in adults receiving moderately emetogenic antineoplastic therapy as per the POGO classification with ondansetron, dexamethasone and aprepitant prophylaxis compared with ondansetron, dexamethasone and placebo. - The text has been revised to indicate that evidence regarding the use of aprepitant for AINV prophylaxis in children receiving moderately emetogenic antineoplastic therapy is a research gap.
There are several additional points regarding NK-1 antagonists. If dexamethasone/5-HT3 antagonist/aprepitant is the recommended treatment for highly emetogenic chemotherapy (Question 2A), then why would 5-HT3 antagonist/aprepitant not be an option for highly emetogenic chemotherapy where corticosteroids are contraindicated (Question 5)?	- The text has been revised to indicate that aprepitant plus 5-HT3 antagonist may be considered as a possibility in children unable to receive corticosteroids. It was not included as a recommendation since there is no supporting evidence available, even in adults. - The use of aprepitant plus ondansetron/granisetron for CINV control in patients unable to receive corticosteroids is already included as a research gap. - No change was made to the guideline.
Also, if your guidelines are specifically designed for the treatment of acute antineoplastic-induced nausea and vomiting, then why do you recommend the full 3-day course of oral aprepitant (Question 6) where the second and third day of treatment specifically addresses delayed emesis?	- Since multiple day antineoplastic treatment is the norm in pediatrics, the designation of days when aprepitant is given as acute or delayed is more of a semantic issue than a practical one. - A comment was added to the guideline text regarding the timing of aprepitant administration relative to the acute vs delayed phase of AINV.
By adult standards, the recommendation for use of a 5-HT3 antagonist for patients receiving low emetogenic chemotherapy would be considered aggressive and unduly expensive. Since by definition patients receiving low emetogenic chemotherapy without antiemetics only experience emesis 10-30% of the time (ie, 70-90% "complete protection"), the finding of 74% complete control with 5-HT3 antagonists cannot be considered to represent significant activity.	- It is true that implementation of the guideline may lead to administration of 5-HT3 antagonists to many children who may not require them to be AINV-free. However, since AINV is known risk factor for uncontrolled AINV in the future, the panel believed that the cost/benefit of giving 5-HT3 antagonists, at least with the first course of antineoplastic therapy of low emetogenicity, was acceptable. If AINV is controlled, AINV prevention strategies can be re-evaluated with subsequent course. - This rationale has been added to the text
Use of more traditional agents, such as low dose prochlorperazine, could also be considered.	- No pediatric evidence for the efficacy of prochlorperazine in controlling AINV was identified. - No changes to the guideline were made.
The toxicity of high dose metoclopramide is a major pediatric concern since this toxicity is known to be inversely age	- A summary statement regarding risk factors for metoclopramide-induced

related. However, such toxicity is also route related and is more common after oral administration than after intravenous administration. This distinction and the added risk of oral administration should be explained in your text.	dystonic reactions was added to the text of recommendation 6.
p.18 high emetic risk: children > 12 yrs aprepitant evidence is based on adult data and one study with 6 adolescents, maybe it should be worded that the advice is to give 5TH3 antagonist + dexa and once the trials on pediatric use of aprepitant have been published then put it in guideline.	- Recommendation is based on observational data in teenagers - No change was made to the guideline
p. 40 dexamethasone dose. As the range of studies and dosages used is wide maybe it would be better to state that range in the recommendation. I find 24 mg/m2 prechemo based on one study extremely high.	- Presentation of the dexamethasone dose as a range was debated at length - Panel members believed that the weight of the evidence was in favour of the higher dose - The guideline text describes the panel's discussion - No change was made to the guideline
p. 49 Ondansetron 10 mg/m^2/dose based on one study of Holdsworth in low emetic group works confusing as you use a lower dose in the other 2 groups. Maybe state the range as recommendation.	- Doses of all drugs are now presented on a per dose basis rather than per day. Thus the reduction in the number of times per day ondansetron is recommended as the emetogenicity decreases is more readily understood.
It is clear that much work and preparation has gone into this very complete review and guideline development. Thank you for taking on this relevant and much needed task! The dronabinol section may need clarification as it states "no studies" yet under nabilone there is a meta-analysis of dronabinol and nabilone. Perhaps the 2 drugs should be combined into 1 section?	- Discussion of the 2 drugs has been combined into 1 section. - The lack of evidence for dronabinol which met criteria for inclusion in the guideline evidence summary has been clarified.
There is certainly room to elaborate on agents listed as research gaps (metopimazine, acupressure, aprepitant, fosaprepitant, olanzapine, BAD and ginger) but this may be out of scope of this project. Overall - excellent project and I look forward to the final product!	- A more detailed review of research gaps is outside the scope of this guideline - No change was made to the guideline

Stakeholders from all of the tertiary (5 centres) and satellite (7 centres) institutions providing pediatric oncology care in Ontario provided feedback on the draft guideline. The stakeholder feedback is summarized below. No changes were made to the guideline recommendations based on the stakeholders' comments though they did prompt clarification of wording and the addition of Appendix I.

Table 5: Stakeholder Agreement with Survey Statements (n=30 responses, except where noted)

Item	Strongly Agree	Agree	Neither agree nor disagree	Disagree	Strongly disagree	Average Rating*
There is a need for a practice guideline on this topic.	63.3% (19)	36.7% (11)	0.0% (0)	0.0% (0)	0.0% (0)	4.63
The literature search described in the report is complete (no key studies were missed).	46.7% (14)	50.0% (15)	3.3% (1)	0.0% (0)	0.0% (0)	4.43
The results of the studies described in the report are interpreted according to my understanding of the data.	46.7% (14)	50.0% (15)	3.3% (1)	0.0% (0)	0.0% (0)	4.43

The recommendations are clear.	56.7% (17)	36.7% (11)	6.7% (2)	0.0% (0)	0.0% (0)	4.50
I agree with the recommendations as stated.	30.0% (9)	53.3% (16)	13.3% (4)	3.3% (1)	0.0% (0)	4.10
I would feel comfortable having these recommendations applied in my hospital.	33.3% (10)	60.0% (18)	0.0% (0)	6.7% (2)	0.0% (0)	4.20
The recommendations are likely to be supported by a majority of my colleagues.	30.0% (9)	50.0% (15)	16.7% (5)	3.3% (1)	0.0% (0)	4.07
Which do you foresee may be obstacles to implementing these recommendations at your institution?						
a) Concern to dose antiemetics as recommended	10.0% (3)	33.3% (10)	20.0% (6)	33.3% (10)	3.3% (1)	3.13
b) Reluctance to standardize practice	3.3% (1)	26.7% (8)	13.3% (4)	50.0% (15)	6.7% (2)	2.70
c) The recommendations conflict with current institutional policies	3.3% (1)	26.7% (8)	16.7% (5)	43.3% (13)	10.0% (3)	2.70
d) Existing pre-printed and electronic order sets would need to be changed**	10.7% (3)	32.1% (9)	17.9% (5)	28.6% (8)	10.7% (3)	3.04
I see myself playing an active role in contributing towards the implementation of this guideline.	43.3% (13)	50.0% (15)	6.7% (2)	0.0% (0)	0.0% (0)	4.37

*5-point scale: Strongly Agree=5, Agree=4, Neither Agree nor Disagree=3; Disagree=2; Strongly Disagree=1

**Number of responses = 28

Table 6: Stakeholders' Opinion of Likelihood of Adoption of Guideline in Their Practice

How likely would you be to use the guideline recommendations in your own practice?	% (n)
Likely	86.7% (26)
Unsure	13.3% (4)
Not likely	0%
Not applicable	0%

Table 7: Additional Comments From Stakeholders And Response Of Guideline Development Panel

Stakeholder Comment	Panel Action/Decision
Thank you so much for giving me the option to review this document. My comments are: This is a very important document which will hopefully reduce AINV. 1. My concern is regarding chlorpromazine. Based on the high prevalence of side-effects-dystonia, should you recommend concomitant benedryl? 2. Though the scope if this document is not to recommend treatment when first line anti emetic treatment fails, there is a high chance that second line will include adding lorazepam or metochlopramide to chlorpromazine. Should there be a recommendation to avoid this based on 32% of dystonia when combined with lorazepam or the concurrent risk of metoclopramide? 3. P25. PARAGRAPH 2- Not sure which 8 studies.	1. None of the studies identified gave children prophylactic diphenhydramine. The addition of diphenhydramine may lead to excessive sedation. The panel opted to add a statement that readers "consider" the concurrent use of diphenhydramine in children receiving chlorpromazine. 2. This is beyond the scope of this guideline. 3. This has been corrected to read "9 studies".
We also use gravel at this institution, and this is not covered in the guideline. We have not used chlorpromazine in our antiemetic regimens at this instution - but in discussion with pharmacy colleagues - this will be worthy of further discussion as a team. We have only recently begun to use aprepitant at our institution (for example..while recently revising my list of meds I can order as NP in oncology - I was asked to remove aprepitant from that list). I really like the decision diagrams/aids; they will be very handy. Your team has done a tremendous amount of c work in developing this comprehensive guidline and should be congratulated! I do think this is a really valuable contribution to the pediatric oncology literature.	There is no evidence to support the use of dimenhydrinate to prevent AINV. It was therefore not included in the guideline.
It would be difficult to have our physicians agree to using higher doses of dexamethasone as well as metoclopramide. Currently we do use as high doses recommended in the POGO guidelines. As well our institution uses Gravol for breakthrough nausea and vomiting and it might be difficult to convince the other practitioners, the patients and their parents to remove Gravol from our alternatives for chemotherapy induced nausea and vomiting.	See above.
Good overall guideline and review of literature. Concern over dosing of dexamethasone as we see a lot of toxicity (blood pressure, GI side effects, behaviour changes, etc) with the dose we are currently using. Concern over the lack of use of dimenhydrinate although I understand the lack of evidence. Most of our patients use this and experience good effect....it will be difficult to change this practice at our site.	No action taken.
Thanks for this comprehensive review. The working group has done a lot of work with limited good evidence. I appreciate the clarity of the quick-review summary. Our site currently uses dimenhydrinate as part of breakthrough AINV and I'm not sure that the clinicians, or the patients/parents, would be willing to abandon it as an option. There may not be much evidence to support its use, but there isn't strong evidence for many of the recommendations. That may be out of the scope of this practice guideline, since the guideline doesn't address treatment of breakthrough AINV or rescue medications. Thank you for the detailed explanations of the rationale and strengths/weaknesses of recommendations for drug dosing. The clinical trials summaries help to justify the recommendations. The following would be potential facilitators for adopting the guidelines at our site: -interdisciplinary journal club to discuss how to implement the guidelines and address barriers and concerns -a separate pre-printed order for the antiemetics. Currently all antiemetics are on our preprinted	No action taken.

Stakeholder Comment	Panel Action/Decision
chemotherapy orders and it would be onerous to update the hundreds of orders that exist.	
dexamethasone dosing should state max dose of possibly 10mg as seen in adults	Panel members decided not to recommend a maximum dexamethasone dose. An appendix of recommended adult antiemetic doses was added.
RE algorithm for highly emetic no reference to metoclopramide yet the dose is in the list of drugs? Re Nabilone use in small children drug only comes in 2 strengths so younger children would be a challenge, is there not an age limit for its use? Why is there no reference to aprepitant under the section corticosteroids contraindicated?	1. This was corrected. 2. There is no evidence for a minimum age for the use of nabilone. 3. There is no evidence to support the use of aprepitant alone or with a 5-HT3 antagonist in children. This was noted as an evidence gap.
This is a very impressive document - and the summary sheets are concise and easy to follow. I foresee a positive impact on how we manage nausea and vomiting in our pediatric patients	
All and all an excellent document. However, I remain very concerned about the lack of a maximum dose of dexamethasone in adolescents.	See above.
This is an excellent review and an impressive body of work. I understand your rational for not listing dose maximums is the tables. However as a front line provider it would be very helpful to have these maximum or at least adult dosing listed, With the current shortages of many antiemetic agents in this country it would seem prudent not to give a dose over the usual adult dose (if a patient fails his antiemetic regimine then dose escalating could be considered). As a clinican it would be helpful for me to have the usual adult dose listed. It would seem prudent for me to give my 17 yr patient the same antiemetic dosing as an 18 yr patient at an adult center across the street.	See above.
I think that you should list IT MTX as minimal emetogenic potential, and where you have intrathecal chemotherapy listed you have triple IT - it is really the cytarabine that is highly emetogenic so this should be listed such that patients receiving only intrathecal cytarabine and not triples would get the same therapy as those getting triple ITs	Emetogenicity was addressed in previous guideline. No action taken.
Excellent job! Thank you for taking this project on.	

Plan for Scheduled Review and Update

The POGO AINV Guideline Development Panel will review this guideline every 3 years and at any time if significant new information becomes available.

IMPLEMENTATION CONSIDERATIONS

The guideline development panel acknowledge that the antiemetic doses recommended in this guideline may not agree with the licensed doses in specific jurisdictions. This may create a barrier to the acceptance of the recommended doses. The doses recommended in this guideline are, however, congruent with the available published evidence.

This guideline offers a platform upon which individual clinicians and institutions may frame local recommendations. Each institution is encouraged to adapt this guideline to their local context. In this way, local values and the local availability of resources can inform the recommendations.

Users of this guideline are encouraged to incorporate the recommendations of the guideline into:

- antineoplastic treatment protocols and road maps
- institutional guidelines for selection of antiemetic agents for the prevention of acute antineoplastic-induced nausea and vomiting
- pre-printed or electronic (e.g. CPOE) order sets that include antineoplastic agents

TOOLS FOR APPLICATION

An algorithm summarizing recommended antiemetic strategies based on the emetogenicity of the antineoplastic therapy being administered is presented in Appendix L. The availability of the algorithm in an electronic format would likely be most readily accepted by clinicians since it would facilitate bedside decision-making as well as facilitate the incorporation of the guideline recommendations into pre-printed or electronic antineoplastic order sets. Development of these tools will be considered by POGO as part of the knowledge translation plan for this guideline.

Use of patient-report tools which assess the AINV experienced by each patient would facilitate communication regarding the severity of AINV and individualization of antiemetic prophylaxis. Tools such as prospective diaries (paper[127] and electronic[128]) and retrospective surveys[115] may be considered.

ORGANIZATIONAL BARRIERS AND COST IMPLICATIONS

Organizational barriers to the acceptance and uptake of this guideline may include:

- dismissal of recommendations based on the relative scarcity of robust paediatric supporting evidence;
- reluctance by some clinicians to use state-of-the-art antiemetic agents including corticosteroid agents;
- reluctance by some clinicians to dose some antiemetics as recommended based on concerns regarding toxicity or satisfaction with the performance of doses currently used, and
- lack of access to recommended antiemetic agents. This will not be an issue in POGO centres and their satellites.

The relative acquisition costs of the antiemetic agents recommended in this guideline in effect in Ontario at the time of guideline development are presented in Appendix M. Drug costs are highly variable and subject to change. Clinicians adapting this guideline for use in their institution are encouraged to verify their local drug acquisition costs.

Costs related to antiemetic agents may increase as a result of this guideline. However, these costs are counter-balanced by potential reductions in admissions due to refractory AINV and/or dehydration following antineoplastic therapy and improvement in the quality of life experienced by paediatric cancer patients during treatment.

KEY REVIEW CRITERIA FOR MONITORING AND/OR AUDIT PURPOSES

Guideline acceptance and adherence may be monitored prospectively or retrospectively indirectly through audit of antiemetic selection. Patient response (level of AINV control) maybe monitored prospectively.

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DISCLAIMER

The information contained in this document was prepared with care. However, any application of this material is expected to be based on judicious independent medical assessment in the context of individual clinical circumstances as well as institutional policies and standards of practice. POGO does not make any guarantees of any kind whatsoever with respect to the content or use or application of this guideline. POGO disclaims any responsibility for the application or use of this guideline.

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Appendix A: Guideline Search Strategy and Citations Evaluated

GUIDELINE SEARCH

Search Strategy

The following processes were used to search for guidelines:

1. Review of scientific literature sources using empirical databases - Medline, All Evidenced Based Medicine (EBM) Reviews (Cochrane DSR, ACP Journal Club, DARE, CCTR, CMR, HTA, and NHSEED), Embase, Cumulative Index to Nursing & Allied Health Literature (CINHAL), were systematically searched using the following search terms:

   Medline Search Terms: nausea, vomiting, combined with terms neoplasm, antineoplastic agents, antiemetics, psychotropic drugs, limited to "all child (0 to 18 years)", consensus development conference or consensus development conference, nih or guideline or practice guideline, guidelines as topic or practice guideline as topic, limited to 24 hr, 24 hrs, 24 hour, 24 hours

   All EBM Reviews Search Terms: cancer, neoplas: or oncolg:, nausea, nauseous, vomit, emesis, anti-emetic, anti emetic, limited to infan:, child:, teen:, adolescent:, young adj2 adult:, pediatric:, paediatric:, limited to acute, 24 hr, 24 hrs, 24 hour, 24 hours

   EMBASE Search Terms: practice guideline, consensus development, good clinical practice, nursing care plan, clinical pathway, guideline, consensus, nausea, vomiting, retching, chemotherapy induced emesis, nausea induced emesis, neoplasm, antineopastic agent, antiemetic agent, psychotropic agent

   CINAHL Search Terms: nausea, vomiting, combined with neoplasms, antineoplastic agents, practice guidelines, protocols, limited to newborn, infant, child, adolescence

2. Review of local, provincial, national and international databases
   1. Professional oncology associations for antiemetics guidelines.
   2. International organizations or agencies or associations whose mandate is focused on systematic reviews or guideline development.

   The organizations and agencies sites that were searched are included in Appendix B.

3. Review of grey literature sources such as annual reports or publications of organizations as identified on the world-wide web - The internet search engine utilized was Google. Search terms included: antiemetics practice guidelines, nausea and vomiting guidelines, paired with terms of children, and pediatric.

Inclusion/Exclusion Criteria

Inclusion:

1. Guidelines focused on clinical practice of practitioners relevant to **pediatric antiemetic guidelines** for pediatric hematology/oncology patients**.**
   a. **Clinical practice guidelines:** those specific to situations in which clinicians are making decisions about direct patient care.
   b. **Best practice guidelines:** those that identify the best choice from a range of appropriate health care options, as defined by a consensus of experts following review of relevant literature using systematic review methods.

2. Published between 1950-2010

Exclusion*:

1. Guidelines for which it was not clear that the guideline statements or recommendations were based on a review of evidence from the literature and/or were not based on a source that used evidence to support the guideline development process

** Excluded guidelines may have still been considered by the panel during the guideline development process, but were not considered for the basis of guideline adaptation.*

1. LITERATURE SEARCH

Search Strategies for Pediatric Oncology Group

Database: Ovid **MEDLINE**(R) 1950 to Present with Daily Update

Search Strategy:

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1 nausea/ or vomiting/ (21152)
2 exp neoplasm/ (2078497)
3 exp Antineoplastic Agents/ (662184)
4 2 or 3 (2449130)
5 1 and 4 (6330)
6 exp Antiemetics/ (114098)
7 exp Psychotropic Drugs/ (281953)
8 6 or 7 (342506)
9 1 and 8 (4914)
10 5 or 9 (8797)
11 limit 10 to "all child (0 to 18 years)" (1799)
12 limit 11 to (consensus development conference or consensus development conference, nih or guideline or practice guideline) (7)
13 guidelines as topic/ or practice guidelines as topic/ (77145)
14 11 and 13 (11)
15 14 not 12 (10)
16 12 or 14 (17)
17 from 16 keep 1-17 (17)
18 from 17 keep 1-17 (17)
19 ("24 hr" or "24 hrs" or "24 hour" or "24 hours").ti,ab. (109845)
20 11 and 19 (117)
21 16 and 19 (0)
22 from 18 keep 5-8,11,13-17 (10)

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1. Anonymous. 5HT3-receptor antagonists as antiemetics in cancer. Drug & Therapeutics Bulletin. 2005;43(8):57-62.
   Not a guideline

2. Roila F, Feyer P, Maranzano E, Olver I, Clark-Snow R, Warr D, Molassiotis A. Antiemetics in children receiving chemotherapy. Supportive Care in Cancer. 2005; 13(2):129-31.
   Selected for consideration
3. Antonarakis ES, Evans JL, Heard GF, Noonan LM, Pizer BL, Hain RD. Prophylaxis of acute chemotherapy-induced nausea and vomiting in children with cancer: what is the evidence?. Pediatric Blood & Cancer. 2004;43(6):651-8.
   Selected for consideration

4. Mandera M. Marcol W. Bierzynska-Macyszyn G. Kluczewska E. Pineal cysts in childhood. Childs Nervous System. 2003;19(10-11):750-5.
   Not a guideline

5. Mertens WC, Higby DJ, Brown D, Parisi R, Fitzgerald J, Benjamin EM, Lindenauer PK. Improving the care of patients with regard to chemotherapy-induced nausea and emesis: the effect of feedback to clinicians on adherence to antiemetic prescribing guidelines. Journal of Clinical Oncology. 2003;21(7):1373-8.
   Not applicable

6. Andria ML, Arens JF, Baker DK Jr, Bolinger AM, Briones GR, Chen JJ, Chin A, Coursin DB, Diener KM, Dranitsaris G, Farrington J, Frazier JL, Gandara DR, Goldspiel BR, Golembiewski JA, Grunberg SM, Henry DW, Hutson PR, McCauley DL, McKenna EF, Perez EA, Philip BK, Shirk MB, Slimowitz R, Solimando DA Jr, Springman SR, Stump LS, Taylor T, Wagner BK, Walton SM. ASHP Therapeutic Guidelines on the Pharmacologic Management of Nausea and Vomiting in Adult and Pediatric Patients Receiving Chemotherapy or Radiation Therapy or Undergoing Surgery. American Journal of Health-System Pharmacy. 1999;56(8):729-64.
   Selected for consideration

7. The Antiemetic Subcommittee of the Multinational Association of Supportive Care in Cancer (MASCC). Prevention of chemotherapy- and radiotherapy-induced emesis: results of Perugia Consensus Conference. Annals of Oncology. 1998;9(8):811-9.
   Selected for initial consideration; excluded because it is considered out of date

8. Feyer PC, Stewart AL, Titlbach OJ. Aetiology and prevention of emesis induced by radiotherapy. Supportive Care in Cancer. 1998;6(3):253-60.
   Not applicable

9. Roila F, Aapro M, Stewart A. Optimal selection of antiemetics in children receiving cancer chemotherapy. Supportive Care in Cancer. 1998;6(3):215-20.
   Selected for initial consideration; excluded because it is not a guideline

10. Currow DC, Noble PD, Stuart-Harris RC. The clinical use of ondansetron. New South Wales Therapeutic Assessment Group. Medical Journal of Australia. 1995;162(3):145-9.
    Not a guideline

Database: **ALL EBM Reviews** - Cochrane DSR, ACP Journal Club, and DARE

1 (cancer: or neoplas: or oncolog:).mp. (59610)
2 (nausea or nauseous or vomit: or emesis or "anti-emetic:" or "anti emetic:" or antiemetic:).mp. (17993)
3 1 and 2 (3673)
4 (infan: or child: or teen: or adolescen: or (young adj2 adult:) or pediatric: or paediatric:).mp. (126457)
5 3 and 4 (498)
6 acute.tw. (51957)
7 ("24 hr" or "24 hrs" or "24 hour" or "24 hours").mp. (15831)
8 6 or 7 (64855)
9 5 and 8 (182)
10 from 9 keep 55,82,88,90-92,95-96,98 (9)
11 from 10 keep 1-9 (9)

1. Kassab S, Cummings M, Berkovitz, S, van Haselen R, Fisher P. Homeopathic medicines for adverse effects of cancer treatments. EBM Reviews - Cochrane Database of Systematic Reviews Cochrane Pain, Palliative and Supportive Care Group Cochrane Database of Systematic Reviews. 4, 2009.
   Not applicable

2. Ezzo J, Richardson M, Vickers A, Allen C, Dibble S, Issell BF, Lao L, Pearl M, Ramirez G, Roscoe JA, Shen J, Shivnan JC, Streitberger K, Treish I, Zhang G. Acupuncture-point stimulation for chemotherapy-induced nausea or vomiting. EBM Reviews - Cochrane Database of Systematic Reviews Cochrane Pain, Palliative and Supportive Care Group Cochrane Database of Systematic Reviews. 4, 2009.
   Not applicable

3. Phillips RS, Gibson F, Gopaul S, Light K, Craig JV, Pizer B.Antiemetic medication for prevention and treatment of chemotherapy induced nausea and vomiting in childhood. EBM Reviews - Cochrane Database of Systematic Reviews Cochrane Childhood Cancer Group Cochrane Database of Systematic Reviews. 4, 2009.
   Not a guideline (it is a protocol for reviewing trials on this subject)

4. Centre for Reviews and Dissemination. Behavioral intervention for cancer treatment side effects. EBM Reviews - Database of Abstracts of Reviews of Effects Database of Abstracts of Reviews of Effects. Issue 1, 2010.
   Not a guideline

5. Centre for Reviews and Dissemination. Cannabinoids for control of chemotherapy induced nausea and vomiting: quantitative systematic review (Structured abstract). EBM Reviews - Database of Abstracts of Reviews of Effects Database of Abstracts of Reviews of Effects. Issue 1, 2010.
   Not a guideline (focus is on role of cannabinoids alone in acute period)

6. Centre for Reviews and Dissemination. Granisetron is equivalent to ondansetron for prophylaxis of chemotherapy-induced nausea and vomiting: results of a meta-analysis of randomized controlled trials (Structured abstract). EBM Reviews - Database of Abstracts of Reviews of Effects Database of Abstracts of Reviews of Effects. Issue 1, 2010.
   Not a guideline (focus on specific agents)

7. Navari RM, Kaplan HG, Gralla RJ, Grunberg SM, Palmer R, Fitts D. Efficacy and safety of granisetron, a selective 5-hydroxytryptamine-3 receptor antagonist, in the prevention of nausea and vomiting induced by high-dose cisplatin. EBM Reviews - Cochrane Central Register of Controlled Trials Journal of clinical oncology: official journal of the American Society of Clinical Oncology. 12(10):2204-10, 1994 Oct.
   Not a guideline

8. Benoit Y, Hulstaert F, Vermylen C, Sariban E, Hoyoux C, Uyttebroeck A, Otten J, Laureys G, De Kerpel I, Nortier D. Control of nausea and vomiting by Navoban (tropisetron) in 131 children receiving cytotoxic chemotherapy. EBM Reviews - Cochrane Central Register of Controlled Trials Anti-cancer drugs. Vol.6 Suppl 1, pp.9-14, 1995 Feb.
   Not a guideline

9. Latreille J, Stewart D, Laberge F, Hoskins P, Rusthoven J, McMurtrie E, Warr D, Yelle L, Walde D, Shepherd F. Dexamethasone improves the efficacy of granisetron in the first 24 h following high-dose cisplatin chemotherapy. EBM Reviews - Cochrane Central Register of Controlled Trials Supportive care in cancer: official journal of the Multinational Association of Supportive Care in Cancer. 3(5):307-12, 1995 Sep.
   Not a guideline

Database: **EMBASE** <1980 to 2010 Week 04>
Search Strategy:
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1 practice guideline/ (113062)
2 consensus development/ or good clinical practice/ or nursing care plan/ (8362)
3 clinical pathway/ (1703)
4 (guideline: or (standard adj2 care) or consensus).mp. (231948)
5 or/1-4 (237030)
6 "nausea and vomiting"/ or chemotherapy induced emesis/ or nausea/ or radiation induced emesis/ or retching/ or vomiting/ (125296)
7 exp neoplasm/ or exp benign tumor/ or exp congenital tumor/ or exp experimental neoplasm/ or exp fetal tumor/ or exp incidentaloma/ or exp malignant neoplastic disease/ or exp metastasis/ or exp mixed tumor/ or exp "neoplasms of uncertain behavior"/ or exp neoplasms subdivided by anatomical site/ or exp "oncogenesis and malignant transformation"/ or exp paraneoplastic syndrome/ or exp "precancer and cancer-in-situ"/ or exp pseudo-meigs syndrome/ or exp tumor/ or exp tumor engraftment/ or exp tumor growth/ or exp tumor necrosis/ or exp tumor recurrence/ or exp tumor regression/ or exp tumor spheroid/ (1554944)
8 exp antineoplastic agent/ (783297)
9 7 or 8 (1957866)
10 6 and 9 (50185)
11 exp antiemetic agent/ (96594)
12 exp psychotropic agent/ or exp mood stabilizer/ or exp nootropic agent/ or exp psychedelic agent/ or exp psychostimulant agent/ or exp tranquilizer/ (391644)
13 11 or 12 (429104)
14 10 and 13 (10390)
15 limit 14 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>) (683)
16 5 and 15 (36)
17 from 16 keep 28-30,33-34,36 (6)
18 from 17 keep 1-6 (6)
19 from 18 keep 1-6 (6)

1. Chow KS, Iceton S. Evaluation of a diary card for tailoring antiemetic therapy for children with cancer. Canadian Journal of Hospital Pharmacy.1999
   Not a guideline

2. Dupuis L.L., Lau R., Greenberg M.L. Effectiveness of strategies for preventing acute antineoplastic-induced nausea and vomiting in children with acute lymphoblastic leukemia. Can. J. Hosp. Pharm. 1999
Not a guideline

3. Andria ML, Arens JF, Baker DK Jr, Bolinger AM, Briones GR, Chen JJ, Chin A, Coursin DB, Diener KM, Dranitsaris G, Farrington J, Frazier JL, Gandara DR, Goldspiel BR, Golembiewski JA, Grunberg SM, Henry DW, Hutson PR, McCauley DL, McKenna EF, Perez EA, Philip BK, Shirk MB, Slimowitz R, Solimando DA Jr, Springman SR, Stump LS, Taylor T, Wagner BK, Walton SM. ASHP Therapeutic Guidelines on the Pharmacologic Management of Nausea and Vomiting in Adult and Pediatric Patients Receiving Chemotherapy or Radiation Therapy or Undergoing Surgery. American Journal of Health-System Pharmacy. 1999;56(8):729-64.
Located in above Medline search

4. Busch AF, Pearce MJ, Allen B, Begg EJ. Compliance with guidelines results in appropriate ondansetron prescribing at Christchurch Hospital. New Zealand Medical Journal. 1996
Not a guideline (focus on ondansetron)

5. Berard CM, Mahoney CD. Cost-reducing treatment algorithms for antineoplastic drug-induced nausea and vomiting. American Journal of Health-System Pharmacy. Language EnglishYear of Publication 1995
Not a guideline

6. Hahlen K, Quintana E, Pinkerton CR, Cedar E. A randomized comparison of intravenously administered granisetron versus chlorpromazine plus dexamethasone in the prevention of ifosfamide-induced emesis in children. J. PEDIATR. 1995
Not a general guideline (focus is ifosfamide; includes children)

Database: **CINHAL** (EBSCO Publishing) <January 12, 2010>
Search Strategy and Results: [reformatted]
Results

S8	S6 or S7	Interface – EBSCOhost - Advanced Search Database - CINAHL 6
S7	S1 and S2	Limiters - Age Groups: Infant, Newborn 0-1 month, Infant, 1-23 months, Child, Preschool 2-5 years, Child, 6-12 years, Adolescence, 13-18 years; Publication Type: Care Plan, Practice Guidelines, Protocol Interface – EBSCOhost - Advanced Search Database - CINAHL 4
S6	S4 and S5	Interface – EBSCOhost - Advanced Search Database - CINAHL 5
S5	(MH "Practice Guidelines") or (MH "Protocols+")	Interface – EBSCOhost - Advanced Search Database - CINAHL 31129
S4	S1 and S2	Limiters - Age Groups: Infant, Newborn 0-1 month, Infant, 1-23 months, Child, Preschool 2-5 years, Child, 6-12 years, Adolescence, 13-18 years Interface – EBSCOhost - Advanced Search Database - CINAHL 96
S3	S1 and S2	Interface – EBSCOhost - Advanced Search Database - CINAHL 713
S2	(MH "Neoplasms+") or (MH "Antineoplastic Agents+")	Interface – EBSCOhost - Advanced Search Database - CINAHL 124052
S1	(MH "Nausea") or (MH "Vomiting") or (MH "Nausea and Vomiting")	Interface – EBSCOhost - Advanced Search Database - CINAHL 3308

EBSCO Publishing Citation Format: Vancouver/ICMJE:

References

1. ASHP reports. ASHP therapeutic guidelines on the pharmacologic management of nausea and vomiting in adult and pediatric patients receiving chemotherapy or radiation therapy or undergoing surgery. American Journal of Health-System Pharmacy [serial on the Internet].
(1999, Apr 15), [cited January 12, 2010]; 56(8): 729-764. Available from: CINAHL.
Located in above Medline search

2. Carpenter C, Noonan C, Duane N, Maloney P, Stebbins K. Congenital infantile fibrosarcoma: a case study. Neonatal Network [serial on the Internet]. (1998, Apr), [cited January 12, 2010]; 17(3): 15-24. Available from: CINAHL.
   Not applicable

3. Cook J, Gallagher A. Evaluation of an anti-emetic protocol. Paediatric Nursing [serial on the Internet]. (1996, Sep), [cited January 12, 2010]; 8(7): 21-23. Available from: CINAHL.
   Selected for consideration

4. Unger J. Pediatric migraine: clinical pearls in diagnosis and therapy. Headache & Pain: Diagnostic Challenges, Current Therapy [serial on the Internet]. (2006, Sep), [cited January 12, 2010]; 17(3): 104-113. Available from: CINAHL.
   Not applicable

5. Walker P, Biglin K, Constance T, Bhambhani K, Sims-McCallum R. Promoting the use of oral ondansetron in children receiving cancer chemotherapy. American Journal of Health-System Pharmacy [serial on the Internet]. (2001, Apr), [cited January 12, 2010]; 58(7): 598-602. Available from: CINAHL.
   Not applicable

6. Kearney N, Miller M, Maguire R, Dolan S, MacDonald R, McLeod J, et al. WISECARE+: results of a European study of a nursing intervention for the management of chemotherapy-related symptoms. European Journal of Oncology Nursing [serial on the Internet]. (2008, Dec), [cited January 12, 2010]; 12(5): 443-448. Available from: CINAHL.
   Not applicable

2. LOCAL, PROVINCIAL, NATIONAL AND INTERNATIONAL WEBSITES SEARCHED FOR GUIDELINES

CANADIAN Sources – Regional

BC Cancer Agency(BCCA) **- not a guideline**
Alberta Health Services (AHS) **- no applicable guideline found**
Cancer Care Manitoba (CCMB) **- no applicable guideline found**
Saskatchewan Cancer Agency **- no applicable guideline found**
Cancer Care Ontario (CCO) Practice Guideline Initiative

1. Cancer Care Ontario. Management of chemotherapy-induced nausea and vomiting. Revised April 2004. Retrieved January 26, 2010. Available from URL: http://www.cancercare.on.ca/search/default.aspx?q=nausea%20and%20vomiting&type=0,6-76,6-40484|-1,1377-78
   Selected for consideration

Ontario Guidelines Advisory Committee (GAC) Recommended Clinical Practice Guidelines **- not a guideline**
Registered Nurses Association of Ontario (RNAO) **- no applicable guideline found**
Direction de la lutte contre le cancer - Ministère de la santé et des services sociaux du Québec **- no applicable guideline found**

The Hospital for Sick Children Intranet
Dupuis L and Greenberg M. Antiemetic Selection for Children Receiving Antineoplastics and/or Radiotherapy. In: **The Hospital for Sick Children 2008-2009** SickKids Drug Handbook and Formulary.
Selected for consideration

CANADIAN Sources - National

Canadian Agency for Drugs and Technology in Health (CADTH) **- no applicable guideline found**
Canadian Medical Association (CMA) Infobase **- guideline for cisplatin but not paediatric**
Society of Obstetricians & Gynecologists of Canada (SOGC) Oncology **- not applicable**
Canadian Task Force on Preventive Health Care (CTFPHC) **- no applicable guideline found**
Canadian Breast Cancer Network **- no applicable guideline found**

USA Sources

National Guideline Clearinghouse (NGC)

1. Editorial Board Palliative Care: Practice Guidelines. Nausea and vomiting. Utrecht, The Netherlands: Association of Comprehensive Cancer Centres (ACCC); 2006 Jan 12. 28 p. [73 references]
   http://www.oncoline.nl/index.php?pagina=/richtlijn/item/pagina.php&richtlijn_id=549
   Selected for consideration; excluded because focus is not on CINV

Food and Drug Administration (FDA)

No applicable guideline found

American Society of Clinical Oncology (ASCO)

ASCO Update 2006 Guidelines.

1. Kris MG, Hesketh PJ, Somerfield MR, Feyer P, Clark-Snow R, Koeller JM, Morrow GR, Chinnery LW, Chesney MJ, Gralla RJ, Grunberg SM. American Society of Clinical Oncology Guidelines for Antiemetics in Oncology: Update 2006. Journal of Clinical Oncology 2006;24(18):2932-47.
   http://jco.ascopubs.org/cgi/reprint/24/18/2932
   Selected for consideration

National Cancer Institute (NCI)

No applicable guideline found

National Comprehensive Cancer Network (NCCN)

1. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology. Antiemesis. V4.2009. [Cited January 31, 2010]. Available from URL:
   http://www.nccn.org/professionals/physician_gls/PDF/antiemesis.pdf
   Selected for consideration

Translating Research Into Practice (TRIP) Guidelines & Technology Assessments

Projects in early-mid production phase (pre-review)

1. Agency for Healthcare Research and Quality: Consideration of Evidence on Antiemetic Drugs for Nausea and Vomiting Associated with Chemotherapy or Radiation Therapy. [Cited January 31, 2010]. Available from URL: http://www.ahrq.gov/clinic/techix.htm
   Not available yet (last cited: January 31, 2010)

Oncology Nursing Society

1. Tipton JM, McDaniel RW. Barbour L, Johnston MP, Kayne M. LeRoy P, Ripple ML. Putting Evidence Into Practice: Evidence-Based Interventions to Prevent, Manage, and Treat Chemotherapy-Induced Nausea and Vomiting. Clinical Journal of Oncology Nursing. 2007;11(1):69-78.
   Selected for consideration

Institute for Clinical Systems Improvement (ICSI)

No applicable guideline found

American Cancer Society

1. Morrow GR. Chemotherapy-Related Nausea and Vomiting: Etiology and Management CA Cancer J Clin 1989;39;89-104.
   Selected for consideration; excluded because considered out of date

INTERNATIONAL Sources

National Library of Guidelines (UK) NLG

No applicable guideline found

Cancer Backup (UK)

No applicable guideline found

National Institute for Clinical Evidence (NICE)

No applicable guideline found

New Zealand Guidelines Group

No applicable guideline found

Scottish Intercollegiate Guidelines Network (SIGN)
No applicable guideline found

National Health and Medical Research Council of Australia (NHMRC)
No applicable guideline found

Agency for Quality in Medicine **(German)**
No applicable guideline found in English

Finnish Medical Society Duodecim
No applicable guideline found

The Cochrane library
http://www.mrw.interscience.wiley.com/cochrane/cochrane_search_fs.html?mode=startsearch&products=all&unitstatus=none&opt1=OR&Query2=&zones2=article-title&opt2=AND&Query3=&zones3=author&opt3=AND&Query4=&zones4=abstract&opt4=AND&Query5=&zones5=tables&FromYear=&ToYear=&Query1=chemotherapy+vomit&zones1=%28article-title%2Cabstract%2Ckeywords%29

1. Phillips RS, Gibson F, Gopaul S, Light K, Craig JV, Pizer B. Antiemetic medication for prevention and treatment of chemotherapy induced nausea and vomiting in childhood (Protocol). *Cochrane Database of Systematic Reviews* 2009, Issue 2. Art. No.: CD007786. DOI: 10.1002/14651858.CD007786.
   Located in above ALL EBM Reviews search

2. Billio A, Morello E, Clarke MJ. Serotonin receptor antagonists for highly emetogenic chemotherapy in adults. *Cochrane Database of Systematic Reviews* 2010, Issue 1. Art. No.: CD006272. DOI: 10.1002/14651858.CD006272.pub2.
   Not a guideline

The Joanna Briggs Institute (Australia)

Multinational Association for Supportive Care in Cancer
1. Kris MG, Hesketh PJ, Herrstedt J, Rittenberg C, Einhorn LH, Grunberg S, Koeller J, Olver I, Borjeson S, Ballatori E. Consensus proposals for the prevention of acute and delayed vomiting and nausea following high-emetic-risk chemotherapy. Supportive Care in Cancer. 2005;13:85-96
   Selected for consideration

2. Herrstedt J, Koeller JM, Roila F, Hesketh PJ, Warr D, Rittenberg C, Dicato M. Acute emesis: moderately emetogentic chemotherapy. Supportive Care in Cancer. 2005;13:97-103.
   Selected for consideration

3. Roila F, Feyer P, Maranzano E, Olver I, Clark-Snow R, Warr D, Molassiotis A. Antiemetics in children receiving chemotherapy.Supportive Care in Cancer. 2005;13(2):129-31.
   Selected for consideration

4. Tonato M, Clark-Snow RA, Osaba D, Del Favero A, Ballatori E, Borjeson S. Emesis induced by low or minimal emetic risk chemotherapy. Supportive Care Cancer. 2005;13:109-111.
   Selected for consideration

5. Antiemetic Subcommittee of the Multinational Association of Supportive Care in Cancer (MASCC). Prevention of chemotherapy- and radiotherapy-induced emesis: results of the 2004 Perugia International Antiemetic Consensus Conference. 2006;17:20-28.
   Selected for initial consideration; excluded because it is a summary document

FRENCH Language Sources

Direction de la lutte contre le cancer - Ministère de la Santé et des Services sociaux du Québec
No applicable guideline found

SOR: Standards, Options et Recommandations
No applicable guideline found

Haute Autorité de Santé (HAS)
No applicable guideline found

CHU de Rouen - Catalogue & Index des Sites Médicaux Francophones (CISMef)

1. Durand JP, Madelaine I, Scotté F. Recommandations pour la prévention et le traitement des nausées et vomissements induits par la chimiothérapie. Bulletin du Cancer. 2009;96(10):951-960.
   Not a guideline.

2. OMéDIT Centre Observatoire des Médicaments, des Dispositifs médicaux et des innovations Thérapeutiques de la région Centre. http://www.omedit-centre.fr/fichiers/upload/Fiche%20Antiemetiques.pdf
   Selected for consideration

3. ONCOLOR Réseau de santé en cancérologie de la région Lorraine **France 2003**
   http://www.oncolor.org/referentiels/support/anti_nausee_acc.htm
   Selected for consideration
4. Ministère de la Santé et des Services sociaux du Québec CEPO - Comité de l'évolution des pratiques en oncologie Canada 2008 Utilisation de l'aprépitant (EmendMC) pour la prévention des nausées et des vomissements consécutifs à l'administration d'une chimiothérapie émétisante. CEPO - Juillet 2008
   Selected for consideration

Bibliothèque médicale AF Lemanissier **– no applicable guideline found**
Agence Française de Séculrité Sanitaire des Produits de Santé (AFSSAPS) **- no applicable guideline found**

3. GREY LITERATURE SEARCH

Google Search terms:
"prevention of acute chemotherapy induced nausea and vomiting in children"

1. Dupuis LL, Nathan PC. Options for the prevention and management of acute chemotherapy-induced nausea and vomiting in children. Paediatric Drugs. 2003;5(9):597-613. Retrieved February 6, 2010. Available from URL: http://www.ncbi.nlm.nih.gov/pubmed/12956617
   Selected for consideration

2. Schore RJ, Williams D. (April 21, 2009). Chemotherapy- Induced Nausea and Vomiting. eMedicine. Retrieved February 6, 2010. Available from URL: http://emedicine.medscape.com/article/1355706-overview
   Selected for consideration

3. Schnell FM. Chemotherapy-induced nausea and vomiting: the importance of acute antiemetic control. The Oncologist. 2003;8:187-198. Retrieved February 6, 2010. Available from URL: http://theoncologist.alphamedpress.org/cgi/reprint/8/2/187
   Selected for initial consideration; excluded because considered out of date

4. National Cancer Institute. Prevention of acute/delayed emesis. Retrieved February 6, 2010. Available from URL: http://www.cancer.gov/cancertopics/pdq/supportivecare/nausea/HealthProfessional/page7
   Not a guideline

5. Phillips RS, Gibson F, Gopaul S, Light K, Craig JV, Pizer B.Antiemetic medication for prevention and treatment of chemotherapy induced nausea and vomiting in childhood. EBM Reviews - Cochrane Database of Systematic Reviews Cochrane Childhood Cancer Group Cochrane Database of Systematic Reviews. 4, 2009. Retrieved February 6, 2010. Available from URL: http://mrw.interscience.wiley.com/cochrane/clsysrev/articles/CD007786/frame.html
   Obtained from above website search; Not a guideline

6. Wiser W, Berger A. Practical management of chemotherapy-induced nausea and vomiting. Oncology. 2005;19(5). Retrieved February 6, 2010. Available from URL: http://www.cancernetwork.com/binary_content_servlet
   Selected for initial consideration; excluded because considered out of date

7. Antonarakis ES, Evans JL, Heard GF, Noonan LM, Pizer BL, Hain RD. Prophylaxis of acute chemotherapy-induced nausea and vomiting in children with cancer: what is the evidence? Pediatric Blood and Cancer. 2004 Nov;43(6):651-8.
Not a guideline

Other Resources

1. Children's Oncology Group (COG). Supportive Care Guidelines. June 20, 2008.
Selected for initial consideration; excluded because it does not address acute AINV

Appendix B – AGREE Scores of Guidelines Reviewed for Possible Adaptation

Antonarakis, 2004

AGREE Inter-Rater Score Spreadsheet Blank (Draft CAN-ADAPTE Kit V1.0 Sept. 2008: CPACC, Queen's University)

Instructions:
1. Enter the Rater number into column C
2. Enter the scores for each rater in their respective rows
3. Domain scores are automatically calculated based on the number of raters (cell C20)
4. Colour code the scores to provide visual aid (ie. 1,2 = red; 3,4 = blue)

	Question >		1	2	3	Scope & Purpose Score	4	5	6	7	Stakeholder Involvement Score	8	9	10	11	12	13	14	Rigor Score	15	16	17	18	Clarity & Presentation Score	19	20	21	Applicability Score	22	23	Editorial Independence Score	recommend?
Guideline	RATERS					TOTAL					TOTAL								TOTAL					TOTAL				TOTAL			TOTAL	
ratings	Rater #	1	3	1	2	6	2	1	1	1	5	4	4	1	3	4	1	1	18	4	4	4	1	13	3	No sco	1	4	1	1	2	R
	Rater #	2	4	4	3	11	1	2	3	2	8	4	4	4	3	4	3	1	23	3	3	3	2	11	3	3	3	9	3	1	4	R
	Rater #	3	4	4	4	12	1	1	3	2	7	3	3	4	2	2	1	1	16	2	3	3	1	9	1	1	2	4	4	1	5	WNR
	Rater #	5	4	4	4	12	1	1	3	1	6	4	4	4	4	4	3	1	24	4	3	4	1	12	1	4	3	8		1	1	U
	Rater #	6	4	4	4	12	1	1	4	1	7	4	4	4	4	3	1	1	21	4	3	4	3	14	2	2	3	7	1	1	2	R
	Rater #	7	4	3	4	11	1	1	1	1	4	4	3	4	4	4	1	1	21	3	4	4	1	12	1	1	2	4	No s	1	1	R
	Rater #					0					0								0					0				0			0	
	Rater #					0					0								0					0				0			0	
	Rater #					0					0								0					0				0			0	
	# of Raters=	6			Obtained Score	64				Obt	37							Obtained Score	123				Obtained Score	71			Obtained Score	36		Obtained Score	15	
					Minimal Score	18				Mini	24							Minimal Score	42				Minimal Score	24			Minimal Score	18		Minimal Score	12	
					Maximum Score	72				Max	96							Maximum Score	168				Maximum Score	96			Maximum Score	72		Maximum Score	48	
					Obtained-Minimal	46				Obt	13							Obtained-Minimal	81				Obtained-Minimal	47			Obtained-Minimal	18		Obtained-Minimal	3	
					Maximum-Minimal	54				Max	72							Maximum-Minimal	126				Maximum-Minimal	72			Maximum-Minima	54		Maximum-Minimal	36	
STANDARDIZED DOMAIN SCORES						85					18								64					65				33			8	

Note: DOMAIN Score Calculations

Formula: (Obtained Score - Minimum Possible Score)/(Maximum Possible Score - Minimum Possible Score) x 100 (expressed as percentage)
NOTE: The score is modified in each case, for each domain, to REFLECT NUMBER OF RATERS

TIP: Colour coding the cells in RED and BLUE according to AGREEMENT (3,4) or DISAGREEMENT(1,2) provides a useful visual aid to guide discussion between raters . It highlights where raters essentially have consensus and where there are specific elements of the guideline that may need some clarification re: rater's individual interpretation and/or possible further review of source evidence

Andria, 1999

AGREE Inter-Rater Score Spreadsheet Blank (Draft CAN-ADAPTE Kit V1.0 Sept. 2008: CPACC, Queen's University)

Instructions:
1. Enter the Rater number into column C
2. Enter the scores for each rater in their respective rows
3. Domain scores are automatically calculated based on the number of raters (cell C20)
4. Colour code the scores to provide visual aid (ie. 1,2 = red; 3,4 = blue)

	Question >		1	2	3	Scope & Purpose Score	4	5	6	7	Stakeholder Involvement Score	8	9	10	11	12	13	14	Rigor Score	15	16	17	18	Clarity & Presentation Score	19	20	21	Applicability Score	22	23	Editorial Independence Score	recommend?
Guideline	RATERS					TOTAL					TOTAL								TOTAL					TOTAL				TOTAL			TOTAL	
ratings	Rater #	1	4	1	4	9	4	1	4	1	10	3	1	1	4	3	3	3	16	4	4	4	2	14	1	1	1	3	1	1	2	WNR
	Rater #	2	4	4	4	12	4	3	4	2	13	4	4	4	4	3	4	3	26	3	3	3	3	12	3	4	3	10	1	3	4	R
	Rater #	6	4	4	4	12	4	1	4	1	10	4	4	4	3	4	4	4	27	4	4	4	4	16	1	4	1	6	1	1	2	R
	Rater #	7	4	4	4	12	3	1	2	1	7	4	4	4	4	4	4	1	25	4	4	3	2	13	2	4	1	7	1	2	3	R
	Rater #					0					0								0					0				0			0	
	Rater #					0					0								0					0				0			0	
	Rater #					0					0								0					0				0			0	
	Rater #					0					0								0					0				0			0	
	# of Raters=	4			Obtained Score	24				Obtained Score	17							Obtained Score	52				Obtained Score	29			Obtained Score	13		Obtained Score	5	
					Minimal Score	12				Minimal Score	16							Minimal Score	28				Minimal Score	16			Minimal Score	12		Minimal Score	8	
					Maximum Score	48				Maximum Score	64							Maximum Score	112				Maximum Score	64			Maximum Score	48		Maximum Score	32	
					Obtained-Minimal	12				Obtained-Minimal	1							Obtained-Minimal	24				Obtained-Minimal	13			Obtained-Minimal	1		Obtained-Minimal	-3	
					Maximum-Minimal	36				Maximum-Minimal	48							Maximum-Minimal	84				Maximum-Minimal	48			Maximum-Minimal	36		Maximum-Minimal	24	
STANDARDIZED DOMAIN SCORES						33					2								29					27				3			-13	

Note: DOMAIN Score Calculations

Formula: (Obtained Score - Minimum Possible Score)/(Maximum Possible Score - Minimum Possible Score) x 100 (expressed as percentage)
NOTE: The score is modified in each case, for each domain, to REFLECT NUMBER OF RATERS

TIP: Colour coding the cells in RED and BLUE according to AGREEMENT (3,4) or DISAGREEMENT(1,2) provides a useful visual aid to guide discussion between raters . It highlights where raters essentially have consensus and where there are specific elements of the guideline that may need some clarification re: rater's individual interpretation and/or possible further review of source evidence

CCO, 2004

AGREE Inter-Rater Score Spreadsheet Blank (Draft CAN-ADAPTE Kit V1.0 Sept. 2008: CPACC, Queen's University)

Instructions:
1. Enter the Rater number into column C
2. Enter the scores for each rater in their respective rows
3. Domain scores are automatically calculated based on the number of raters (cell C20)
4. Colour code the scores to provide visual aid (ie. 1,2 = red; 3,4 = blue)

	Question >		1	2	3	Scope & Purpose Score	4	5	6	7	Stakeholder Involvement Score	8	9	10	11	12	13	14	Rigor Score	15	16	17	18	Clarity & Presentation Score	19	20	21	Applicability Score	22	23	Editorial Independence Score	recommend?
Guideline	RATERS					TOTAL					TOTAL								TOTAL					TOTAL				TOTAL			TOTAL	
ratings	Rater #	1	3	1	2	6	1	1	1	1	4	1	1	1	2	1	1	1	8	4	3	4	1	12	1	1	1	3	1	1	2	R
	Rater #	2	3	3	1	7	1	2	2	1	6	1	1	1	2	2	1	1	9	2	2	2	1	7	1	1	1	3	2	1	3	WNR
	Rater #	3	3	1	1	5	1	1	1	1	4	1	1	1	1	2	1	1	8	2	2	2	2	8	1	1	1	3	3	1	4	WNR
	Rater #	4	3	1	1	5	1	1	1	1	4	1	1	3	2	4	1	1	13	4	3	4	1	12	2	3	1	6	3	3	6	WNR
	Rater #					0					0								0					0				0			0	
	Rater #					0					0								0					0				0			0	
	Rater #					0					0								0					0				0			0	
	Rater #					0					0								0					0				0			0	
	# of Raters=	4			Obtained Score	23				Obtained Score	18							Obtained Score	38				Obtained Score	39			Obtained Score	15		Obtained Score	15	
					Minimal Score	12				Minimal Score	16							Minimal Score	28				Minimal Score	16			Minimal Score	12		Minimal Score	8	
					Maximum Score	48				Maximum Score	64							Maximum Score	112				Maximum Score	64			Maximum Score	48		Maximum Score	32	
					Obtained-Minimal	11				Obtained-Minimal	2							Obtained-Minimal	10				Obtained-Minimal	23			Obtained-Minimal	3		Obtained-Minimal	7	
					Maximum-Minimal	36				Maximum-Minimal	48							Maximum-Minimal	84				Maximum-Minimal	48			Maximum-Minimal	36		Maximum-Minimal	24	
STANDARDIZED DOMAIN SCORES						31					4								12					48				8			29	

Note: DOMAIN Score Calculations

Formula: (Obtained Score - Minimum Possible Score)/(Maximum Possible Score - Minimum Possible Score) x 100 (expressed as percentage)
NOTE: The score is modified in each case, for each domain, to REFLECT NUMBER OF RATERS

TIP: Colour coding the cells in RED and BLUE according to AGREEMENT (3,4) or DISAGREEMENT(1,2) provides a useful visual aid to guide discussion between raters . It highlights where raters essentially have consensus and where there are specific elements of the guideline that may need some clarification re: rater's individual interpretation and/or possible further review of source evidence

Cook, 1996

AGREE Inter-Rater Score Spreadsheet Blank (Draft CAN-ADAPTE Kit V1.0 Sept. 2008: CPACC, Queen's University)

Instructions:
1. Enter the Rater number into column C
2. Enter the scores for each rater in their respective rows
3. Domain scores are automatically calculated based on the number of raters (cell C20)
4. Colour code the scores to provide visual aid (ie. 1,2 = red; 3,4 = blue)

	Question >		1	2	3	Scope & Purpose Score	4	5	6	7	Stakeholder Involvement Score	8	9	10	11	12	13	14	Rigor Score	15	16	17	18	Clarity & Presentation Score	19	20	21	Applicability Score	22	23	Editorial Independence Score	recommend?
Guideline	RATERS					TOTAL					TOTAL								TOTAL					TOTAL				TOTAL			TOTAL	
ratings	Rater #	1	not a guideline			0					0								0					0				0			0	
	Rater #	2	3	3	3	9	1	3	3	3	10	1	1	1	2	1	1	1	8	2	1	2	1	6	1	1	1	3	1	2	3	WNR
	Rater #	3	3	3	3	9	1	1	1	1	4	1	1	1	1	1	1	1	7	2	2	1	1	6	1	1	1	3	4	1	5	WNR
	Rater #	7	1	2	2	5	1	1	1	1	4	1	1	2	1	1	1	1	8	2	2	2	1	7	1	1	3	5	1	1	2	WNR
	Rater #					0					0								0					0				0			0	
	Rater #					0					0								0					0				0			0	
	Rater #					0					0								0					0				0			0	
	# of Raters=	4			Obtained Score	23				Obtained Score	18							Obtained Score	23				Obtained Score	19			Obtained Score	11		Obtained Score	10	
					Minimal Score	12				Minimal Score	16							Minimal Score	28				Minimal Score	16			Minimal Score	12		Minimal Score	8	
					Maximum Score	48				Maximum Score	64							Maximum Score	112				Maximum Score	64			Maximum Score	48		Maximum Score	32	
					Obtained-Minimal	11				Obtained-Minimal	2							Obtained-Minimal	-5				Obtained-Minimal	3			Obtained-Minimal	-1		Obtained-Minimal	2	
					Maximum-Minimal	36				Maximum-Minimal	48							Maximum-Minimal	84				Maximum-Minimal	48			Maximum-Minimal	36		Maximum-Minimal	24	
STANDARDIZED DOMAIN SCORES						31					4								-6					6				-3			8	

Note: DOMAIN Score Calculations

Formula: (Obtained Score - Minimum Possible Score)/(Maximum Possible Score - Minimum Possible Score) x 100 (expressed as percentage)
NOTE: The score is modified in each case, for each domain, to REFLECT NUMBER OF RATERS

TIP: Colour coding the cells in RED and BLUE according to AGREEMENT (3,4) or DISAGREEMENT(1,2) provides a useful visual aid to guide discussion between raters . It highlights where raters essentially have consensus and where there are specific elements of the guideline that may need some clarification re: rater's individual interpretation and/or possible further review of source evidence

Abla, 2010

AGREE Inter-Rater Score Spreadsheet Blank (Draft CAN-ADAPTE Kit V1.0 Sept. 2008: CPACC, Queen's University)

Instructions:
1. Enter the Rater number into column C
2. Enter the scores for each rater in their respective rows
3. Domain scores are automatically calculated based on the number of raters (cell C20)
4. Colour code the scores to provide visual aid (ie. 1,2 = red; 3,4 = blue)

	Question >		1	2	3	Scope & Purpose Score	4	5	6	7	Stakeholder Involvement Score	8	9	10	11	12	13	14	Rigor Score	15	16	17	18	Clarity & Presentation Score	19	20	21	Applicability Score	22	23	Editorial Independence Score	*recommend?*
Guideline	*RATERS*					*TOTAL*					*TOTAL*								TOTAL					TOTAL				TOTAL			TOTAL	
	Rater #	2	2	2	3	7	2	2	3	2	9	2	1	2	3	2	2	1	13	3	2	3	3	11	2	3	1	6	2	1	3	WNR
ratings	Rater #	3	2	2	3	7	1	1	2	1	5	2	2	1	2	2	1	1	11	2	3	3	2	10	1	2	1	4	4	4	8	WNR
	Rater #	4	2	4	4	10	1	1	3	1	6	2	1	2	1	2	1	1	10	4	3	4	1	12	1	1	1	3	1	1	2	R
	Rater #	6	4	4	4	12	1	1	2	1	5	1	1	1	1	1	1	1	7	3	3	4	4	14	1	1	1	3	1	1	2	U
	Rater #					0					0								0					0				0			0	
	Rater #					0					0								0					0				0			0	
	Rater #					0					0								0					0				0			0	
	Rater #					0					0								0					0				0			0	
	# of Raters=	4			Obtained Score	29				Obtained Score	16							Obtained Score	28				Obtained Score	36			Obtained Score	10		Obtained Score	12	
					Minimal Score	12				Minimal Score	16							Minimal Score	28				Minimal Score	16			Minimal Score	12		Minimal Score	8	
					Maximum Score	48				Maximum Score	64							Maximum Score	112				Maximum Score	64			Maximum Score	48		Maximum Score	32	
					Obtained-Minimal	17				Obtained-Minimal	0							Obtained-Minimal	0				Obtained-Minimal	20			Obtained-Minimal	-2		Obtained-Minimal	4	
					Maximum-Minimal	36				Maximum-Minimal	48							Maximum-Minimal	84				Maximum-Minimal	48			Maximum-Minimal	36		Maximum-Minimal	24	
STANDARDIZED DOMAIN SCORES						47					0								0					42				-6			17	

Note: DOMAIN Score Calculations

Formula: (Obtained Score - Minimum Possible Score)/(Maximum Possible Score - Minimum Possible Score) x 100 (expressed as percentage)
NOTE: The score is modified in each case, for each domain, to REFLECT NUMBER OF RATERS

TIP: Colour coding the cells in RED and BLUE according to AGREEMENT (3,4) or DISAGREEMENT(1,2) provides a useful visual aid to guide discussion between raters . It highlights where raters essentially have consensus and where there are specific elements of the guideline that may need some clarification re: rater's individual interpretation and/or possible further review of source evidence

Dupuis, 2003

Instructions:
1. Enter the Rater number into column C
2. Enter the scores for each rater in their respective rows
3. Domain scores are automatically calculated based on the number of raters (cell C20)
4. Colour code the scores to provide visual aid (ie. 1,2 = red; 3,4 = blue)

	Question >		1	2	3	Scope & Purpose Score	4	5	6	7	Stakeholder Involvement Score	8	9	10	11	12	13	14	Rigor Score	15	16	17	18	Clarity & Presentation Score	19	20	21	Applicability Score	22	23	Editorial Independence Score	*recommend?*
Guideline	*RATERS*					*TOTAL*					*TOTAL*								TOTAL					TOTAL				TOTAL			TOTAL	
ratings	Rater #	2	3	3	3	9	2	2	3	2	9	1	1	1	3	3	3	1	13	3	3	3	2	11	2	2	1	5	4	4	8	WNR
	Rater #	3	3	3	3	10	1	1	2	1	5	1	2	1	2	3	1	1	11	3	3	3	2	11	1	1	1	3	4	4	8	WNR
	Rater #	4	4	4	4	12	2	1	3	2	8	4	2	3	2	4	3	2	20	4	4	4	2	14	2	2	1	5	4	4	8	SR
	Rater #	5	4	4	4	12	2	3	2	1	8	1	2	3	3	3	2	1	15	4	3	3	2	12	2	2	1	5	4	4	8	WNR
	Rater #					0					0								0					0				0			0	
	Rater #					0					0								0					0				0			0	
	Rater #					0					0								0					0				0			0	
	Rater #					0					0								0					0				0			0	
	# of Raters=	3			Obtained Score	34				Obtained Score	21							Obtained Score	46				Obtained Score	37			Obtained Score	13		Obtained Score	24	
					Minimal Score	9				Minimal Score	12							Minimal Score	21				Minimal Score	12			Minimal Score	9		Minimal Score	6	
					Maximum Score	36				Maximum Score	48							Maximum Score	84				Maximum Score	48			Maximum Score	36		Maximum Score	24	
					Obtained-Minimal	25				Obtained-Minimal	9							Obtained-Minimal	25				Obtained-Minimal	25			Obtained-Minimal	4		Obtained-Minimal	18	
					Maximum-Minimal	27				Maximum-Minimal	36							Maximum-Minimal	63				Maximum-Minimal	36			Maximum-Minimal	27		Maximum-Minimal	18	
STANDARDIZED DOMAIN SCORES						93					25								40					69				15			100	

Note: DOMAIN Score Calculations

Formula: (Obtained Score - Minimum Possible Score)/(Maximum Possible Score - Minimum Possible Score) x 100 (expressed as percentage)
NOTE: The score is modified in each case, for each domain, to REFLECT NUMBER OF RATERS

TIP: Colour coding the cells in RED and BLUE according to AGREEMENT (3,4) or DISAGREEMENT(1,2) provides a useful visual aid to guide discussion between raters . It highlights where raters essentially have consensus and where there are specific elements of the guideline that may need some clarification re: rater's individual interpretation and/or possible further review of source evidence

Kris, 2006

AGREE Inter-Rater Score Spreadsheet Blank (Draft CAN-ADAPTE Kit V1.0 Sept. 2008: CPACC, Queen's University)

Instructions:
1. Enter the Rater number into column C
2. Enter the scores for each rater in their respective rows
3. Domain scores are automatically calculated based on the number of raters (cell C20)
4. Colour code the scores to provide visual aid (ie. 1,2 = red; 3,4 = blue)

	Question >		1	2	3	Scope & Purpose Score	4	5	6	7	Stakeholder Involvement Score	8	9	10	11	12	13	14	Rigor Score	15	16	17	18	Clarity & Presentation Score	19	20	21	Applicability Score	22	23	Editorial Independence Score	recommend?
Guideline	RATERS					TOTAL					TOTAL								TOTAL					TOTAL				TOTAL			TOTAL	
ratings	Rater #	1	1	1	2	4	3	3	2	1	10	4	2	1	2	4	3	3	19	3	4	4	1	13	1	1	1	3	1	3	5	R
	Rater #	2	3	3	3	9	2	3	2	2	8	3	4	4	4	4	4	2	26	4	4	4	3	15	1	2	2	5	3	3	7	R
	Rater #	3	3	4	3	10	3	1	3	2	9	3	3	3	3	3	4	3	19	3	3	4	2	12	1	2	1	4	3	3	7	R
	Rater #	4	4	4	4	12	3	1	2	2	8	4	4	4	3	4	4	3	27	4	3	4	1	12	1	1	1	3	3	3	7	R
	Rater #	5	2	3	2	7	4	4	2	2	11	4	4	4	2	4	3	3	25	4	4	4	2	14	1	1	1	3	3	3	7	R
	Rater #	6	3	4	4	12	1	1	4	1	7	4	4	4	1	4	4	3	24	4	3	4	3	15	1	1	1	3	4	3	8	R
	Rater #	7	2	2	2	6	4	4	2	2	11	4	4	2	2	4	4	2	20	4	4	4	1	13	1	2	1	4	1	3	5	R
	Rater #					0					0								0					0				0			0	
	Rater #					0					0								0					0				0			0	
	Rater #					0					0								0					0				0			0	
	# of Raters=	7			Obtained Score	60				Obtained Score	64						Obtained Score		160				Obtained Score	94			Obtained Score	25		Obtained Score	46	
					Minimal Score	21				Minimal Score	28						Minimal Score		49				Minimal Score	28			Minimal Score	21		Minimal Score	14	
					Maximum Score	84				Maximum Score	112						Maximum Score		196				Maximum Score	112			Maximum Score	84		Maximum Score	56	
					Obtained-Minimal	39				Obtained-Minimal	36						Obtained-Minimal		111				Obtained-Minimal	66			Obtained-Minimal	4		Obtained-Minimal	32	
					Maximum-Minimal	63				Maximum-Minimal	84						Maximum-Minimal		147				Maximum-Minimal	84			Maximum-Minimal	63		Maximum-Minimal	42	
STANDARDIZED DOMAIN SCORES						62					43								76					79				6			76	

Note: DOMAIN Score Calculations

Formula: (Obtained Score - Minimum Possible Score)/(Maximum Possible Score - Minimum Possible Score) x 100 (expressed as percentage)
NOTE: The score is modified in each case, for each domain, to REFLECT NUMBER OF RATERS

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MASCC, 2005

AGREE Inter-Rater Score Spreadsheet Blank (Draft CAN-ADAPTE Kit V1.0 Sept. 2008: CPACC, Queen's University)

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4. Colour code the scores to provide visual aid (ie. 1,2 = red; 3,4 = blue)

	Question >		1	2	3	Scope & Purpose Score	4	5	6	7	Stakeholder Involvement Score	8	9	10	11	12	13	14	Rigor Score	15	16	17	18	Clarity & Presentation Score	19	20	21	Applicability Score	22	23	Editorial Independence Score	recommend?
Guideline	RATERS					TOTAL					TOTAL								TOTAL					TOTAL				TOTAL			TOTAL	
ratings	Rater #	1	3	2	2	7	?4	1	1	1	3		2	4	1	4	1	4	16	4	4	3	1	13	1	1	1	3	1	?1	1	R
	Rater #	2	3	3	2	8	4	2	2	2	10	3	3	3	3	3	2	2	19	2	3	2	1	8	2	2	1	5	3	1	4	WNR
	Rater #	7	2	3	3	8	2	1	1	1	5	2	3	2	2	3	2	1	15	4	3	3	1	11	1	2	1	4	1	1	2	WNR
	Rater #	4	3	3	3	9	1	1	1	1	4		3	2	1	1	3	1	11	1	1	1	1	4	1	1	1	3	3	1	4	R
	Rater #		3	2	2	7	1	1	1	1	4	4	4	3	2	3	3	1	20	3	2	3	1	9	1	1	1	3	3	1	4	R
	Rater #		4	4	3	11	2	1	1	1	5	4	4	4	3	4	4	1	24	2	2	2	1	7	1	1	2	4	3	1	4	WNR
	Rater #		2	2	2	6	1	1	1	1	4	1	1	2	1	3	4	1	13	1	1	1	1	4	1	2	1	4	3	1	4	WNR
	Rater #					0					0								0					0				0			0	
	# of Raters=	4			Obtained Score	56				Obtained Score	35						Obtained Score		118				Obtained Score	56			Obtained Score	26		Obtained Score	23	
					Minimal Score	12				Minimal Score	16						Minimal Score		28				Minimal Score	16			Minimal Score	12		Minimal Score	8	
					Maximum Score	48				Maximum Score	64						Maximum Score		112				Maximum Score	64			Maximum Score	48		Maximum Score	32	
					Obtained-Minimal	44				Obtained-Minimal	19						Obtained-Minimal		90				Obtained-Minimal	40			Obtained-Minimal	14		Obtained-Minimal	15	
					Maximum-Minimal	36				Maximum-Minimal	48						Maximum-Minimal		84				Maximum-Minimal	48			Maximum-Minimal	36		Maximum-Minimal	24	
STANDARDIZED DOMAIN SCORES						122					40								107					83				39			63	

Note: DOMAIN Score Calculations

Formula: (Obtained Score - Minimum Possible Score)/(Maximum Possible Score - Minimum Possible Score) x 100 (expressed as percentage)
NOTE: The score is modified in each case, for each domain, to REFLECT NUMBER OF RATERS

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NCCN, 2009

AGREE Inter-Rater Score Spreadsheet Blank (Draft CAN-ADAPTE Kit V1.0 Sept. 2008: CPACC, Queen's University)

Instructions:
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	Question >		1	2	3	Scope & Purpose Score	4	5	6	7	Stakeholder Involvement Score	8	9	10	11	12	13	14	Rigor Score	15	16	17	18	Clarity & Presentation Score	19	20	21	Applicability Score	22	23	Editorial Independence Score	recommend?
Guideline	RATERS					TOTAL					TOTAL								TOTAL					TOTAL				TOTAL			TOTAL	
ratings	Rater #	1	1	2	2	5	3	1	1	1	6	1	1	1	1	3	1	1	9	4		4	1	9	1	1	1	3	1	1	2	R
	Rater #	2	3	3	2	8	3	1	2	2	8	2	1	1	3	2	2	3	14	4	4	4	2	14	2	2	2	6	2	4	6	R
	Rater #	3	3	3	1	7	3	1	1	1	7	2	1	1	3	3	2	1	13	3	4	4	2	13	1	1	2	4	2	4	6	R, WITH SOM
	Rater #	5	2	3	2	7	3	1	2	2	8	2	2	2	2	3	3	3	17	4	4	4	2	14	1	1	3	5	2	4	6	R
	Rater #	6	4	4	4	12	3	1	3	1	8	1	1	3	3	2	1	4	15	4	4	4	4	16	1	1	1	3	1	1	2	R
	Rater #					0					0								0					0				0			0	
	# of Raters=	5			Obtained Score	39				Obtained Score	37							Obtained Score	68				Obtained Score	66			Obtained Score	21		Obtained Score	22	
					Minimal Score	15				Minimal Score	20							Minimal Score	35				Minimal Score	20			Minimal Score	15		Minimal Score	10	
					Maximum Score	60				Maximum Score	80							Maximum Score	140				Maximum Score	80			Maximum Score	60		Maximum Score	40	
					Obtained-Minimal	24				Obtained-Minimal	17							Obtained-Minimal	33				Obtained-Minimal	46			Obtained-Minimal	6		Obtained-Minimal	12	
					Maximum-Minimal	45				Maximum-Minimal	60							Maximum-Minimal	105				Maximum-Minimal	60			Maximum-Minimal	45		Maximum-Minimal	30	
STANDARDIZED DOMAIN SCORES						53					28								31					77				13			40	

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division betwe
- principles of e
- uncertain why

Note: DOMAIN Score Calculations

Formula: (Obtained Score - Minimum Possible Score)/(Maximum Possible Score - Minimum Possible Score) x 100 (expressed as percentage)
NOTE: The score is modified in each case, for each domain, to REFLECT NUMBER OF RATERS

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Schore, 2009

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	Question >		1	2	3	Scope & Purpose Score	4	5	6	7	Stakeholder Involvement Score	8	9	10	11	12	13	14	Rigor Score	15	16	17	18	Clarity & Presentation Score	19	20	21	Applicability Score	22	23	Editorial Independence Score	recommend?
Guideline	RATERS					TOTAL					TOTAL								TOTAL					TOTAL				TOTAL			TOTAL	
ratings	Rater #	2	2	2	2	6	2	2	2	2	8	2	2	2	3	2	2	1	14	1	2	1	2	6	1	1	1	3	2	1	3	WNR
	Rater #	4	2	1	2	5	1	1	1	1	4	1	1	3	1	1		1	8	4	2	4	1	11	1	1	1	3		4	4	WNR
	Rater #	5	2	2	2	6	1	1	1	1	4	1	1	2	2	2	1	1	10	2	2	2	1	7	1	1	1	3		4	4	WNR
	Rater #	7	1	1	1	3	1	1	1	1	4	1	1	1	1	1	1	1	7	2	2	1	1	6	1	1	1	3	1	1	2	WNR
	Rater #					0					0								0					0				0			0	
	Rater #					0					0								0					0				0			0	
	Rater #					0					0								0					0				0			0	
	Rater #					0					0								0					0				0			0	
	# of Raters=	4			Obtained Score	20				Obtained Score	20							Obtained Score	39				Obtained Score	30			Obtained Score	12		Obtained Score	13	
					Minimal Score	12				Minimal Score	16							Minimal Score	28				Minimal Score	16			Minimal Score	12		Minimal Score	8	
					Maximum Score	48				Maximum Score	64							Maximum Score	112				Maximum Score	64			Maximum Score	48		Maximum Score	32	
					Obtained-Minimal	8				Obtained-Minimal	4							Obtained-Minimal	11				Obtained-Minimal	14			Obtained-Minimal	0		Obtained-Minimal	5	
					Maximum-Minimal	36				Maximum-Minimal	48							Maximum-Minimal	84				Maximum-Minimal	48			Maximum-Minimal	36		Maximum-Minimal	24	
STANDARDIZED DOMAIN SCORES						22					8								13					29				0			21	

Note: DOMAIN Score Calculations

Formula: (Obtained Score - Minimum Possible Score)/(Maximum Possible Score - Minimum Possible Score) x 100 (expressed as percentage)
NOTE: The score is modified in each case, for each domain, to REFLECT NUMBER OF RATERS

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Tipton, 2007

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Instructions:
1. Enter the Rater number into column C
2. Enter the scores for each rater in their respective rows
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	Question >		1	2	3	Scope & Purpose Score	4	5	6	7	Stakeholder Involvement Score	8	9	10	11	12	13	14	Rigor Score	15	16	17	18	Clarity & Presentation Score	19	20	21	Applicability Score	22	23	Editorial Independence Score	recommend?
Guideline	RATERS					TOTAL					TOTAL								TOTAL					TOTAL				TOTAL			TOTAL	
	Rater #	1	4	2	3	9	1	1	3	1	6	4	4	3	3	3	1	1	19	4	4	4	3,2	12	1	1	1	3	1	1	2	R
ratings	Rater #	2	3	3	1	7	1	2	2	1	6	3	3	2	2	1	1	1	13	2	2	3	2	9	1	2	1	4	3	3	6	WNR
	Rater #	3	4	4	4	12	1	1	3	1	6	4	3	3	2	1	1	1	15	1	2	1	1	5	1	1	1	3	3	3	6	WNR
	Rater #	4	3	3	1	7	1	1	1	1	4	3	3	4	3	4	4	2	23	3	4	2	1	10	1	1	1	3	1	1	2	R
	Rater #	5	4	4	2	10	1	1	3	1	6	4	4	4	3	4	4	3	26	3	3	3	1	10	1	2	1	4	3	2	5	R
	Rater #	6	4	4	4	12	1	1	4	1	7	4	4	4	3	3	1	1	20	3	3	4	1	11	1	1	1	3	1	1	2	R
	Rater #	7	2	2	2	6	1	1	1	1	4	4	4	3	4	3	1	1	20	3	4	3	1	11	1	2	2	5	2	1	3	WNR
	Rater #					0					0								0					0				0			0	
	# of Raters=	6			Obtained Score	47				Obtained Score	27							Obtained Score	104				Obtained Score	47			Obtained Score	18		Obtained Score	18	
					Minimal Score	18				Minimal Score	24							Minimal Score	42				Minimal Score	24			Minimal Score	18		Minimal Score	12	
					Maximum Score	72				Maximum Score	96							Maximum Score	168				Maximum Score	96			Maximum Score	72		Maximum Score	48	
					Obtained-Minimal	29				Obtained-Minimal	3							Obtained-Minimal	62				Obtained-Minimal	23			Obtained-Minimal	0		Obtained-Minimal	6	
					Maximum-Minimal	54				Maximum-Minimal	72							Maximum-Minimal	126				Maximum-Minimal	72			Maximum-Minimal	54		Maximum-Minimal	36	
STANDARDIZED DOMAIN SCORES						54					4								49					32				0			17	

Note: DOMAIN Score Calculations

Formula: (Obtained Score - Minimum Possible Score)/(Maximum Possible Score - Minimum Possible Score) x 100 (expressed as percentage)
NOTE: The score is modified in each case, for each domain, to REFLECT NUMBER OF RATERS

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OnMeDit

AGREE Inter-Rater Score Spreadsheet Blank (Draft CAN-ADAPTE Kit V1.0 Sept. 2008: CPACC, Queen's University)

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	Question >		1	2	3	Scope & Purpose Score	4	5	6	7	Stakeholder Involvement Score	8	9	10	11	12	13	14	Rigor Score	15	16	17	18	Clarity & Presentation Score	19	20	21	Applicability Score	22	23	Editorial Independence Score	recommend?
Guideline	RATERS					TOTAL					TOTAL								TOTAL					TOTAL				TOTAL			TOTAL	
ratings	Rater #	1	1	1	2	4	1	1	1	1	4	1	1	1	1	1	1	1	7	4	4	3	1	12	1	1	1	3	1	1	2	WNR
	Rater #	5	1	3	3	7	3	1	1	1	6	1	1	1	2	1	1	1	8	3	3	3	2	11	1	1	1	3	1	1	2	WNR
	Rater #	6	4	4	4	12	1	1	2	1	5	1	1	1	1	1	1	1	7	4	3	4	4	15	1	1	1	3	1	1	2	U
	Rater #					0					0								0					0				0			0	
	Rater #					0					0								0					0				0			0	
	Rater #					0					0								0					0				0			0	
	Rater #					0					0								0					0				0			0	
	Rater #					0					0								0					0				0			0	
	# of Raters=	3			Obtained Score	23				Obtained Score	15							Obtained Score	22				Obtained Score	38			Obtained Score	9		Obtained Score	6	
					Minimal Score	9				Minimal Score	12							Minimal Score	21				Minimal Score	12			Minimal Score	9		Minimal Score	6	
					Maximum Score	36				Maximum Score	48							Maximum Score	84				Maximum Score	48			Maximum Score	36		Maximum Score	24	
					Obtained-Minimal	14				Obtained-Minimal	3							Obtained-Minimal	1				Obtained-Minimal	26			Obtained-Minimal	0		Obtained-Minimal	0	
					Maximum-Minimal	27				Maximum-Minimal	36							Maximum-Minimal	63				Maximum-Minimal	36			Maximum-Minimal	27		Maximum-Minimal	18	
STANDARDIZED DOMAIN SCORES						52					8								2					72				0			0	

Note: DOMAIN Score Calculations

Formula: (Obtained Score - Minimum Possible Score)/(Maximum Possible Score - Minimum Possible Score) x 100 (expressed as percentage)
NOTE: The score is modified in each case, for each domain, to REFLECT NUMBER OF RATERS

TIP: Colour coding the cells in RED and BLUE according to AGREEMENT (3,4) or DISAGREEMENT(1,2) provides a useful visual aid to guide discussion between raters . It highlights where raters essentially have consensus and where there are specific elements of the guideline that may need some clarification re: rater's individual interpretation and/or possible further review of source evidence

MSSS, 2008

AGREE Inter-Rater Score Spreadsheet Blank (Draft CAN-ADAPTE Kit V1.0 Sept. 2008: CPACC, Queen's University)

Instructions:
1. Enter the Rater number into column C
2. Enter the scores for each rater in their respective rows
3. Domain scores are automatically calculated based on the number of raters (cell C20)
4. Colour code the scores to provide visual aid (ie. 1,2 = red; 3,4 = blue)

	Question >		1	2	3	Scope & Purpose Score	4	5	6	7	Stakeholder Involvement Score	8	9	10	11	12	13	14	Rigor Score	15	16	17	18	Clarity & Presentation Score	19	20	21	Applicability Score	22	23	Editorial Independence Score	recommend?
Guideline	RATERS					TOTAL					TOTAL								TOTAL					TOTAL				TOTAL			TOTAL	
ratings	Rater #	1	4	4	2	10	4	1	4	1	10	3		2	2	3	4	1	15	4	2	4	1	11	1	1	1	3	1	4	5	R
	Rater #	5	4	4	3	11	2	1	4	1	8	4	3	3	2	3	4	1	20	4	2	4	1	11	1	1	1	3	1	4	5	R
	Rater #	6	4	2	4	12	3	1	3	1	8	4	3	4	4	4	4	1	25	3	3	3	2	11	1	1	1	3	4	4	8	WNR
	Rater #					0					0								0					0				0			0	
	Rater #					0					0								0					0				0			0	
	Rater #					0					0								0					0				0			0	
	Rater #					0					0								0					0				0			0	
	Rater #					0					0								0					0				0			0	
	# of Raters=	3			Obtained Score	33				Obtained Score	26							Obtained Score	60				Obtained Score	33			Obtained Score	9		Obtained Score	18	
					Minimal Score	9				Minimal Score	12							Minimal Score	21				Minimal Score	12			Minimal Score	9		Minimal Score	6	
					Maximum Score	36				Maximum Score	48							Maximum Score	84				Maximum Score	48			Maximum Score	36		Maximum Score	24	
					Obtained-Minimal	24				Obtained-Minimal	14							Obtained-Minimal	39				Obtained-Minimal	21			Obtained-Minimal	0		Obtained-Minimal	12	
					Maximum-Minimal	27				Maximum-Minimal	36							Maximum-Minimal	63				Maximum-Minimal	36			Maximum-Minimal	27		Maximum-Minimal	18	
STANDARDIZED DOMAIN SCORES						89					39								62					58				0			67	

Note: DOMAIN Score Calculations

Formula: (Obtained Score - Minimum Possible Score)/(Maximum Possible Score - Minimum Possible Score) x 100 (expressed as percentage)
NOTE: The score is modified in each case, for each domain, to REFLECT NUMBER OF RATERS

TIP: Colour coding the cells in RED and BLUE according to AGREEMENT (3,4) or DISAGREEMENT(1,2) provides a useful visual aid to guide discussion between raters . It highlights where raters essentially have consensus and where there are specific elements of the guideline that may need some clarification re: rater's individual interpretation and/or possible further review of source evidence

Durand, 2009

AGREE Inter-Rater Score Spreadsheet Blank (Draft CAN-ADAPTE Kit V1.0 Sept. 2008: CPACC, Queen's University)

Instructions:
1. Enter the Rater number into column C
2. Enter the scores for each rater in their respective rows
3. Domain scores are automatically calculated based on the number of raters (cell C20)
4. Colour code the scores to provide visual aid (ie. 1,2 = red; 3,4 = blue)

	Question >		1	2	3	Scope & Purpose Score	4	5	6	7	Stakeholder Involvement Score	8	9	10	11	12	13	14	Rigor Score	15	16	17	18	Clarity & Presentation Score	19	20	21	Applicability Score	22	23	Editorial Independence Score	recommend?	
Guideline	RATERS					TOTAL					TOTAL								TOTAL					TOTAL				TOTAL			TOTAL		
ratings	Rater #	1	3	1	1	5	1	1	1	1	4	1	1	1	1	3	1	1	9	3	3	2	1	9	1	1	1	3	No sc	1	1	WNR	
	Rater #	5	4	4	4	12	2	1	3	1	7	1	1	3	4	3	1	1	14	4	4	4	1	13	3	1	1	5	2	1	3	R	Adult-base
	Rater #	6	4	4	4	12	1	1	2	1	5	1	2	2	1	4	1	1	12	4	1	4	4	13	1	1	1	3	1	1	2	R	
	Rater #					0					0								0					0				0			0		
	Rater #					0					0								0					0				0			0		
	Rater #					0					0								0					0				0			0		
	Rater #					0					0								0					0				0			0		
	Rater #					0					0								0					0				0			0		
	# of Raters=	3			Obtained Score	29				Obtained Score	16						Obtained Score		35				Obtained Score	35			Obtained Score	11		Obtained Score	6		
					Minimal Score	9				Minimal Score	12						Minimal Score		21				Minimal Score	12			Minimal Score	9		Minimal Score	6		
					Maximum Score	36				Maximum Score	48						Maximum Score		84				Maximum Score	48			Maximum Score	36		Maximum Score	24		
					Obtained-Minimal	20				Obtained-Minimal	4						Obtained-Minimal		14				Obtained-Minimal	23			Obtained-Minimal	2		Obtained-Minimal	0		
					Maximum-Minimal	27				Maximum-Minimal	36						Maximum-Minimal		63				Maximum-Minimal	36			Maximum-Minimal	27		Maximum-Minimal	18		
STANDARDIZED DOMAIN SCORES						74					11								22					64				7			0		

Note: DOMAIN Score Calculations

Formula: (Obtained Score - Minimum Possible Score)/(Maximum Possible Score - Minimum Possible Score) x 100 (expressed as percentage)
NOTE: The score is modified in each case, for each domain, to REFLECT NUMBER OF RATERS

TIP: Colour coding the cells in RED and BLUE according to AGREEMENT (3,4) or DISAGREEMENT(1,2) provides a useful visual aid to guide discussion between raters . It highlights where raters essentially have consensus and where there are specific elements of the guideline that may need some clarification re: rater's individual interpretation and/or possible further review of source evidence

Appendix C: Primary Pediatric Oncology Search Strategy and Flowchart

1. LITERATURE SEARCH

Search strategies for Pediatric Oncology Group

Database: Ovid **MEDLINE**(R) 1950 to Present with Daily Update

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1 nausea/ or vomiting/ (21152)
2 exp neoplasm/ (2078497)
3 exp Antineoplastic Agents/ (662184)
4 2 or 3 (2449130)
5 1 and 4 (6330)
6 exp Antiemetics/ (114098)
7 exp Psychotropic Drugs/ (281953)
8 6 or 7 (342506)
9 1 and 8 (4914)
10 5 or 9 (8797)
11 limit 10 to "all child (0 to 18 years)" (1799)
12 limit 11 to (consensus development conference or consensus development conference, nih or guideline or practice guideline) (7)
13 guidelines as topic/ or practice guidelines as topic/ (77145)
14 11 and 13 (11)
15 14 not 12 (10)
16 12 or 14 (17)
17 from 16 keep 1-17 (17)
18 from 17 keep 1-17 (17)
19 ("24 hr" or "24 hrs" or "24 hour" or "24 hours").ti,ab. (109845)
20 11 and 19 (117)
21 16 and 19 (0)
22 from 18 keep 5-8,11,13-17 (10)

****

1. Anonymous. 5HT3-receptor antagonists as antiemetics in cancer. Drug & Therapeutics Bulletin. 2005;43(8):57-62.
   Not a guideline

2. Roila F, Feyer P, Maranzano E, Olver I, Clark-Snow R, Warr D, Molassiotis A. Antiemetics in children receiving chemotherapy. Supportive Care in Cancer. 2005; 13(2):129-31.
   Selected for consideration

3. Antonarakis ES, Evans JL, Heard GF, Noonan LM, Pizer BL, Hain RD. Prophylaxis of acute chemotherapy-induced nausea and vomiting in children with cancer: what is the evidence?. Pediatric Blood & Cancer. 2004;43(6):651-8.
   Selected for consideration

4. Mandera M. Marcol W. Bierzynska-Macyszyn G. Kluczewska E. Pineal cysts in childhood. Childs Nervous System. 2003;19(10-11):750-5.
   Not a guideline

5. Mertens WC, Higby DJ, Brown D, Parisi R, Fitzgerald J, Benjamin EM, Lindenauer PK. Improving the care of patients with regard to chemotherapy-induced nausea and emesis: the effect of feedback to clinicians on adherence to antiemetic prescribing guidelines. Journal of Clinical Oncology. 2003;21(7):1373-8.
   Not applicable

6. Andria ML, Arens JF, Baker DK Jr, Bolinger AM, Briones GR, Chen JJ, Chin A, Coursin DB, Diener KM, Dranitsaris G, Farrington J, Frazier JL, Gandara DR, Goldspiel BR, Golembiewski JA, Grunberg SM, Henry DW, Hutson PR, McCauley DL, McKenna EF, Perez EA, Philip BK, Shirk MB, Slimowitz R, Solimando DA Jr, Springman SR, Stump LS, Taylor T, Wagner BK, Walton SM. ASHP Therapeutic Guidelines on the Pharmacologic Management of Nausea and Vomiting in Adult and Pediatric Patients Receiving Chemotherapy or Radiation Therapy or Undergoing Surgery. American Journal of Health-System Pharmacy. 1999;56(8):729-64.
   Selected for consideration

7. The Antiemetic Subcommittee of the Multinational Association of Supportive Care in Cancer (MASCC). Prevention of chemotherapy- and radiotherapy-induced emesis: results of Perugia Consensus Conference. Annals of Oncology. 1998;9(8):811-9.
   Selected for initial consideration; excluded because it is considered out of date

8. Feyer PC, Stewart AL, Titlbach OJ. Aetiology and prevention of emesis induced by radiotherapy. Supportive Care in Cancer. 1998;6(3):253-60.
   Not applicable

9. Roila F, Aapro M, Stewart A. Optimal selection of antiemetics in children receiving cancer chemotherapy. Supportive Care in Cancer. 1998;6(3):215-20.
   Selected for initial consideration; excluded because it is not a guideline

10. Currow DC, Noble PD, Stuart-Harris RC. The clinical use of ondansetron. New South Wales Therapeutic Assessment Group. Medical Journal of Australia. 1995;162(3):145-9.
    Not a guideline

Database: **ALL EBM Reviews** - Cochrane DSR, ACP Journal Club, and DARE

1 (cancer: or neoplas: or oncolog:).mp. (59610)
2 (nausea or nauseous or vomit: or emesis or "anti-emetic:" or "anti emetic:" or antiemetic:).mp. (17993)
3 1 and 2 (3673)
4 (infan: or child: or teen: or adolescen: or (young adj2 adult:) or pediatric: or paediatric:).mp. (126457)
5 3 and 4 (498)
6 acute.tw. (51957)
7 ("24 hr" or "24 hrs" or "24 hour" or "24 hours").mp. (15831)
8 6 or 7 (64855)
9 5 and 8 (182)
10 from 9 keep 55,82,88,90-92,95-96,98 (9)
11 from 10 keep 1-9 (9)

****

1. Kassab S, Cummings M, Berkovitz, S, van Haselen R, Fisher P. Homeopathic medicines for adverse effects of cancer treatments. EBM Reviews - Cochrane Database of Systematic Reviews Cochrane Pain, Palliative and Supportive Care Group Cochrane Database of Systematic Reviews. 4, 2009.
   Not applicable

2. Ezzo J, Richardson M, Vickers A, Allen C, Dibble S, Issell BF, Lao L, Pearl M, Ramirez G, Roscoe JA, Shen J, Shivnan JC, Streitberger K, Treish I, Zhang G. Acupuncture-point stimulation for chemotherapy-induced nausea or vomiting. EBM Reviews - Cochrane Database of Systematic Reviews Cochrane Pain, Palliative and Supportive Care Group Cochrane Database of Systematic Reviews. 4, 2009.
   Not applicable

3. Phillips RS, Gibson F, Gopaul S, Light K, Craig JV, Pizer B.Antiemetic medication for prevention and treatment of chemotherapy induced nausea and vomiting in childhood. EBM Reviews - Cochrane Database of Systematic Reviews Cochrane Childhood Cancer Group Cochrane Database of Systematic Reviews. 4, 2009.
   Not a guideline (it is a protocol for reviewing trials on this subject)

4. Centre for Reviews and Dissemination. Behavioral intervention for cancer treatment side effects. EBM Reviews - Database of Abstracts of Reviews of Effects Database of Abstracts of Reviews of Effects. Issue 1, 2010.
   Not a guideline

5. Centre for Reviews and Dissemination. Cannabinoids for control of chemotherapy induced nausea and vomiting: quantitative systematic review (Structured abstract). EBM Reviews - Database of Abstracts of Reviews of Effects Database of Abstracts of Reviews of Effects. Issue 1, 2010.
   Not a guideline (focus is on role of cannabinoids alone in acute period)

6. Centre for Reviews and Dissemination. Granisetron is equivalent to ondansetron for prophylaxis of chemotherapy-induced nausea and vomiting: results of a meta-analysis of randomized controlled trials (Structured abstract). EBM Reviews - Database of Abstracts of Reviews of Effects Database of Abstracts of Reviews of Effects. Issue 1, 2010.
   Not a guideline (focus on specific agents)

7. Navari RM, Kaplan HG, Gralla RJ, Grunberg SM, Palmer R, Fitts D. Efficacy and safety of granisetron, a selective 5-hydroxytryptamine-3 receptor antagonist, in the prevention of nausea and vomiting induced by high-dose cisplatin. EBM Reviews - Cochrane Central Register of Controlled Trials Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 12(10):2204-10, 1994 Oct.
   Not a guideline

8. Benoit Y, Hulstaert F, Vermylen C, Sariban E, Hoyoux C, Uyttebroeck A, Otten J, Laureys G, De Kerpel I, Nortier D. Control of nausea and vomiting by Navoban (tropisetron) in 131 children receiving cytotoxic chemotherapy. EBM Reviews - Cochrane Central Register of Controlled Trials Anti-cancer drugs. Vol.6 Suppl 1, pp.9-14, 1995 Feb.
   Not a guideline

9. Latreille J, Stewart D, Laberge F, Hoskins P, Rusthoven J, McMurtrie E, Warr D, Yelle L, Walde D, Shepherd F. Dexamethasone improves the efficacy of granisetron in the first 24 h following high-dose cisplatin chemotherapy. EBM Reviews - Cochrane Central Register of Controlled Trials Supportive care in cancer: official journal of the Multinational Association of Supportive Care in Cancer. 3(5):307-12, 1995 Sep.
   Not a guideline

Database: **EMBASE** <1980 to 2010 Week 04>
Search Strategy:
---
1 practice guideline/ (113062)
2 consensus development/ or good clinical practice/ or nursing care plan/ (8362)
3 clinical pathway/ (1703)
4 (guideline: or (standard adj2 care) or consensus).mp. (231948)
5 or/1-4 (237030)
6 "nausea and vomiting"/ or chemotherapy induced emesis/ or nausea/ or radiation induced emesis/ or retching/ or vomiting/ (125296)
7 exp neoplasm/ or exp benign tumor/ or exp congenital tumor/ or exp experimental neoplasm/ or exp fetal tumor/ or exp incidentaloma/ or exp malignant neoplastic disease/ or exp metastasis/ or exp mixed tumor/ or exp "neoplasms of uncertain behavior"/ or exp neoplasms subdivided by anatomical site/ or exp "oncogenesis and malignant transformation"/ or exp paraneoplastic syndrome/ or exp "precancer and cancer-in-situ"/ or exp pseudo-meigs syndrome/ or exp tumor/ or exp tumor engraftment/ or exp tumor growth/ or exp tumor necrosis/ or exp tumor recurrence/ or exp tumor regression/ or exp tumor spheroid/ (1554944)
8 exp antineoplastic agent/ (783297)
9 7 or 8 (1957866)
10 6 and 9 (50185)
11 exp antiemetic agent/ (96594)
12 exp psychotropic agent/ or exp mood stabilizer/ or exp nootropic agent/ or exp psychedelic agent/ or exp psychostimulant agent/ or exp tranquilizer/ (391644)
13 11 or 12 (429104)
14 10 and 13 (10390)

15 limit 14 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>) (683)
16 5 and 15 (36)
17 from 16 keep 28-30,33-34,36 (6)
18 from 17 keep 1-6 (6)
19 from 18 keep 1-6 (6)

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1. Chow KS, Iceton S. Evaluation of a diary card for tailoring antiemetic therapy for children with cancer. Canadian Journal of Hospital Pharmacy.1999
   Not a guideline

2. Dupuis L.L., Lau R., Greenberg M.L. Effectiveness of strategies for preventing acute antineoplastic-induced nausea and vomiting in children with acute lymphoblastic leukemia. Can. J. Hosp. Pharm. 1999
   Not a guideline

3. Andria ML, Arens JF, Baker DK Jr, Bolinger AM, Briones GR, Chen JJ, Chin A, Coursin DB, Diener KM, Dranitsaris G, Farrington J, Frazier JL, Gandara DR, Goldspiel BR, Golembiewski JA, Grunberg SM, Henry DW, Hutson PR, McCauley DL, McKenna EF, Perez EA, Philip BK, Shirk MB, Slimowitz R, Solimando DA Jr, Springman SR, Stump LS, Taylor T, Wagner BK, Walton SM. ASHP Therapeutic Guidelines on the Pharmacologic Management of Nausea and Vomiting in Adult and Pediatric Patients Receiving Chemotherapy or Radiation Therapy or Undergoing Surgery. American Journal of Health-System Pharmacy. 1999;56(8):729-64.
   Located in above Medline search

4. Busch AF, Pearce MJ, Allen B, Begg EJ. Compliance with guidelines results in appropriate ondansetron prescribing at Christchurch Hospital. New Zealand Medical Journal. 1996
   Not a guideline (focus on ondansetron)

5. Berard CM, Mahoney CD. Cost-reducing treatment algorithms for antineoplastic drug-induced nausea and vomiting. American Journal of Health-System Pharmacy. Language EnglishYear of Publication 1995
   Not a guideline

6. Hahlen K, Quintana E, Pinkerton CR, Cedar E. A randomized comparison of intravenously administered granisetron versus chlorpromazine plus dexamethasone in the prevention of ifosfamide-induced emesis in children. J. PEDIATR. 1995
   Not a general guideline (focus is ifosfamide; includes children)

Database: **CINHAL** (EBSCO Publishing) <January 12, 2010>
Search Strategy and Results: [reformatted]
Results

S8	S6 or S7	Interface – EBSCOhost - Advanced Search Database - CINAHL 6
S7	S1 and S2	Limiters - Age Groups: Infant, Newborn 0-1 month, Infant, 1-23 months, Child, Preschool 2-5 years, Child, 6-12 years, Adolescence, 13-18 years; Publication Type: Care Plan, Practice Guidelines, Protocol Interface – EBSCOhost - Advanced Search Database - CINAHL 4
S6	S4 and S5	Interface – EBSCOhost - Advanced Search Database - CINAHL 5
S5	(MH "Practice Guidelines") or (MH "Protocols+")	Interface – EBSCOhost - Advanced Search Database - CINAHL 31129
S4	S1 and S2	Limiters - Age Groups: Infant, Newborn 0-1 month, Infant, 1-23 months, Child, Preschool 2-5 years, Child, 6-12 years, Adolescence, 13-18 years Interface – EBSCOhost - Advanced Search Database - CINAHL 96
S3	S1 and S2	Interface – EBSCOhost - Advanced Search Database - CINAHL 713
S2	(MH "Neoplasms+") or (MH "Antineoplastic Agents+")	Interface – EBSCOhost - Advanced Search Database - CINAHL 124052
S1	(MH "Nausea") or (MH "Vomiting") or (MH "Nausea and Vomiting")	Interface – EBSCOhost - Advanced Search Database - CINAHL 3308

EBSCO Publishing Citation Format: Vancouver/ICMJE:

References

1. ASHP reports. ASHP therapeutic guidelines on the pharmacologic management of nausea and vomiting in adult and pediatric patients receiving chemotherapy or radiation therapy or undergoing surgery. American Journal of Health-System Pharmacy [serial on the Internet]. (1999, Apr 15), [cited January 12, 2010]; 56(8): 729-764. Available from: CINAHL.
   Located in above Medline search

2. Carpenter C, Noonan C, Duane N, Maloney P, Stebbins K. Congenital infantile fibrosarcoma: a case study. Neonatal Network [serial on the Internet]. (1998, Apr), [cited January 12, 2010]; 17(3): 15-24. Available from: CINAHL.
   Not applicable

3. Cook J, Gallagher A. Evaluation of an anti-emetic protocol. Paediatric Nursing [serial on the Internet]. (1996, Sep), [cited January 12, 2010]; 8(7): 21-23. Available from: CINAHL.
   Selected for consideration

4. Unger J. Pediatric migraine: clinical pearls in diagnosis and therapy. Headache & Pain: Diagnostic Challenges, Current Therapy [serial on the Internet]. (2006, Sep), [cited January 12, 2010]; 17(3): 104-113. Available from: CINAHL.
   Not applicable

5. Walker P, Biglin K, Constance T, Bhambhani K, Sims-McCallum R. Promoting the use of oral ondansetron in children receiving cancer chemotherapy. American Journal of Health-System Pharmacy [serial on the Internet]. (2001, Apr), [cited January 12, 2010]; 58(7): 598-602. Available from: CINAHL.
   Not applicable

6. Kearney N, Miller M, Maguire R, Dolan S, MacDonald R, McLeod J, et al. WISECARE+: results of a European study of a nursing intervention for the management of chemotherapy-related symptoms. European Journal of Oncology Nursing [serial on the Internet]. (2008, Dec), [cited January 12, 2010]; 12(5): 443-448. Available from: CINAHL.
   Not applicable

2. LOCAL, PROVINCIAL, NATIONAL AND INTERNATIONAL WEBSITES SEARCHED FOR GUIDELINES

CANADIAN Sources – Regional

EBSCO Publishing Citation Format: Vancouver/ICMJE:

CANADIAN Sources – Regional

BC Cancer Agency(BCCA) **- not a guideline**
Alberta Health Services (AHS) **- no applicable guideline found**
Cancer Care Manitoba (CCMB) **- no applicable guideline found**
Saskatchewan Cancer Agency **- no applicable guideline found**
Cancer Care Ontario (CCO) Practice Guideline Initiative

1. Cancer Care Ontario. Management of chemotherapy-induced nausea and vomiting. Revised April 2004. Retrieved January 26, 2010. Available from URL: http://www.cancercare.on.ca/search/default.aspx?q=nausea%20and%20vomiting&type=0,6-76,6-40484|-1,1377-78
   Selected for consideration

The Hospital for Sick Children Intranet

Dupuis L and Greenberg M. Antiemetic Selection for Children Receiving Antineoplastics and/or Radiotherapy. In: **The Hospital for Sick Children 2008-2009** SickKids Drug Handbook and Formulary.
Selected for consideration

CANADIAN Sources - National

Canadian Agency for Drugs and Technology in Health (CADTH) **- no applicable guideline found**
Canadian Medical Association (CMA) Infobase **- guideline for cisplatin but not paediatric**
Society of Obstetricians & Gynecologists of Canada (SOGC) Oncology **- not applicable**
Canadian Task Force on Preventive Health Care (CTFPHC) **- no applicable guideline found**
Canadian Breast Cancer Network **- no applicable guideline found**

USA Sources

National Guideline Clearinghouse (NGC)

2. Editorial Board Palliative Care: Practice Guidelines. Nausea and vomiting. Utrecht, The Netherlands: Association of Comprehensive Cancer Centres (ACCC); 2006 Jan 12. 28 p. [73 references]
   http://www.oncoline.nl/index.php?pagina=/richtlijn/item/pagina.php&richtlijn_id=549
   Selected for consideration; excluded because focus is not on CINV

Food and Drug Administration (FDA)
No applicable guideline found

American Society of Clinical Oncology (ASCO)
ASCO Update 2006 Guidelines.

2. Kris MG, Hesketh PJ, Somerfield MR, Feyer P, Clark-Snow R, Koeller JM, Morrow GR, Chinnery LW, Chesney MJ, Gralla RJ, Grunberg SM. American Society of Clinical Oncology Guidelines for Antiemetics in Oncology: Update 2006. Journal of Clinical Oncology 2006;24(18):2932-47.
   http://jco.ascopubs.org/cgi/reprint/24/18/2932
   Selected for consideration

National Cancer Institute (NCI)
No applicable guideline found

National Comprehensive Cancer Network (NCCN)

1. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology. Antiemesis. V4.2009. [Cited January 31, 2010]. Available from URL:
   http://www.nccn.org/professionals/physician_gls/PDF/antiemesis.pdf
   Selected for consideration

Translating Research Into Practice (TRIP) Guidelines & Technology Assessments
Projects in early-mid production phase (pre-review)

1. Agency for Healthcare Research and Quality: Consideration of Evidence on Antiemetic Drugs for Nausea and Vomiting Associated with Chemotherapy or Radiation Therapy. [Cited January 31, 2010]. Available from URL: http://www.ahrq.gov/clinic/techix.htm
   Not available yet (last cited: January 31, 2010)

Oncology Nursing Society

1. Tipton JM, McDaniel RW. Barbour L, Johnston MP, Kayne M. LeRoy P, Ripple ML. Putting Evidence Into Practice: Evidence-Based Interventions to Prevent, Manage, and Treat Chemotherapy-Induced Nausea and Vomiting. Clinical Journal of Oncology Nursing. 2007;11(1):69-78.
   Selected for consideration

Institute for Clinical Systems Improvement (ICSI)
No applicable guideline found

American Cancer Society

1. Morrow GR. Chemotherapy-Related Nausea and Vomiting: Etiology and Management CA Cancer J Clin 1989;39;89-104.
   Selected for initial consideration; excluded because considered out of date

INTERNATIONAL Sources

National Library of Guidelines (UK) NLG
No applicable guideline found

Cancer Backup (UK)
No applicable guideline found

National Institute for Clinical Evidence (NICE)
No applicable guideline found

New Zealand Guidelines Group
No applicable guideline found

Scottish Intercollegiate Guidelines Network (SIGN)
No applicable guideline found

National Health and Medical Research Council of Australia (NHMRC)
No applicable guideline found

Agency for Quality in Medicine **(German)**
No applicable guideline found in English

Finnish Medical Society Duodecim
No applicable guideline found

The Cochrane library
http://www.mrw.interscience.wiley.com/cochrane/cochrane_search_fs.html?mode=startsearch&products=all&unitstatus=none&opt1=OR&Query2=&zones2=article-title&opt2=AND&Query3=&zones3=author&opt3=AND&Query4=&zones4=abstract&opt4=AND&Query5=&zones5=tables&FromYear=&ToYear=&Query1=chemotherapy+vomit&zones1=%28article-title%2Cabstract%2Ckeywords%29

1. Phillips RS, Gibson F, Gopaul S, Light K, Craig JV, Pizer B. Antiemetic medication for prevention and treatment of chemotherapy induced nausea and vomiting in childhood (Protocol). *Cochrane Database of Systematic Reviews* 2009, Issue 2. Art. No.: CD007786. DOI: 10.1002/14651858.CD007786.
   Located in above ALL EBM Reviews search

2. Billio A, Morello E, Clarke MJ. Serotonin receptor antagonists for highly emetogenic chemotherapy in adults. *Cochrane Database of Systematic Reviews* 2010, Issue 1. Art. No.: CD006272. DOI: 10.1002/14651858.CD006272.pub2.
   Not a guideline

The Joanna Briggs Institute (Australia)

Multinational Association for Supportive Care in Cancer
1. Kris MG, Hesketh PJ, Herrstedt J, Rittenberg C, Einhorn LH, Grunberg S, Koeller J, Olver I, Borjeson S, Ballatori E. Consensus proposals for the prevention of acute and delayed vomiting and nausea following high-emetic-risk chemotherapy. Supportive Care in Cancer. 2005;13:85-96
   Selected for consideration

2. Herrstedt J, Koeller JM, Roila F, Hesketh PJ, Warr D, Rittenberg C, Dicato M. Acute emesis: moderately emetogentic chemotherapy. Supportive Care in Cancer. 2005;13:97-103.
   Selected for consideration

3. Roila F, Feyer P, Maranzano E, Olver I, Clark-Snow R, Warr D, Molassiotis A. Antiemetics in children receiving chemotherapy.Supportive Care in Cancer. 2005;13(2):129-31.
   Selected for consideration

4. Tonato M, Clark-Snow RA, Osaba D, Del Favero A, Ballatori E, Borjeson S. Emesis induced by low or minimal emetic risk chemotherapy. Supportive Care Cancer. 2005;13:109-111.
   Selected for consideration

5. Antiemetic Subcommittee of the Multinational Association of Supportive Care in Cancer (MASCC). Prevention of chemotherapy- and radiotherapy-induced emesis: results of the 2004 Perugia International Antiemetic Consensus Conference. 2006;17:20-28.
   Selected for initial consideration; excluded because it is a summary document

FRENCH Language Sources

Direction de la lutte contre le cancer - Ministère de la Santé et des Services sociaux du Québec
No applicable guideline found

SOR :Standards, Options et Recommandations
No applicable guideline found

Haute Autorité de Santé (HAS)
No applicable guideline found

CHU de Rouen - Catalogue & Index des Sites Médicaux Francophones (CISMef)

1. Durand JP, Madelaine I, Scotté F. Recommandations pour la prévention et le traitement des nausées et vomissements induits par la chimiothérapie. Bulletin du Cancer. 2009;96(10):951-960.
   Not a guideline.

2. OMéDIT Centre Observatoire des Médicaments, des Dispositifs médicaux et des innovations Thérapeutiques de la région Centre. http://www.omedit-centre.fr/fichiers/upload/Fiche%20Antiemetiques.pdf
   Selected for consideration

3. ONCOLOR Réseau de santé en cancérologie de la région Lorraine **France 2003**
   http://www.oncolor.org/referentiels/support/anti_nausee_acc.htm
   Selected for consideration

4. Ministère de la Santé et des Services sociaux du Québec CEPO - Comité de l'évolution des pratiques en oncologie Canada 2008 Utilisation de l'aprépitant (EmendMC) pour la prévention des nausées et des vomissements consécutifs à l'administration d'une chimiothérapie émétisante. CEPO - Juillet 2008
   Selected for consideration

Bibliothèque médicale AF Lemanissier **– no applicable guideline found**
Agence Française de Séculrité Sanitaire des Produits de Santé (AFSSAPS) **- no applicable guideline found**

3. GREY LITERATURE SEARCH

Google Search terms:
"prevention of acute chemotherapy induced nausea and vomiting in children"

1. Dupuis LL, Nathan PC. Options for the prevention and management of acute chemotherapy-induced nausea and vomiting in children. Paediatric Drugs. 2003;5(9):597-613. Retrieved February 6, 2010. Available from URL: http://www.ncbi.nlm.nih.gov/pubmed/12956617
   Selected for consideration

2. Schore RJ, Williams D. (April 21, 2009). Chemotherapy- Induced Nausea and Vomiting. eMedicine. Retrieved February 6, 2010. Available from URL: http://emedicine.medscape.com/article/1355706-overview
   Selected for consideration

3. Schnell FM. Chemotherapy-induced nausea and vomiting: the importance of acute antiemetic control. The Oncologist. 2003;8:187-198. Retrieved February 6, 2010. Available from URL: http://theoncologist.alphamedpress.org/cgi/reprint/8/2/187
   Selected for initial consideration; excluded because considered out of date

4. National Cancer Institute. Prevention of acute/delayed emesis. Retrieved February 6, 2010. Available from URL: http://www.cancer.gov/cancertopics/pdq/supportivecare/nausea/HealthProfessional/page7
Not a guideline

5. Phillips RS, Gibson F, Gopaul S, Light K, Craig JV, Pizer B.Antiemetic medication for prevention and treatment of chemotherapy induced nausea and vomiting in childhood. EBM Reviews - Cochrane Database of Systematic Reviews Cochrane Childhood Cancer Group Cochrane Database of Systematic Reviews. 4, 2009. Retrieved February 6, 2010. Available from URL: http://mrw.interscience.wiley.com/cochrane/clsysrev/articles/CD007786/frame.html
Obtained from above website search; Not a guideline

6. Wiser W, Berger A. Practical management of chemotherapy-induced nausea and vomiting. Oncology. 2005;19(5). Retrieved February 6, 2010. Available from URL: http://www.cancernetwork.com/binary_content_servlet
Selected for initial consideration; excluded because considered out of date

7. Antonarakis ES, Evans JL, Heard GF, Noonan LM, Pizer BL, Hain RD. Prophylaxis of acute chemotherapy-induced nausea and vomiting in children with cancer: what is the evidence? Pediatric Blood and Cancer. 2004 Nov;43(6):651-8.
Not a guideline

Other resources

1. Children's Oncology Group (COG). Supportive Care Guidelines. June 20, 2008.
Selected for initial consideration; excluded because it does not address acute AINV

Primary Literature Search for Pediatric Studies – Results and Citations

Computerized Literature Search

MEDLINE:

The search strategy for MEDLINE (Ovid MEDLINE(R) 1948 to Present with Daily Update; November 1, 2011) retrieved **379** references. We used a combination of MeSH and free text terms for this search.

Set	History	Results
1	nausea/ or vomiting/	22816
2	exp neoplasms/ or (cancer* or neoplas* or tumo* or malignan*).ti,ab.	2649258
3	1 and 2	5763
4	nausea/ci or vomiting/ci	9171
5	3 or 4	11214
6	exp Antiemetics/ or receptors, serotonin/ or receptors, serotonin, 5-ht3/ or ("serotonin 3" or "5-ht3" or "5 ht3" or "5 hydroxytryptamine" or "5-hydroxytryptamine").mp. or Serotonin Antagonists/ or indoles/ or ("mdl 73147" or "mdl73147" or "mdl 73147ef" or "mdl73147ef" or dolasetron or anemet or anzemet).mp. or (endoprol or endostem or "ics 205 930" or "ics205 930" or "ics205930" or navoban or novaban or novoban or tropisetron).mp. or (emend or "l 754030" or "l754030" or "mk 0869" or "mk0869" or "mk869" or "mk 869" or "ono 7436" or "ono7436" or aprepitant).mp. or receptors, neurotransmitter/ or receptors, neurokinin-1/ or RECEPTORS, NEUROKININ-1 (nm) or substance p/ or ("l-758298" or "l758298" or prodrug).mp. or (alizapride or limican or "ms 5080" or ms5080 or plitican or vergentan).mp. or (metopimazine or "exp 999" or exp999 or "rp 9965" or rp9965 or vogalene).mp. or (Nabilone or Cesamet or cesametic or "compound 109514" or compound109514 or (coumpound adj2 "109514") or "cpd 109514" or cpd109514 or "lilly 109514" or lilly109514).mp. or Cisapride/ or (Cisapride or propulsid or "r-51619" or "r 51619" or r51619).mp. or gamma-Aminobutyric Acid/ or (Gabapentin or "ci 945" or ci945 or "go 3450" or go3450 or "goe 3450" or goe3450 or neurontin or neurotonin).mp. or ("6 azamianserin" or 6azamianserin or "aza mianserin" or mirtazepine or "org 3370" or org3770 or remergil or remergon or remeron or "remeron soltab" or zispin).mp. or (Olanzapine or Lanzac or "ly 170053" or ly170053 or midax or olansek or zydis or zyprex or zyprexa or zyprexa velotab or zyprexa zydis).mp. or (palonosetron or Aloxi or onicit or "rs 25259" or "rs 25259 197" or rs25259197 or	269772

	rs25259 or rs25259 197).mp. or (ramosetron or nasea or "ym 060" or ym060).mp. or (Indisetron or "n 3389" or n3389 or sinseron).mp. or (casopitant or "compound 679769" or (Compound adj2 "679769") or compound679769 or "gsk 679769" or gsk679769 or "gw 679769" or "gw 679769x" or gw679769 or gw679769x or rezonic).mp. or (vestipitant or "gw 597599" or "gw597599b" or gw597599 or gw597599b).mp. or (netupitant or "sch 619734" or sch619734).mp. or midazolam/ or exp Scopolamine/ or ("gr 38032" or "gr 38032f" or gr38032 or gr38032f).mp.	
7	5 and 6	3044
8	limit 7 to "all child (0 to 18 years)"	488
9	(infan* or child* or teen* or adolescen* or pediatric* or paediatric*).mp.	2845549
10	7 and 9	510
11	8 or 10	510
12	randomized controlled trial.pt. or clinical trial, phase i.pt. or clinical trial, phase ii.pt. or clinical trial, phase iii.pt. or clinical trial, phase iv.pt. or controlled clinical trial.pt. or meta analysis.pt. or multicenter study.pt. or randomized controlled trials as topic/ or controlled clinical trials as topic/ or clinical trials as topic/ or clinical trials, phase i as topic/ or clinical trials, phase ii as topic/ or clinical trials, phase iii as topic/ or clinical trials, phase iv as topic/ or meta analysis as topic/ or randomized controlled trials/ or random allocation/ or double-blind method/ or single-blind method/ or (random* or (doubl* adj2 dummy) or ((Singl* or doubl* or trebl* or tripl*) adj5 (blind* or mask*)) or RCT or RCTs or (control* adj5 trial*) or multicent* or placebo* or metaanalys* or (meta adj5 analys*) or sham or effectiveness or efficacy or compar*).ti,ab. or multicenter studies as topic/	3808892
13	11 and 12	**379**

MEDLINE: Complementary and Alternative Medicine (CAM) Search
The search strategy for MEDLINE (Ovid MEDLINE(R) 1948 to Present with Daily Update; November 1, 2010) retrieved **93** references. We used a combination of MeSH and free text terms for this search.

Set	History	Results
1	nausea/ or vomiting/	22816
2	exp neoplasms/ or (cancer* or neoplas* or tumo* or malignan*).ti,ab.	2649258
3	1 and 2	5763
4	nausea/ci or vomiting/ci	9177
5	3 or 4	11214
6	exp Complementary Therapies/ or Acupuncture/ or acustimulation.mp. or exp Cannabinoids/ or cannabaceae/ or cannabis/ or exp Receptors, Cannabinoid/ or Endocannabinoids/ or cannabinoid*.mp. or Marijuana Smoking/ or (marijuana or marihuana or hashish).mp. or Patient Education as Topic/ or psychoeducat*.mp. or exp Physical Therapy Modalities/ or exp exercise/ or exp leisure activities/ or exp plants/ or ginger/ or exp Plant Extracts/ or exp Pharmacognosy/ or exp Herb-Drug Interactions/ or exp Sensory Art Therapies/ or (progressive adj2 muscle adj2 relaxation).ti,ab. or exp Muscle Relaxation/ or (virtual adj2 reality).ti,ab. or computer simulation/ or user-computer interface/ or video games/	1084543
7	5 and 6.	814
8	(randomized controlled trial or clinical trial, phase i or clinical trial, phase ii or clinical trial, phase iii or clinical trial, phase iv or controlled clinical trial or meta analysis or multicenter study).pt. or randomized controlled trials as topic/ or controlled clinical trials as topic/ or clinical trials as topic/ or clinical trials, phase i as topic/ or clinical trials, phase ii as topic/ or clinical trials, phase iii as topic/ or clinical trials, phase iv as topic/ or meta analysis as topic/ or randomized controlled trials/ or random allocation/ or double-blind method/ or single-blind method/ or (random* or (doubl* adj2 dummy) or ((Singl* or doubl* or trebl* or tripl*) adj5 (blind* or mask*)) or RCT or RCTs or (control* adj5 trial*) or multicent* or placebo* or metaanalys* or (meta adj5 analys*) or sham or effectiveness or efficacy or compar*).ti,ab. or multicenter studies as topic/	3808892
9	7 and 8	344
10	limit 9 to "all child (0 to 18 years)"	82
11	(infan* or child* or teen* or adolescen* or pediatric* or paediatric*).mp.	2845549

Set	History	Results
12	10 or (9 and 11).	**93**

Embase
The search strategy for Embase (1980 to 2011 Week 42) retrieved **378** references. We used a combination of EMBASE and free text terms for this search.

Set	History	Results
1	exp neoplasm/	2667969
2	"nausea and vomiting"/ or nausea/ or retching/ or vomiting/	16164410
3	1 and 2	50686
4	chemotherapy induced emesis/ or radiation induced emesis/	4736
5	3 or 4	52250
6	exp antiemetic agent/ or serotonin receptor/ or serotonin 3 receptor/ or ("serotonin 3" or "5-ht3" or "5 ht3" or "5 hydroxytryptamine" or "5-hydroxytryptamine").mp. or exp serotonin antagonist/ or exp dolasetron mesilate/ or exp indole/ or exp indole derivative/ or ("mdl 73147" or "mdl73147" or "mdl 73147ef" or "mdl73147ef" or dolasetron or anemet or anzemet).mp. or 115956-13-3.rn. or exp tropisetron/ or (endoprol or endostem or "ics 205 930" or "ics205 930" or "ics205930" or navoban or novaban or novoban or tropisetron).mp. or 89565-68-4.rn. or exp aprepitant/ or (emend or "l 754030" or "l754030" or "mk 0869" or "mk0869" or "mk869" or "mk 869" or "ono 7436" or "ono7436" or aprepitant).mp. or 170729-80-3.rn. or exp neurotransmitter receptor/ or exp neurokinin 1 receptor/ or exp substance P/ or exp fosaprepitant/ or exp alizapride/ or exp metopimazine/ or exp nabilone/ or 51022-71-0.rn. or exp cisapride/ or 81098-60-4.rn. or exp gabapentin/ or 60142-96-3.rn. or exp mirtazapine/ or 61337-67-5.rn. or exp olanzapine/ or 132539-06-1.rn. or exp palonosetron/ or (135729-61-2 or 135729-62-3).rn. or exp ramosetron/ or exp indisetron/ or exp casopitant/ or exp vestipitant/ or 334476-64-1.rn. or (netupitant or "sch 619734" or sch619734).mp. or exp midazolam/ or exp scopolamine/ or ("gr 38032" or "gr 38032f" or gr38032 or gr38032f).mp.	508261
7	5 and 6	10113
8	clinical trial/ or phase 1 clinical trial/ or phase 2 clinical trial/ or phase 3 clinical trial/ or phase 4 clinical trial/ or controlled clinical trial/ or randomized controlled trial/ or multicenter study/ or meta analysis/ or cohort analysis/ or crossover procedure/ or cross-sectional study/ or double blind procedure/ or single blind procedure/ or triple blind procedure/ or ct.fs. or (rct or rcts or ((singl: or doubl: or tripl: or trebl:) and (mask: or blind:))).mp.	1118120
9	7 and 8	6206
10	limit 6 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>)	248
11	(infan* or child* or teen* or adolescen* or pediatric* or paediatric*).mp.	2565627
12	7 or (6 and 8)	**378**

Embase: CAM Search
The search strategy for Embase (1980 to 2011 Week 43) retrieved **103** references. We used a combination of MeSH and free text terms for this search.

Set	History	Results
1	exp neoplasm/	2667969
2	"nausea and vomiting"/ or or nausea/ or retching/ or vomiting/	164410
3	1 and 2	50686
4	chemotherapy induced emesis/ or radiation induced emesis/	4763
5	3 or 4	52250
6	exp alternative medicine/ or exp acupuncture/ or acustimulation.mp. or exp cannabinoid/ or cannabaceae/ or exp cannabinoid receptor/ or exp endocannabinoid/ or cannabinoid*.mp. or exp cannabis smoking/ or (marijuana or marihuana or	508261

Set	History	Results
	hashish).mp. or exp patient education/ or psychoeducat*.mp. or exp physiotherapy/ or exp exercise/ or exp leisure/ or exp recreation/ or exp plant/ or exp ginger/ or exp medicinal plant/ or exp plant extract/ or exp pharmacognosy/ or exp herb drug interaction/ or exp herb/ or exp Chinese herb/ or exp art therapy/ or exp relaxation training/ or exp muscle relaxation/ or exp virtual reality/ or exp computer simulation/ or exp simulation/ or exp computer interface/	
7	5 and 6	2185
8	clinical trial/ or phase 1 clinical trial/ or phase 2 clinical trial/ or phase 3 clinical trial/ or phase 4 clinical trial/ or controlled clinical trial/ or randomized controlled trial/ or multicenter study/ or meta analysis/ or cohort analysis/ or crossover procedure/ or cross-sectional study/ or double blind procedure/ or single blind procedure/ or triple blind procedure/ or ct.fs. or (rct or rcts or ((singl: or doubl: or tripl: or trebl:) and (mask: or blind:))).mp.	1118120
9	7 and 8	1148
10	limit 9 to (infant or child or preschool child <1 to 6 years> or school child <7 to 12 years> or adolescent <13 to 17 years>)	46
11	(infan* or child* or teen* or adolescen* or pediatric* or paediatric*).mp.	2565627
12	10 or (9 and 11)	**103**

EBM Reviews - Cochrane Central Register of Controlled Trials: Search
The search strategy for CCTR (1980 to 4th Quarter 2011) retrieved **209** references. We used a combination of MeSH and free text terms for this search. This database consists exclusively of RCTs, no study design terms were used.

Set	History	Results
1	nausea/ or vomiting/	3433
2	exp neoplasms/ or (cancer* or neoplas* or tumo* or malignan*).ti,ab.	60219
3	1 and 2	975
4	nausea/ci or vomiting/ci	2090
5	3 or 4	2283
6	exp Antiemetics/ or receptors, serotonin/ or receptors, serotonin, 5-ht3/ or ("serotonin 3" or "5-ht3" or "5 ht3" or "5 hydroxytryptamine" or "5-hydroxytryptamine").mp. or Serotonin Antagonists/ or indoles/ or ("mdl 73147" or "mdl73147" or "mdl 73147ef" or "mdl73147ef" or dolasetron or anemet or anzemet).mp. or (endoprol or endostem or "ics 205 930" or "ics205 930" or "ics205930" or navoban or novaban or novoban or tropisetron).mp. or (emend or "l 754030" or "l754030" or "mk 0869" or "mk0869" or "mk869" or "mk 869" or "ono 7436" or "ono7436" or aprepitant).mp. or receptors, neurotransmitter/ or receptors, neurokinin-1/ or RECEPTORS, NEUROKININ-1 (nm) or substance p/ or ("l-758298" or "l758298" or prodrug).mp. or (alizapride or limican or "ms 5080" or ms5080 or plitican or vergentan).mp. or (metopimazine or "exp 999" or exp999 or "rp 9965" or rp9965 or vogalene).mp. or (Nabilone or Cesamet or cesametic or "compound 109514" or compound109514 or (coumpound adj2 "109514") or "cpd 109514" or cpd109514 or "lilly 109514" or lilly109514).mp. or Cisapride/ or (Cisapride or propulsid or "r-51619" or "r 51619" or r51619).mp. or gamma-Aminobutyric Acid/ or (Gabapentin or "ci 945" or ci945 or "go 3450" or go3450 or "goe 3450" or goe3450 or neurontin or neurotonin).mp. or ("6 azamianserin" or 6azamianserin or "aza mianserin" or mirtazepine or "org 3370" or org3770 or remergil or remergon or remeron or "remeron soltab" or zispin).mp. or (Olanzapine or Lanzac or "ly 170053" or ly170053 or midax or olansek or zydis or zyprex or zyprexa or zyprexa velotab or zyprexa zydis).mp. or (palonosetron or Aloxi or onicit or "rs 25259" or "rs 25259 197" or rs25259197 or rs25259 or rs25259 197).mp. or (ramosetron or nasea or "ym 060" or ym060).mp. or (Indisetron or "n 3389" or n3389 or sinseron).mp. or (casopitant or "compound 679769" or (Compound adj2 "679769") or compound679769 or "gsk 679769" or gsk679769 or "gw 679769" or "gw 679769x" or gw679769 or gw679769x or rezonic).mp. or (vestipitant or "gw 597599" or "gw597599b" or gw597599 or gw597599b).mp. or (netupitant or "sch 619734" or sch619734).mp. or midazolam/ or exp Scopolamine/ or ("gr 38032" or "gr	18048

Set	History	Results
	38032f" or gr38032 or gr38032f).mp.	
7	5 and 6	858
8	(infan* or child* or teen* or adolescen* or pediatric* or paediatric*).mp.	121307
9	7 and 8	**209**

EBM Reviews - Cochrane Central Register of Controlled Trials: CAM Search
The search strategy for CCTR (1980 to 4th Quarter 2011) retrieved **41** references. This database consists exclusively of RCTs, no study design terms were used. We used a combination of MeSH and free text terms for this search.

Set	History	Results
1	nausea/ or vomiting/	3433
2	exp neoplasms/ or (cancer* or neoplas* or tumo* or malignan*).ti,ab.	60219
3	1 and 2	975
4	nausea/ci or vomiting/ci	2090
5	3 or 4	2283
6	exp Complementary Therapies/ or Acupuncture/ or acustimulation.mp. or exp Cannabinoids/ or cannabaceae/ or cannabis/ or exp Receptors, Cannabinoid/ or Endocannabinoids/ or cannabinoid*.mp. or Marijuana Smoking/ or (marijuana or marihuana or hashish).mp. or Patient Education as Topic/ or psychoeducat*.mp. or exp Physical Therapy Modalities/ or exp exercise/ or exp leisure activities/ or exp plants/ or ginger/ or exp Plant Extracts/ or exp Pharmacognosy/ or exp Herb-Drug Interactions/ or exp Sensory Art Therapies/ or (progressive adj2 muscle adj2 relaxation).ti,ab. or exp Muscle Relaxation/ or (virtual adj2 reality).ti,ab. or computer simulation/ or user-computer interface/ or video games/	42958
7	5 and 6	144
8	(infan* or child* or teen* or adolescen* or pediatric* or paediatric*).mp.	121307
9	7 and 8	**41**

AMED
The search strategy for (Allied and Complementary Medicine) 1985 to October 2011 retrieved **4** references. We used a combination of AMED subject headings and free text terms for this search

Set	History	Results
1	nausea/ or vomiting/ or (nausea or nauseous or vomit*).mp.	823
2	exp neoplasms/ or (cancer* or neoplas* or tumo* or malignan*).mp.	14911
3	exp Antiemetics/ or receptors, serotonin/ or receptors, serotonin, 5-ht3/ or ("serotonin 3" or "5-ht3" or "5 ht3" or "5 hydroxytryptamine" or "5-hydroxytryptamine").mp. or Serotonin Antagonists/ or indoles/ or ("mdl 73147" or "mdl73147" or "mdl 73147ef" or "mdl73147ef" or dolasetron or anemet or anzemet).mp. or (endoprol or endostem or "ics 205 930" or "ics205 930" or "ics205930" or navoban or novaban or novoban or tropisetron).mp. or (emend or "l 754030" or "l754030" or "mk 0869" or "mk0869" or "mk869" or "mk 869" or "ono 7436" or "ono7436" or aprepitant).mp. or receptors, neurotransmitter/ or receptors, neurokinin-1/ or RECEPTORS, NEUROKININ-1/ or substance p/ or ("l-758298" or "l758298" or prodrug).mp. or (alizapride or limican or "ms 5080" or ms5080 or plitican or vergentan).mp. or (metopimazine or "exp 999" or exp999 or "rp 9965" or rp9965 or vogalene).mp. or (Nabilone or Cesamet or cesametic or "compound 109514" or compound109514 or (coumpound adj2 "109514") or "cpd 109514" or cpd109514 or "lilly 109514" or lilly109514).mp. or Cisapride/ or (Cisapride or propulsid or "r-51619" or "r 51619" or r51619).mp. or gamma-Aminobutyric Acid/ or (Gabapentin or "ci 945" or ci945 or "go 3450" or go3450 or "goe 3450" or goe3450 or neurontin or neurotonin).mp. or ("6 azamianserin" or 6azamianserin or "aza mianserin" or mirtazepine or "org 3370" or org3770 or remergil or remergon or remeron or "remeron soltab" or zispin).mp. or (Olanzapine or Lanzac or "ly 170053" or ly170053 or midax or olansek or zydis or zyprex or zyprexa or zyprexa velotab or zyprexa zydis).mp. or (palonosetron or Aloxi or onicit or "rs 25259" or "rs 25259 197" or rs25259197 or rs25259 or rs25259	390

Set	History	Results
	197).mp. or (ramosetron or nasea or "ym 060" or ym060).mp. or (Indisetron or "n 3389" or n3389 or sinseron).mp. or (casopitant or "compound 679769" or (Compound adj2 "679769") or compound679769 or "gsk 679769" or gsk679769 or "gw 679769" or "gw 679769x" or gw679769 or gw679769x or rezonic).mp. or (vestipitant or "gw 597599" or "gw597599b" or gw597599 or gw597599b).mp. or (netupitant or "sch 619734" or sch619734).mp. or midazolam/ or exp Scopolamine/ or ("gr 38032" or "gr 38032f" or gr38032 or gr38032f).mp	
4	1 and 2 and 3	13
5	randomized controlled trial.pt. or randomized controlled trials as topic/ or randomized controlled trials/ or random allocation/ or double-blind method/ or single-blind method/ or (random* or (doubl* adj2 dummy) or ((Singl* or doubl* or trebl* or tripl*) adj5 (blind* or mask*)) or RCT or RCTs or (control* adj5 trial*) or multicent* or placebo* or metaanalys* or (meta adj5 analys*) or sham or effectiveness or efficacy or compar*).ti,ab.3 and 4	48263
6	4 and 5	**4**

AMED: CAM Search

The search strategy for (Allied and Complementary Medicine) 1985 to October 2011 retrieved **57** references. We used a combination of AMED subject headings and free text terms for this search

Set	History	Results
1	nausea/ or vomiting/ or (nausea or nauseous or vomit*).mp.	823
2	exp neoplasms/ or (cancer* or neoplas* or tumo* or malignan*).mp.	14911
3	exp Complementary Therapies/ or Acupuncture/ or acustimulation.mp. or exp Cannabinoids/ or cannabaceae/ or cannabis/ or exp Receptors, Cannabinoid/ or Endocannabinoids/ or cannabinoid*.mp. or Marijuana Smoking/ or (marijuana or marihuana or hashish).mp. or Patient Education as Topic/ or psychoeducat*.mp. or exp Physical Therapy Modalities/ or exp exercise/ or exp leisure activities/ or exp plants/ or ginger/ or exp Plant Extracts/ or exp Pharmacognosy/ or exp Herb-Drug Interactions/ or exp Sensory Art Therapies/ or (progressive adj2 muscle adj2 relaxation).mp. or exp Muscle Relaxation/ or (virtual adj2 reality).mp. or computer simulation/ or user-computer interface/ or video games/ or ((complementary adj5 therap*) or acupuncture or (patient adj5 educat*) or ((physical or rehab*) adj5 therap*) or exercise or sport* or walk* or yoga or meditat* or ginger).mp	104519
4	1 and 2 and 3	122
5	randomized controlled trial.pt. or randomized controlled trials as topic/ or randomized controlled trials/ or random allocation/ or double-blind method/ or single-blind method/ or (random* or (doubl* adj2 dummy) or ((Singl* or doubl* or trebl* or tripl*) adj5 (blind* or mask*)) or RCT or RCTs or (control* adj5 trial*) or multicent* or placebo* or metaanalys* or (meta adj5 analys*) or sham or effectiveness or efficacy or compar*).ti,ab.	45283
6	exp Complementary Therapies/ or Acupuncture/ or acustimulation.mp. or exp Cannabinoids/ or cannabaceae/ or cannabis/ or exp Receptors, Cannabinoid/ or Endocannabinoids/ or cannabinoid*.mp. or Marijuana Smoking/ or (marijuana or marihuana or hashish).mp. or Patient Education as Topic/ or psychoeducat*.mp. or exp Physical Therapy Modalities/ or exp exercise/ or exp leisure activities/ or exp plants/ or ginger/ or exp Plant Extracts/ or exp Pharmacognosy/ or exp Herb-Drug Interactions/ or exp Sensory Art Therapies/ or (progressive adj2 muscle adj2 relaxation).mp. or exp Muscle Relaxation/ or (virtual adj2 reality).mp. or computer simulation/ or user-computer interface/ or video games/ or ((complementary adj5 therap*) or acupuncture or (patient adj5 educat*) or ((physical or rehab*) adj5 therap*) or exercise or sport* or walk* or yoga or meditat* or ginger).mp.	98830
7	5 and 6	**57**

HTA

The search strategy for EBM Reviews - Health Technology Assessment 4th Quarter retrieved 1 reference. This database consists exclusively of meta-analyses; no study design terms were used. MeSH and textword terms were adapted to this strategy.

Set	History	Results
1	nausea/ or vomiting/ or (nausea or nauseous or vomit*).mp.	60
2	exp neoplasms/ or (cancer* or neoplas* or tumo* or malignan*).mp.	2003
3	nausea/ci or vomiting/ci	1
4	(1 and 2) or 3	14
5	exp Antiemetics/ or receptors, serotonin/ or receptors, serotonin, 5-ht3/ or ("serotonin 3" or "5-ht3" or "5 ht3" or "5 hydroxytryptamine" or "5-hydroxytryptamine").mp. or Serotonin Antagonists/ or indoles/ or ("mdl 73147" or "mdl73147" or "mdl 73147ef" or "mdl73147ef" or dolasetron or anemet or anzemet).mp. or (endoprol or endostem or "ics 205 930" or "ics205 930" or "ics205930" or navoban or novaban or novoban or tropisetron).mp. or (emend or "l 754030" or "l754030" or "mk 0869" or "mk0869" or "mk869" or "mk 869" or "ono 7436" or "ono7436" or aprepitant).mp. or receptors, neurotransmitter/ or receptors, neurokinin-1/ or RECEPTORS, NEUROKININ-1/ or substance p/ or ("l-758298" or "l758298" or prodrug).mp. or (alizapride or limican or "ms 5080" or ms5080 or plitican or vergentan).mp. or (metopimazine or "exp 999" or exp999 or "rp 9965" or rp9965 or vogalene).mp. or (Nabilone or Cesamet or cesametic or "compound 109514" or compound109514 or (coumpound adj2 "109514") or "cpd 109514" or cpd109514 or "lilly 109514" or lilly109514).mp. or Cisapride/ or (Cisapride or propulsid or "r-51619" or "r 51619" or r51619).mp. or gamma-Aminobutyric Acid/ or (Gabapentin or "ci 945" or ci945 or "go 3450" or go3450 or "goe 3450" or goe3450 or neurontin or neurotonin).mp. or ("6 azamianserin" or 6azamianserin or "aza mianserin" or mirtazepine or "org 3370" or org3770 or remergil or remergon or remeron or "remeron soltab" or zispin).mp. or (Olanzapine or Lanzac or "ly 170053" or ly170053 or midax or olansek or zydis or zyprex or zyprexa or zyprexa velotab or zyprexa zydis).mp. or (palonosetron or Aloxi or onicit or "rs 25259" or "rs 25259 197" or rs25259197 or rs25259 or rs25259 197).mp. or (ramosetron or nasea or "ym 060" or ym060).mp. or (Indisetron or "n 3389" or n3389 or sinseron).mp. or (casopitant or "compound 679769" or (Compound adj2 "679769") or compound679769 or "gsk 679769" or gsk679769 or "gw 679769" or "gw 679769x" or gw679769 or gw679769x or rezonic).mp. or (vestipitant or "gw 597599" or "gw597599b" or gw597599 or gw597599b).mp. or (netupitant or "sch 619734" or sch619734).mp. or midazolam/ or exp Scopolamine/ or ("gr 38032" or "gr 38032f" or gr38032 or gr38032f).mp.	63
6	4 and 5	**1**

HTA: CAM Search

The search strategy for EBM Reviews - Health Technology Assessment 4th Quarter 2011 retrieved **1** reference. This database consists exclusively of meta-analyses, no study design terms were used. MeSH and textword terms were adapted to this strategy.

Set	History	Results
1	nausea/ or vomiting/ or (nausea or nauseous or vomit*).mp.	60
2	exp neoplasms/ or (cancer* or neoplas* or tumo* or malignan*).mp.	2003
3	nausea/ci or vomiting/ci	1
4	(1 and 2) or 3	14
5	exp Complementary Therapies/ or Acupuncture/ or acustimulation.mp. or exp Cannabinoids/ or cannabaceae/ or cannabis/ or exp Receptors, Cannabinoid/ or Endocannabinoids/ or cannabinoid*.mp. or Marijuana Smoking/ or (marijuana or marihuana or hashish).mp. or Patient Education as Topic/ or psychoeducat*.mp. or exp Physical Therapy Modalities/ or exp exercise/ or exp leisure activities/ or exp plants/ or ginger/ or exp Plant Extracts/ or exp Pharmacognosy/ or exp Herb-Drug	587

Set	History	Results
	Interactions/ or exp Sensory Art Therapies/ or (progressive adj2 muscle adj2 relaxation).mp. or exp Muscle Relaxation/ or (virtual adj2 reality).mp. or computer simulation/ or user-computer interface/ or video games/ or ((complementary adj5 therap*) or acupuncture or (patient adj5 educat*) or ((physical or rehab*) adj5 therap*) or exercise or sport* or walk* or yoga or meditat* or ginger).mp.	
6	4 and 5	**1**

NHSEED
HTA

The search strategy for EBM Reviews - NHS Economic Evaluation Database 4th Quarter 2011 retrieved **26** references. This database consists exclusively of meta-analyses, no study design terms were used. MeSH and textword terms were adapted to this strategy.

Set	History	Results
1	nausea/ or vomiting/ or (nausea or nauseous or vomit*).mp.	254
2	exp neoplasms/ or (cancer* or neoplas* or tumo* or malignan*).mp.	2247
3	nausea/ci or vomiting/ci	18
4	(1 and 2) or 3	81
5	exp Antiemetics/ or receptors, serotonin/ or receptors, serotonin, 5-ht3/ or ("serotonin 3" or "5-ht3" or "5 ht3" or "5 hydroxytryptamine" or "5-hydroxytryptamine").mp. or Serotonin Antagonists/ or indoles/ or ("mdl 73147" or "mdl73147" or "mdl 73147ef" or "mdl73147ef" or dolasetron or anemet or anzemet).mp. or (endoprol or endostem or "ics 205 930" or "ics205 930" or "ics205930" or navoban or novaban or novoban or tropisetron).mp. or (emend or "l 754030" or "l754030" or "mk 0869" or "mk0869" or "mk869" or "mk 869" or "ono 7436" or "ono7436" or aprepitant).mp. or receptors, neurotransmitter/ or receptors, neurokinin-1/ or RECEPTORS, NEUROKININ-1/ or substance p/ or ("l-758298" or "l758298" or prodrug).mp. or (alizapride or limican or "ms 5080" or ms5080 or plitican or vergentan).mp. or (metopimazine or "exp 999" or exp999 or "rp 9965" or rp9965 or vogalene).mp. or (Nabilone or Cesamet or cesametic or "compound 109514" or compound109514 or (coumpound adj2 "109514") or "cpd 109514" or cpd109514 or "lilly 109514" or lilly109514).mp. or Cisapride/ or (Cisapride or propulsid or "r-51619" or "r 51619" or r51619).mp. or gamma-Aminobutyric Acid/ or (Gabapentin or "ci 945" or ci945 or "go 3450" or go3450 or "goe 3450" or goe3450 or neurontin or neurotonin).mp. or ("6 azamianserin" or 6azamianserin or "aza mianserin" or mirtazepine or "org 3370" or org3770 or remergil or remergon or remeron or "remeron soltab" or zispin).mp. or (Olanzapine or Lanzac or "ly 170053" or ly170053 or midax or olansek or zydis or zyprex or zyprexa or zyprexa velotab or zyprexa zydis).mp. or (palonosetron or Aloxi or onicit or "rs 25259" or "rs 25259 197" or rs25259197 or rs25259 or rs25259 197).mp. or (ramosetron or nasea or "ym 060" or ym060).mp. or (Indisetron or "n 3389" or n3389 or sinseron).mp. or (casopitant or "compound 679769" or (Compound adj2 "679769") or compound679769 or "gsk 679769" or gsk679769 or "gw 679769" or "gw 679769x" or gw679769 or gw679769x or rezonic).mp. or (vestipitant or "gw 597599" or "gw597599b" or gw597599 or gw597599b).mp. or (netupitant or "sch 619734" or sch619734).mp. or midazolam/ or exp Scopolamine/ or ("gr 38032" or "gr 38032f" or gr38032 or gr38032f).mp.	279
6	4 and 5	**26**

NHSEED: CAM Search
The search strategy for EBM Reviews - NHS Economic Evaluation Database 4th Quarter 2011 retrieved **9** references. This database consists exclusively of meta-analyses, no study design terms were used. MeSH and textword terms were adapted to this strategy.

Set	History	Results
1	nausea/ or vomiting/ or (nausea or nauseous or vomit*).mp.	254
2	exp neoplasms/ or (cancer* or neoplas* or tumo* or malignan*).mp.	2247

Set	History	Results
3	nausea/ci or vomiting/ci	18
4	(1 and 2) or 3	26
5	exp Complementary Therapies/ or Acupuncture/ or acustimulation.mp. or exp Cannabinoids/ or cannabaceae/ or cannabis/ or exp Receptors, Cannabinoid/ or Endocannabinoids/ or cannabinoid*.mp. or Marijuana Smoking/ or (marijuana or marihuana or hashish).mp. or Patient Education as Topic/ or psychoeducat*.mp. or exp Physical Therapy Modalities/ or exp exercise/ or exp leisure activities/ or exp plants/ or ginger/ or exp Plant Extracts/ or exp Pharmacognosy/ or exp Herb-Drug Interactions/ or exp Sensory Art Therapies/ or (progressive adj2 muscle adj2 relaxation).mp. or exp Muscle Relaxation/ or (virtual adj2 reality).mp. or computer simulation/ or user-computer interface/ or video games/ or ((complementary adj5 therap*) or acupuncture or (patient adj5 educat*) or ((physical or rehab*) adj5 therap*) or exercise or sport* or walk* or yoga or meditat* or ginger).mp.	1285
6	4 and 5	**9**

CINHAL via EBSCO Host November 1, 2011
The search strategy for CINAHL(November 1, 2011 retrieved 64references for antinausea references and **31** for complementary therapies. CINAHL and textword terms were adapted to this strategy.
Search History

Set	History	Results
S1	(MH "Nausea") or (MH "Vomiting") or (MH "Nausea and Vomiting")	4100
S2	(MH "Neoplasms+") or (MH "Antineoplastic Agents+")	153511
S3	S1 and S2	833
S4	(MH "Nausea and Vomiting"/CI) OR (MH "Nausea"/CI) OR (MH "Vomiting/CI")	199
S5	S3 OR S4	945
S6	(MH "Antiemetics+") OR (MH "Serotonin Agonists+") OR (MH "Serotonin Antagonists+") OR (MH "Indoles+") OR (MH "Receptors, Neurotransmitter+") OR (MH "Cisapride") OR (MH "Aminobutyric Acids+") OR (MH "Olanzapine") OR (MH "Ondansetron")	10917
S7	S5 and S6	333
S8	(MH "Clinical Trials") OR (MH "Randomized Controlled Trials") OR (MH "Single-Blind Studies") OR (MH "Triple-Blind Studies") OR (MH "Therapeutic Trials") OR (MH "Nonrandomized Trials")	82801
S9	S7 and S8	64
S10	(MH "Plants, Medicinal+") OR (MH "Alternative Therapies+") OR (MH "Patient Education") OR (MH "Physical Therapy+") OR (MH "Exercise+") OR (MH "Leisure Activities+") OR (MH "Physical Fitness") OR (MH "Sports+") OR (MH "Plant Extracts+") OR (MH "Drug-Herb Interactions") OR (MH "Drug-Food Interactions") OR (MH "Ginger") OR (MH "Art Therapy") OR (MH "Muscle Relaxation") OR (MH "Virtual Reality") OR (MH "Computer Simulation") OR (MH "User-Computer Interface+") OR (MH "Video Games") OR (MH "Yoga") OR ...	271236
S11	S5 and S10	196
S12	S8 and S11	**31**

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Excluded

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Excluded

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Excluded

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Excluded

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Excluded

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Excluded

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Excluded

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Excluded

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Excluded

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Excluded

461. Van Hoff J, Hockenberry-Eaton MJ, Patterson K, et al. A survey of antiemetic use in children with cancer. American Journal of Diseases of Children 1991:145(7):773-778.
Excluded

462. Van Hoff J, Olszewski D. Lorazepam for the control of chemotherapy-related nausea and vomiting in children. Journal of Pediatrics 1988:113(1 Pt 1):146-149.
Excluded

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Excluded

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Excluded

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Excluded

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Excluded

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Excluded

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Excluded

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Excluded

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Excluded

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Excluded

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Excluded

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Excluded

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Excluded

477. Wilder-Smith CH, Schuler L, Osterwalder B, et al. Patient-controlled antiemesis for cancer chemotherapy-induced nausea and vomiting. Journal of Pain & Symptom Management 1990:5(6):375-378.
Excluded

478. Wilkinson S, Barnes K, Storey L. Massage for symptom relief in patients with cancer: systematic review. Journal of Advanced Nursing 2008:63(5):430-439.
Excluded

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Excluded

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Excluded

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Excluded

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Excluded

483. Yang Y, Zhang Y, Jing NC, et al. Electroacupuncture at Zusanli (ST 36) for treatment of nausea and vomiting caused by the chemotherapy of the malignant tumor: a multicentral randomized controlled trial. [Chinese]. Zhongguo zhen jiu = Chinese acupuncture & moxibustion 2009:29(12):955-958.
Excluded

484. Yang Y, Zhang Y, Jing N, et al. Electro-acupuncture at Zusanli (ST36) for the treatment of nausea and vomiting caused by chemotherapy for malignant tumor: A multi-center randomized control trial. International:19(2):53-59.
Excluded

485. Yen CC, Hsieh RK, Chiou TJ, et al. Navoban (tropisetron, ICS 205-930) and dexamethasone combination in the prevention of vomiting for patients receiving preconditioning high-dose chemotherapy before marrow transplantation. Japanese Journal of Clinical Oncology 1998:28(2):129-133.
Excluded

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Excluded

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Excluded

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Excluded

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Excluded

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Excluded

491. Zeltzer LK, Dolgin MJ, LeBaron S, et al. A randomized, controlled study of behavioral intervention for chemotherapy distress in children with cancer. Pediatrics 1991:88(1):34-42.
Excluded

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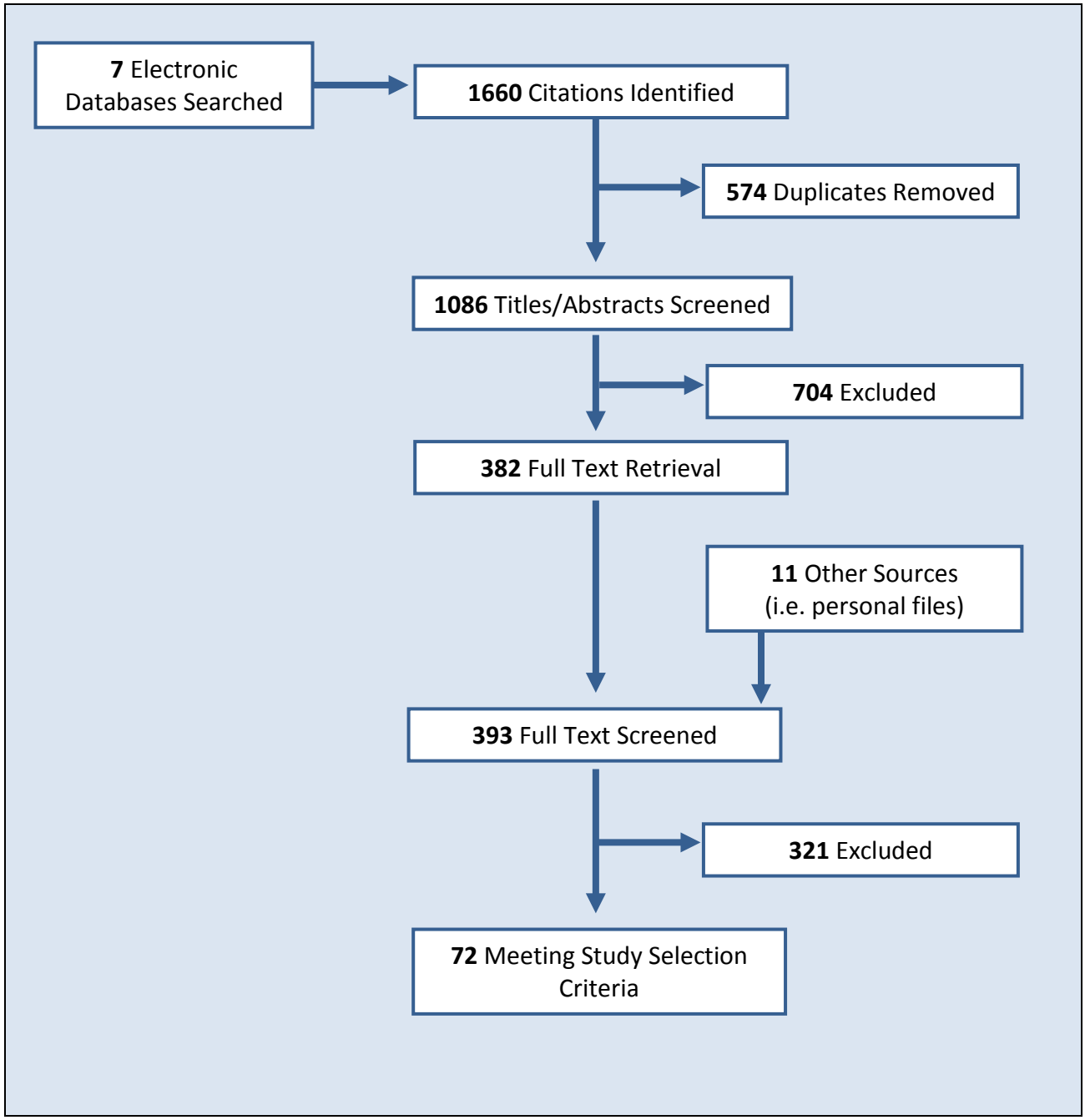
Excluded

493. Zeng, X. Y., A. H. Wang, et al. (2001). "Ramosetron for the management of chemotherapy-induced gastrointestinal events in patients with hematological malignancies." Methods and Findings in Experimental and Clinical Pharmacology 23(4): 191-195.
Excluded

494. Zhang JD, Liu YP, Teng YE, et al. [Preventive effects of ramosetron and granisetron in prevention of gastrointestinal reaction associated with chemotherapeutic agents: a comparative study]. Zhonghua yi xue za zhi 2003:83(23):2058-2060.
Excluded

495. Zoubek A, Kronberger M, Puschmann A, et al. Ondansetron in the control of chemotherapy-induced and radiotherapy-induced emesis in children with malignancies. Anti-Cancer Drugs 1993:4 Suppl 2:17-21.
Excluded

Literature Search for Pediatric Studies Results Flowchart



Appendix D: Additional Literature Search: Dronabinol and Levomepromazine

Computerized Literature Search: Dronabinol

MEDLINE:
The search strategy for MEDLINE (Ovid MEDLINE(R) 1948 to Present with Daily Update retrieved **25** references and excluded 11 based on our inclusion criteria or if included in our original literature search. The remaining **14** citations were reviewed from full text. We used a combination of MeSH and free text terms for this search.

Set	History	Results
1	nausea/ or vomiting/	22540
2	exp neoplasms/ or (cancer* or neoplas* or tumo* or malignan*).ti,ab.	2617844
3	1 and 2	5708
4	nausea/ci or vomiting/ci	9146
5	3 or 4	11141
6	exp tetrahydrocannabinol/ or delta 1 3,4 trans tetrahydrocannabinol.mp. or delta 1 tetrahydrocannabinol.mp. or delta 1 trans tetrahydrocannabinol.mp. or delta 1,2 tetrahydrocannabinol.mp. or delta 9 tetrahydrocannabinol.mp. or delta 9 trans tetrahydrocannabinol.mp. or delta1 3,4 trans tetrahydrocannabinol.mp. or delta1 cis tetrahydrocannabinol.mp. or delta1 tetrahydrocannabinol.mp. or delta1 thc.mp. or delta1 trans tetrahydrocannabinol.mp. or delta9 tetrahydro cannabinol.mp. or delta9 tetrahydrocannabinol.mp. or delta9 trans tetrahydrocannabinol.mp. or ea 1477.mp. or ea1477.mp. or l delta 9 trans tetrahydrocannabinol.mp. or levo delta 1 tetrahydrocannabinol.mp. or levo delta 9 tetrahydrocannabinol.mp. or qcd 84924.mp. or tetrahydrocannabinol 1 ene.mp. or tetrahydrocannabinol delta1.mp. or tetrahydrocannabinol delta9.mp. or tetranabinex.mp. or trans delta 9 tetrahydrocannabinol.mp. or u1 tetrahydrocannabinol.mp. or u9 tetrahydrocannabinol.mp.	5991
7	5 and 6	154
8	limit 7 to "all child (0 to 18 years)"	23
9	(infan* or child* or teen* or adolescen* or pediatric* or paediatric*).mp.	2817397
10	7 and 9	25
11	8 or 10	25
12	limit 11 to randomized controlled trial	15
13	randomized controlled trial.pt.	316968
14	clinical trial, phase i.pt.	11643
15	clinical trial, phase ii.pt.	18390
16	clinical trial, phase iii.pt.	6549
17	clinical trial, phase iv.pt.	642
18	controlled clinical trial.pt.	83518
19	meta analysis.pt.	30780
20	multicenter study.pt.	136622
21	randomized controlled trials as topic/	76575
22	controlled clinical trials as topic/	4556
23	clinical trials as topic/	158179
24	clinical trials, phase i as topic/	3542
25	clinical trials, phase ii as topic/	4883
26	clinical trials, phase iii as topic/	4883
27	clinical trials, phase iv as topic/	170
28	meta analysis as topic/	11802
29	randomized controlled trials/ or random allocation/ or double-blind method/ or single-blind method/	261197
30	(random* or (doubl* adj2 dummy) or ((Singl* or doubl* or trebl* or tripl*) adj5 (blind* or mask*)) or RCT or RCTs or (control* adj5 trial*) or multicent* or placebo* or metaanalys* or (meta adj5 analys*) or sham or effectiveness or efficacy or compar*).ti,ab.	3506106
31	multicenter studies as topic/	14186

Set	History	Results
32	or/13-31	3763049
33	11 and 32	21
34	11 not 33	4
35	from 34 keep 1-126	21
36	from 33 keep 1-371	4
37	35 or 36	25
38	from 37 keep 1-25	25
39	from 38 keep 2, 6, 9-15, 17, 19-20, 23-24	**14**

Citations

1. Darmani NA, Janoyan JJ, Crim J, Ramirez J. Receptor mechanism and antiemetic activity of structurally-diverse cannabinoids against radiation-induced emesis in the least shrew.. European Journal of Pharmacology. 2007;563(1-3):187-96.
   Excluded

2. Meiri E, Jhangiani H, Vredenburgh JJ, Barbato LM, Carter FJ, Yang HM, Baranowski V. Efficacy of dronabinol alone and in combination with ondansetron versus ondansetron alone for delayed chemotherapy-induced nausea and vomiting.. Current Medical Research & Opinion. 2007;23(3):533-43.
   Excluded

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   Excluded

4. Baron M. Appetite stimulants: the unsolved truth.. Health Care Food & Nutrition Focus. 2000;16(10):5-7.
   Excluded

5. Abrahamov A, Abrahamov A, Mechoulam R. An efficient new cannabinoid antiemetic in pediatric oncology.. Life Sciences. 1995;56(23-24):2097-102.
   Included in original AINV search

6. Cunningham D, Bradley CJ, Forrest GJ, Hutcheon AW, Adams L, Sneddon M, Harding M, Kerr DJ, Soukop M, Kaye SB. A randomized trial of oral nabilone and prochlorperazine compared to intravenous metoclopramide and dexamethasone in the treatment of nausea and vomiting induced by chemotherapy regimens containing cisplatin or cisplatin analogues.. European Journal of Cancer & Clinical Oncology. 1988;24(4):685-9.
   Excluded

7. Chan HS, Correia JA, MacLeod SM. Nabilone versus prochlorperazine for control of cancer chemotherapy-induced emesis in children: a double-blind, crossover trial.. Pediatrics. 1987;79(6):946-52.
   Included in original AINV literature search

8. Dalzell AM, Bartlett H, Lilleyman JS. Nabilone: an alternative antiemetic for cancer chemotherapy. Archives of Disease in Childhood. 1986;61(5):502-5.
   Included in original AINV literature search

9. Ungerleider JT, Sarna G, Fairbanks LA, Goodnight J, Andrysiak T, Jamison K. THC or Compazine for the cancer chemotherapy patient--the UCLA study. Part II: Patient drug preference.. American Journal of Clinical Oncology. 1985;8(2):142-7.
   Excluded

10. George M, Pejovic MH, Thuaire M, Kramar A, Wolff JP. [Randomized comparative trial of a new anti-emetic: nabilone, in cancer patients treated with cisplatin]. [in French] Biomedicine & Pharmacotherapy. 1983;37(1):24-7.
    Excluded

11. Levitt M. Nabilone vs. placebo in the treatment of chemotherapy-induced nausea and vomiting in cancer patients. Cancer Treatment Reviews. 1982 [cited 1982 Dec];9 Suppl B49-53.
Excluded

12. Wada JK, Bogdon DL, Gunnell JC, Hum GJ, Gota CH, Rieth TE. Double-blind, randomized, crossover trial of nabilone vs. placebo in cancer chemotherapy.. Cancer Treatment Reviews. 1982;9 Suppl B39-44.
Excluded

13. Johansson R, Kilkku P, Groenroos M. A double-blind, controlled trial of nabilone vs. prochlorperazine for refractory emesis induced by cancer chemotherapy.. Cancer Treatment Reviews. 1982;9 Suppl B25-33.
Excluded
14. Ungerleider JT, Andrysiak T, Fairbanks L, Goodnight J, Sarna G, Jamison K. Cannabis and cancer chemotherapy: a comparison of oral delta-9-THC and prochlorperazine. Cancer. 1982;50(4):636-45.
Excluded

15. Einhorn LH, Nagy C, Furnas B, Williams SD. Nabilone: an effective antiemetic in patients receiving cancer chemotherapy.. Journal of Clinical Pharmacology. 1981;21(8-9 Suppl):64S-69S.
Excluded

16. Cronin CM, Sallan SE, Gelber R, Lucas VS, Laszlo J. Antiemetic effect of intramuscular levonantradol in patients receiving anticancer chemotherapy.. Journal of Clinical Pharmacology. 1981;21(8-9 Suppl):43S-50S.
Included in original AINV literature search

17. Dow GJ, Meyers FH. The California program for the investigational use of THC and marihuana in heterogeneous populations experiencing nausea and vomiting from anticancer therapy. Journal of Clinical Pharmacology. 1981;21(8-9 Suppl):128S-132S.
Excluded

EMBASE:
The search strategy for Embase (1980 to 2011 Week 37) retrieved **5** references which were excluded based on our inclusion criteria or if included in our original literature search. We used a combination of MeSH and free text terms for this search.

Set	History	Results
1	exp neoplasm/	2632165
2	"nausea and vomiting"/ or chemotherapy induced emesis/ or nausea/ or radiation induced emesis/ or retching/ or vomiting/	163449
3	dronabinol/ or 6a-trans isomer tetrahydrocannabinol.mp. or 6ar-cis-isomer tetrahydrocannabinol.mp. or trans-+--isomer tetrahydrocannabinol.mp. or thc.mp. or delta9-tetrahydrocannabinol.mp. or delta1-thc.mp. or 6as-cis-isomer tetrahydrocannabinol.mp. or 9 ene tetrahydrocannabinol.mp. or delta9-thc.mp. or 9-ene-tetrahydrocannabinol.mp. or tetrahydrocannabinol.mp. or trans-isomer tetrahydrocannabinol.mp. or solvay brand of tetrahydrocannabinol.mp. or trans isomer tetrahydrocannabinol.mp. or delta1-tetrahydrocannabinol.mp.	10133
4	1 and 2	50736
5	clinical trial/ or phase 1 clinical trial/ or phase 2 clinical trial/ or phase 3 clinical trial/ or phase 4 clinical trial/ or controlled clinical trial/ or randomized controlled trial/ or multicenter study/ or meta analysis/ or cohort analysis/ or crossover procedure/ or cross-sectional study/ or double blind procedure/ or single blind procedure/ or triple blind procedure/ or ct.fs. or (rct or rcts or ((singl: or doubl: or tripl: or trebl:) and (mask: or blind:))).mp.	1098570
6	3 and 4	164
7	limit 6 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>)	8
8	(infan* or child* or teen* or adolescen* or pediatric* or paediatric*).mp.	2534812
9	7 or 8	2534812

Set	History	Results
10	6 and 9	16
11	5 and 10	7
12	from 11 keep 1-5	5

Citations

1. Dewan P, Singhal S, Harit D. Management of Chemotherapy-Induced Nausea and Vomiting. Indian Pediatr. 2010;47(2):149-155.
   Excluded

2. Hall W, Christie M, Currow D. Cannabinoids and cancer: Causation, remediation, and palliation. Lancet Oncol. 2005;6(1):35-42.
   Excluded

3. Grotenhermen F, Muller-Vahl K. IACM 2nd Conference on Cannabinoids in Medicine. Expert Opin. Pharmacother. 2003;4(12):2367-2371.
   Excluded

4. Ries F, Dicato MA. Emesis control in hematological-oncology. Leukemia & Lymphoma. 1992;7(Suppl 2):83-89.
   Excluded

5. Van Hoff J, Hockenberry-Eaton MJ, Patterson K, Hutter JJ. A survey of antiemetic use in children with cancer. Am J Dis Child. 1991;145(7):773-778.
   Included in original AINV literature search

Computerized Literature Search: Levomepromazine

MEDLINE:
The search strategy for MEDLINE (Ovid MEDLINE(R) 1948 to Present with Daily Update retrieved **zero** relevant references. We used a combination of MeSH headings and free text terms for this search.

Set	History	Results
1	nausea/ or vomiting/	22540
2	exp neoplasms/ or (cancer* or neoplas* or tumo* or malignan*).ti,ab.	2617844
3	1 and 2	5708
4	nausea/ci or vomiting/ci	9146
5	3 or 4	11141
6	exp methotrimeprazine/ or ((((levomepromazine or 10 3 dimethylamino 2 methylpropyl 2 methoxyphenothiazine or 2 methoxy 10 2 methyl 3 dimethylaminopropyl phenothiazine or 2 methoxytrimeprazine or 3 methoxy 10 3 dimethylamino 2 methylpropyl phenothiazine or apo-methoprazine or bayer 1213 or cl 36467 or cl 39743 or cl36467 or cl39743 or hirnamin or l 10 3 dimethylamino 2 methylpropyl 2 methoxyphenothiazine or l 10 3 dimethylamino 2 methylpropyl 2 methoxyphenothiazine or l mepromazine or levium or levo mepromazine or levo promazine or levomeprazine or levomepromazine hydrogen maleate or levomepromazine maleate or levopromazin or levopromazine or levoprome or levozin or mepromazine or methotrimeprazine or methotrimeprazine maleate 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 sinogan debil).mp. or sk) and f 5116.mp.) or skf 5116.mp. or skf5116.mp. or tiscerin.mp. or tisercin.mp. or veractil.mp.).mp.	656
7	5 and 6	13
8	limit 7 to "all child (0 to 18 years)"	1
9	(infan* or child* or teen* or adolescen* or pediatric* or paediatric*).mp.	2817397
10	7 and 9	1

Set	History	Results
11	8 or 10	1
12	limit 11 to randomized controlled trial	0
13	randomized controlled trial.pt.	316968
14	clinical trial, phase i.pt.	11643
15	clinical trial, phase ii.pt.	18390
16	clinical trial, phase iii.pt.	6549
17	clinical trial, phase iv.pt.	642
18	controlled clinical trial.pt.	83518
19	meta analysis.pt.	30780
20	multicenter study.pt.	136622
21	randomized controlled trials as topic/	76575
22	controlled clinical trials as topic/	4556
23	clinical trials as topic/	158179
24	clinical trials, phase i as topic/	3542
25	clinical trials, phase ii as topic/	4883
26	clinical trials, phase iii as topic/	4883
27	clinical trials, phase iv as topic/	170
28	meta analysis as topic/	11802
29	randomized controlled trials/ or random allocation/ or double-blind method/ or single-blind method/	261197
30	(random* or (doubl* adj2 dummy) or ((Singl* or doubl* or trebl* or tripl*) adj5 (blind* or mask*)) or RCT or RCTs or (control* adj5 trial*) or multicent* or placebo* or metaanalys* or (meta adj5 analys*) or sham or effectiveness or efficacy or compar*).ti,ab.	3506106
31	multicenter studies as topic/	14186
32	or/13-31	3763049
33	11 and 32	1
34	11 not 33	0
35	from 34 keep 1	**1**

Citations

1. Radnay PA, Becsey LS, Shah NK, Foldes FF. Comparison of methotrimeprazine and meperidine as components of balanced anesthesia. Anesthesia & Analgesia. 1975;54(6):749-55.
   Excluded

EMBASE:

The search strategy for Embase (1980 to 2011 Week 37) retrieved zero relevant references. We used a combination of MeSH and free text terms for this search.

Set	History	Results
1	exp neoplasm/	2632165
2	"nausea and vomiting"/ or chemotherapy induced emesis/ or nausea/ or radiation induced emesis/ or retching/ or vomiting/	163449
3	exp levomepromazine/ or Methotrimeprazine.mp. or levopromazine.mp. or levopromazine.mp. or methotrimeprazine.mp. or levomepromazine.mp. or levomeprazin.mp. or tisercin.mp. or tizertsin.mp. or 10H-Phenothiazine-10-propanamine, R-2-methoxy-N,N,beta-trimethyl.mp.	4104
4	1 and 2	50736
5	clinical trial/ or phase 1 clinical trial/ or phase 2 clinical trial/ or phase 3 clinical trial/ or phase 4 clinical trial/ or controlled clinical trial/ or randomized controlled trial/ or multicenter study/ or meta analysis/ or cohort analysis/ or crossover procedure/ or cross-sectional study/ or double blind procedure/ or single blind procedure/ or triple blind procedure/ or ct.fs. or (rct or rcts or ((singl: or doubl: or tripl: or trebl:) and (mask: or blind:))).mp.	1098570

Set	History	Results
6	3 and 4	85
7	limit 6 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>)	1
8	(infan* or child* or teen* or adolescen* or pediatric* or paediatric*).mp.	2534812
9	7 or 8	2534812
10	6 and 9	2
11	5 and 10	1
12	from 11 keep 1-5	1

Citations

1. Csaki C., Ferencz T., Koos R., Schuler D., Borsi J.D.. The role of the 5-HT3 receptor antagonist ondansetron in the control of chemotherapy-induced emesis in children wich malignant diseases. PADIATR. PADOL. [Internet]. 1994 29(2):39-42.
   Included in original AINV literature search

Appendix E: Quality of Evidence and Strength of Recommendations

Quality of Evidence[10]

High Quality	Further research is very unlikely to change our confidence in the estimate of effect
Moderate Quality	Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate
Low Quality	Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate
Very Low Quality	Any estimate of effect is very uncertain

Strength of Recommendations[129]

Strength of recommendation	Benefit vs risk and burdens	Methodology	Implications
1A Strong recommendation, high-quality evidence	Desirable effects clearly outweigh undesirable effects or *vice versa*	Evidence from well done RCTs or Exceptional observational studies	Apply to most patients in most circumstances Further research unlikely to change recommendation
1B Strong recommendation, moderate quality evidence	Desirable effects clearly outweigh undesirable effects or *vice versa*	Evidence from RCTs with some flaws in study or Very strong evidence from observational studies	Apply to most patients in most circumstances Further research might be helpful
1C Strong recommendation, poor quality evidence	Desirable effects clearly outweigh undesirable effects or *vice versa*	Evidence of at least one critical outcome from observational studies, case series or RCTs with flaws	Apply to most patients in many circumstances Further research would be helpful
2A Weak recommendation, high quality evidence	Desirable effects closely balanced with undesirable effects	Consistent evidence from RCTs without important flaws or Exceptionally strong evidence from observational studies	Best action may depend on circumstances or patient or society values Further research unlikely to change recommendation
2B Weak recommendation, moderate quality evidence	Desirable effects closely balanced with undesirable effects	Evidence from RCTs with important flaws or Very strong evidence from observational studies	Best action dependent on patient circumstances or patient or society values Further research may change recommendation
2C Weak recommendation with poor quality evidence	Desirable effects closely balanced with undesirable effects	Evidence of at least one critical outcome from observational studies, case series or RCTs with serious flaws	Other alternatives may be equally reasonable Further research very likely to change recommendation

Appendix F: Tables of Included Studies

Table F.1a: Summary of studies used to inform recommendation 2a: highly emetogenic antineoplastic therapy as ranked by POGO Guideline for Classification of the Acute Emetogenic Potential of Antineoplastic Medication in Pediatric Cancer Patients

First Author (Year of Publication)	Antiemetic Agents Evaluated	Study Design	Number of Patients	Age Range (years)	Number of Patients who were Chemo Naïve	Method of Nausea Assessment	Response Definition and Results
5-HT3 ANTAGONIST, CORTICOSTEROID PLUS APREPITANT							
Hesketh (2003) and Pregent E, Merck Frosst Canada Ltd., March 14, 2007.	ondansetron, dexamethasone + placebo vs ondansetron, dexamethasone + aprepitant	Randomized, double-blind	6	12-18	0	Unvalidated scale	*Complete control defined as: no vomiting and no use of breakthrough antiemetic agents* Complete control: ondansetron, dexametha-sone + aprepitant: **100%** (3/3)
5-HT3 ANTAGONIST PLUS CORTICOSTEROID							
Alvarez (1995)	ondansetron + placebo vs ondansetron + dexamethasone	Double blind, placebo controlled, randomized cross-over	25	3-18	16	Unvalidated scale	*Complete control defined as: no vomiting or retching* Complete control: ondansetron + dexamethasone: **61%** (17/28)
Hesketh, PJ et al. 2003 and personal com-munication Pregent E, Merck Frosst Canada Ltd., March 14, 2007.	ondansetron, dexamethasone + placebo vs ondansetron, dexamethasone + aprepitant	Randomized, double-blind	6	12-18	0	Unvalidated scale	*Complete control defined as: no vomiting and no use of breakthrough antiemetic agents* Complete control: ondansetron, dexamethasone + placebo: **67%** (2/3)
Holdsworth (2006) (supplementary data)	ondansetron +/- dexamethasone	Prospective, descriptive	224 (1256 anti-neoplastic blocks; 137 patients during highly emeto-genic antineo-plastic blocks)	0-19	Not stated	Validated retrospective survey	*Complete control defined as: no vomiting, no retching and no nausea.* Complete control: ondansetron + dexamethasone: **49%** (67/137) of patients receiving first highly emetogenic antineoplastic block
Ozkan (1999)	tropisetron +/- dexamethasone	Prospective, observational	100 (350 antineo-plastic blocks; 15 patients received cisplatin	0.5-15	Not stated	Unvalidated scale	*Complete control defined as: no nausea and no vomiting.* Complete control: tropisetron + dexamethasone: **65%** (13/20)

First Author (Year of Publication)	Antiemetic Agents Evaluated	Study Design	Number of Patients	Age Range (years)	Number of Patients who were Chemo Naïve	Method of Nausea Assessment	Response Definition and Results
			during 40 antineo-plastic blocks)				
5HT-3 ANTAGONISTS PLUS OTHER							
No study Available							
5-HT3 ANTAGONIST ALONE							
Alvarez (1995)	ondansetron + placebo vs ondansetron + dexamethasone	Double blind, placebo controlled, randomized cross-over	25	3-18	16	Unvalidated scale	*Complete control defined as: no vomiting or retching* Complete control: ondansetron + placebo: **23%** (7/30)
Berberoglu (1995)	tropisetron	Prospective, open label	15	0.5-17	0	Not stated	*Complete control defined as: no vomiting and no nausea* Complete control: tropisetron: **53.3%**
Hachimi-Idrissi (1993)*	tropisetron	Prospective, observational	19 (169 antineo-plastic blocks; 27 patients received 93 highly emeto-genic antineo-plastic blocks	2-16	0	Not stated	*Complete control defined as: no nausea, no vomiting and no retching.* Complete control: tropisetron: **76%** (71/93)
Hewitt (1993)*	ondansetron	Open, non-comparative, prospective	200 (25 received cisplatin)	0.9-18	Not stated	Unvalidated scale	*Complete control defined as: no vomiting or retching.* Complete control: ondansetron: **12%** (3/25) No nausea in 16%.
Holdsworth (2006)* (supplementary data)	ondansetron +/- dexamethasone	Prospective, descriptive	224 (1256 anti-neoplastic blocks; 30 patients received highly emeto-genic antineo-plastic blocks)	0-19	Not stated	Validated retrospective survey	*Complete control defined as: no vomiting, no retching and no nausea.* Complete control: ondansetron: **53%** (16/30) of patients receiving first highly emetogenic antineoplastic block
Koseoglu (1998)	ondansetron vs	Randomized	18 antineo-	Mean	100%	Not stated	*Complete control defined as: no vomiting*

First Author (Year of Publication)	Antiemetic Agents Evaluated	Study Design	Number of Patients	Age Range (years)	Number of Patients who were Chemo Naïve	Method of Nausea Assessment	Response Definition and Results
	metoclopramide + diphen-hydramine		plastic blocks	age: 7.6			*and no nausea.* Complete control: ondansetron: **56%** (5/9)
Miyajima (1994)	granisetron vs metoclopramide + promethazine	Prospective, open, crossover	22	0.9-12	Not stated	Unvalidated scale	*Complete control defined as: no vomiting and no more than mild nausea.* Complete control: granisetron: **59%** (13/22)
Otten (1994)	tropisetron	Prospective, observational	24 (92 antineo-plastic blocks; 16 cisplatin-containing blocks)	0.75-16	0	Not stated	*Complete control defined as: no nausea and no vomiting.* Complete control: tropisetron: **70%** Note: complete control observed in 37% (6/16) of those receiving cisplatin
Ozkan (1999)	tropisetron +/- dexamethasone	Prospective, observational	100 (350 antineo-plastic blocks; 15 patients received cisplatin during 40 antineo-plastic blocks)	0.5-15	Not stated	Unvalidated scale	*Complete control defined as: no nausea and no vomiting.* Complete control: tropisetron: **50%** (10/20)
Pinkerton (1990)*	ondansetron	Prospective, observational	30 (31anti-neoplastic blocks; 26 highly emeto-genic antineo-plastic blocks)	2-16	12	Unvalidated scale	*Complete control defined as: no vomiting* Complete control: ondansetron: **71%** (22/31)
Rosso (1994)	tropisetron	Prospective, observational	10 (20 anti-neoplastic blocks)	1.7- 15	0	Not stated	*Complete control defined as: no vomiting* Complete response: tropisetron: **70%** No nausea: 40%
Uysal (1999)*	tropisetron	Prospective, observational	22 (unknown number received highly emeto-genic antineo-plastic blocks over total of 258	3-18	Not stated	Not stated	*Complete control defined as: no vomiting and no nausea.* Complete control: tropisetron: **69%** of days

First Author (Year of Publication)	Antiemetic Agents Evaluated	Study Design	Number of Patients	Age Range (years)	Number of Patients who were Chemo Naïve	Method of Nausea Assessment	Response Definition and Results
			days)				
OTHER							
Koseoglu (1998)	ondansetron vs metoclopramide + diphen-hydramine	Randomized	18 antineo-plastic blocks	Mean age: 7.6	100%	Not stated	*Complete control defined as: no vomiting and no nausea.* <u>Complete control:</u> metoclopramide + diphenhydramine: **11%** (1/9)
Marshall (1989)	chlorpromazine + placebo vs metoclopramide, dexamethasone, benztropine, lorazepam + placebo	Randomized, double-blind crossover	26	4-15	3	Not assessed	*Complete control defined as: no vomiting.* <u>Complete control:</u> chlorpromazine + placebo: **19%** (5/26) metoclopramide, dexamethasone, benztropine, lorazepam + placebo: **46%** (12/26)
Miyajima (1994)	granisetron vs metoclopramide + promethazine	Prospective, open, crossover	22	0.9-12	Not stated	Unvalidated scale	*Complete control defined as: no vomiting and no more than mild nausea.* <u>Complete control:</u> metoclopramide + promethazine: **0%** (0/22)

Table F.1b: Summary of studies used to inform recommendation 2a: highly emetogenic antineoplastic therapy as ranked by study investigators where insufficient information available to assign emetogenic risk using the POGO Guideline for Classification of the Acute Emetogenic Potential of Antineoplastic Medication in Pediatric Cancer Patients

Study	Antiemetic Agents Evaluated	Study Design	Number of Patients	Age Range (years)	Number of Patients who were Chemo Naïve	Method of Nausea Assessment	Response Definition and Results
5-HT3 ANTAGONIST, CORTICOSTEROID PLUS APREPITANT							
No study available							
5-HT3 ANTAGONIST, CORTICOSTEROID PLUS OTHER							
No study available							
5-HT3 ANTAGONIST PLUS CORTICOSTEROID							
No study available							
5-HT3 ANTAGONIST PLUS OTHER							
No study available							
5-HT3 ANTAGONIST ALONE							
Aksoylar (2001)	tropisetron vs granisetron	Prospective, randomized	51 (133 antineo-plastic blocks; 49 very highly emeto-genic antineo-plastic blocks)	1-17	13	Assessment by health care provider	*Complete control defined as: no vomiting and no nausea.* Complete control: tropisetron: **30%** (8/27) granisetron: **32%** (7/22)
Brock (1996)*	ondansetron	Double-blind, randomized, parallel group	159	1.9-16.7	Not stated	Not stated	*Complete control defined as: no vomiting and no retching* Complete control: loading dose: **44%** no loading dose: **42%**
Cappelli (2005)	tropisetron	Prospective, observational	50 (182 anti-neoplastic blocks; 116 highly emeto-genic antineo-plastic blocks)	0.5-19	23	Not assessed	*Complete control defined as: no vomiting* Complete control: tropisetron: **85%** (99/116)
OTHER							
No study available							

**Data extracted from results*

Table F.2a: Summary of studies used to inform recommendation 2b: moderately emetogenic antineoplastic therapy as ranked by POGO Guideline for Classification of the Acute Emetogenic Potential of Antineoplastic Medication in Pediatric Cancer Patients

Study	Antiemetic Agents Evaluated	Study Design	Number of Patients	Age Range (years)	Number of Patients who were Chemo Naïve	Method of Nausea Assessment	Response Definition and Results
5-HT3 ANTAGONIST, CORTICOSTEROID PLUS APREPITANT							
No study available							
5-HT3 ANTAGONIST, CORTICOSTEROID PLUS OTHER							
No study available							
5-HT3 ANTAGONIST PLUS CORTICOSTEROID							
No study available							
5-HT3 ANTAGONIST PLUS OTHER ANTIEMETIC AGENTS							
No study available							
5-HT3 ANTAGONIST ALONE							
Coppes (1999a)	dolasetron (IV)	Open-label , non-rando-mized, multi-center, dose escalation study	46	3-17	11	Not stated	*Complete control defined as: no emetic episodes and no use of escape antiemetic therapy* <u>Complete control:</u> dolasetron: 0.6mg/kg: **10%** (1/10) 1.2mg/kg: **25%** (3/12) 1.8mg/kg: **67%** (8/12) 2.4mg/kg: **33%** (4/12)
Coppes (1999b)	dolasetron (oral)	Open-label , non-rando-mized, multi-center, dose escalation study	32	3-17	1	Not stated	*Complete control defined as: no emetic episodes and no use of escape antiemetic therapy* <u>Complete control:</u> dolasetron: 0.6mg/kg: **33%** 3/9 1.2mg/kg: **31%** (4/13) 1.8mg/kg: **50%** (5/10) Note: 4 patients received corticosteroids as part of treatment protocol
Corapcioglu (2005)	ondansetron oral vs IV	Prospective, randomized trial	22 (95 antineo-plastic blocks)	3-17	Not stated	Not assessed	*Complete control defined as: no vomiting or retching* <u>Complete control:</u> oral ondansetron: **80%** (19/24) IV ondansetron: **75**% (24/32) (p=0.931)

Study	Antiemetic Agents Evaluated	Study Design	Number of Patients	Age Range (years)	Number of Patients who were Chemo Naïve	Method of Nausea Assessment	Response Definition and Results
Craft (1995)	granisetron	Prospective, observational	38 (40 antineo-plastic blocks)	2-16	38	Not stated	*Complete control defined as: no nausea, vomiting or retching* Complete control: granisetron: **28%** (11/40)
Hachimi-Idrissi (1993)	tropisetron	Prospective, observational	19 (169 antineo-plastic blocks; 13 patients received 64 mode-rately emeto-genic anti-neoplastic blocks)	2-16	0	Not stated	*Complete control defined as: no nausea or vomiting* Complete control: tropisetron: **78%** (50/64)
Hahlen (1995)	granisetron vs chlorproperazine+ dexamethasone	Single blinded, randomized comparison	88 (moder-ately and highly emeto-genic antineo-plastic blocks)	2-17	Approxi-mately 67%	Unvalidated scale	*Complete control defined as: no worse than mild nausea, no vomiting and no rescue antiemetics required:* Complete control: granisetron: **21.7%** (10/46)
Hewitt (1993)	ondansetron	Open, non-comparative, prospective	183 (40 received ifosfa-mide)	0.9-18	Not stated	Unvalidated scale	*Complete control defined as: no vomiting or retching.* Complete control: ondansetron: **28%** (11/40) No nausea: **35%**
Holdsworth (1998)	ondansetron	Prospective, observational	63 (159 antineo-plastic blocks)	1-17	0	Validated, retrospective survey	*Complete control defined as: no nausea, vomiting or retching* Complete control: IV ondansetron: **40%** (14/35) oral ondansetron: **25%** (4/16)

Study	Antiemetic Agents Evaluated	Study Design	Number of Patients	Age Range (years)	Number of Patients who were Chemo Naïve	Method of Nausea Assessment	Response Definition and Results
Holdsworth (2006)* (supplementary data)	ondansetron	Prospective, descriptive	224 (1256 anti-neoplastic blocks; 171 patients received moderate-ly emeto-genic antineo-plastic blocks)	0-19	Not stated	Validated retrospective survey	*Complete control defined as: no vomiting, no retching and no nausea.* <u>Complete control:</u> ondansetron: **74%** (127/171) of patients receiving first moderately emetogenic antineoplastic block
Mabro (2000)	granisetron	Randomized, double blind	294	1 - 16	64%	Unvalidated assessment by patient or parent	*Complete control defined as: no vomiting, no more than mild nausea, no use of other antiemetic agents and no withdrawal from study.* <u>Complete control:</u> low dose granisetron: **51**% (73/143) high dose granisetron: **53**% (80/151)
Nadaraja (2012)	palonosetron	Prospective, observational	53 (138 antineo-plastic blocks)	2-18 (mean: 6.6 ± 4.5)	0	Unvalidated visual analogue scale	*Complete control defined as: no emetic episodes and no use of rescue medication* <u>Complete control:</u> palonosetron: 84.1%
Ozkan (1999)*	tropisetron	Prospective, observational	100 (61 patients received moderate-ly to highly emeto-genic antineo-plastic blocks)	0.5-15	Not stated	Unvalidated scale	*Complete control defined as: no nausea and no vomiting.* <u>Complete control:</u> tropisetron: **50%** (30/61)
Parker (2001)*	ondansetron	Randomized, double-blind, placebo-controlled	26 (146 antineo-plastic blocks)	1.5-15	Not stated	Not assessed	*Complete control defined as: no vomiting.* <u>Complete control:</u> placebo: **37%** (19/51) high-dose ondansetron: **85.4%** (41/48) low-dose ondansetron: **72.3%** (34/47)

Study	Antiemetic Agents Evaluated	Study Design	Number of Patients	Age Range (years)	Number of Patients who were Chemo Naïve	Method of Nausea Assessment	Response Definition and Results
Stevens (1991)	ondansetron	Open, non-comparative	44	4-18	0	Unvalidated scale	*Complete control defined as: no vomiting and no retching* Complete control: **87%** on first day of treatment
OTHER ANTIEMETIC AGENTS							
Hahlen (1995)	granisetron vs chlorproperazine+ dexamethasone	Single blinded, randomized comparison	88 (moder-ately and highly emeto-genic antineo-plastic blocks)	2-17	Approxi-mately 67%	Unvalidated scale	*Complete control defined as: no worse than mild nausea, no vomiting and no rescue antiemetics required:* Complete r control: chlorproperazine + dexamethasone: **9.5%** (4/42)
Mehta (1986)*	methylpred-nisolone vs chlorpromazine	Randomized, double-blind	20	2-22	Not stated	Not stated	*Complete control defined as: no vomiting and no nausea.* Complete control: methylprednisolone: **40%** (4/10) chlorpromazine: **30%** (3/10)

Table F.2b: Summary of studies used to inform recommendation 2b: moderate emetogenic antineoplastic therapy as ranked by study investigators where insufficient information available to assign emetogenic risk using the POGO Guideline for Classification of the Acute Emetogenic Potential of Antineoplastic Medication in Pediatric Cancer Patients

Study	Antiemetic Agents Evaluated	Study Design	Number of Patients	Age Range (years)	Number of Patients who were Chemo Naïve	Method of Nausea Assessment	Response Definition and Results
5-HT3 ANTAGONIST, CORTICOSTEROID PLUS APREPITANT							
No study available							
5-HT3 ANTAGONIST, CORTICOSTEROID PLUS OTHER							
No study available							
5-HT3 ANTAGONIST PLUS CORTICOSTEROID							
White (2000)	ondansetron IV + dexamethasone vs ondansetron oral + dexamethasone	Randomized, double-blind, parallel group trial	28	1-17	Not stated	Unvalidated scale	*Complete control defined as: no emesis (vomiting and retching) or no nausea (reported separately).* Complete control of emesis on Day 1:

Study	Antiemetic Agents Evaluated	Study Design	Number of Patients	Age Range (years)	Number of Patients who were Chemo Naïve	Method of Nausea Assessment	Response Definition and Results
							IV ondansetron + dexamethasone: **81%** (172/212) oral ondansetron + dexamethasone: **78%** (168/216) <u>Complete control of nausea on Day 1:</u> IV ondansetron + dexamethasone: **73%** (155/212) oral ondansetron + dexamethasone: **70%** (151/216)
5-HT3 ANTAGONIST PLUS OTHER							
No study available							
5-HT3 ANTAGONIST ALONE							
Cappelli (2005)*	tropisetron	Prospective, observational	50 (182 anti-neoplastic blocks; 56 moderate-ly emeto-genic anti-neoplastic blocks)	0.5-19	23	Not assessed	*Complete control defined as: no vomiting* <u>Complete control:</u> tropisetron: **81%** (45/56)
Dick (1995)	ondansetron vs metoclopra-mide, dexamethasone + procyclidine	Randomized comparison	30	1.5-15	Not stated	Unvalidated scale	*Complete control defined as: no emesis (vomiting and retching) or no nausea (reported separately).* <u>Complete control of emesis on Day 1:</u> ondansetron: **73%** (11/15) <u>Complete control of nausea on Day 1:</u> Not reported
Jaing (2004)	granisetron vs ondansetron	Randomized, open-label, crossover	33 (66 antineo-plastic blocks)	3 - 18	Not stated	Not stated	*Complete control defined as: no emetic episodes and no need for rescue medication* <u>Complete control:</u> granisetron: **61%** (20/33) ondansetron: **45.5%** (15/33)
OTHER ANTIEMETIC AGENTS							
Chan (1987)	nabilone vs	Randomized,	30	3.5-17.8	0	Not assessed	*Complete control defined as: no vomiting*

Study	Antiemetic Agents Evaluated	Study Design	Number of Patients	Age Range (years)	Number of Patients who were Chemo Naïve	Method of Nausea Assessment	Response Definition and Results
	prochlorpera-zine	double-blind, crossover					*and no retching.* Complete control: nabilone: **10%** (3/30) prochlorperazine: **10%** (3/30)
Dick (1995)	ondansetron vs metoclopramide, dexamethasone + procyclidine	Randomized comparison	30	1.5-15	Not stated	Unvalidated scale	*Complete control defined as: no emesis (vomiting and retching) or no nausea (reported separately).* Complete control of emesis on Day 1: metoclopramide, dexamethasone + procyclidine: **20%** (3/15) Complete control of nausea on Day 1: Not reported

*Data extracted from results

Table F.3a: Summary of studies used to inform recommendation 2c: antineoplastic therapy of low emetic risk as ranked by POGO Guideline for Classification of the Acute Emetogenic Potential of Antineoplastic Medication in Pediatric Cancer Patients

Study	Antiemetic Agents Evaluated	Study Design	Number of Patients	Age Range (years)	Number of Patients who were Chemo Naïve	Method of Nausea Assessment	Response Definition and Results
5-HT3 ANTAGONIST, CORTICOSTEROID PLUS APREPITANT							
No study available							
5-HT3 ANTAGONIST, CORTICOSTEROID PLUS OTHER							
No study available							
5-HT3 ANTAGONIST PLUS CORTICOSTEROID							
Hirota T (1993)	granisetron vs granisetron + methylpredni-solone	Randomized, controlled, crossover	10 (20 antineo-plastic blocks; 12 highly emetogenic, 6 moderately emetogenic and 2 blocks of low emeto-genicity)	4-18	Not stated	Unvalidated scale	*Complete control defined as: no vomiting, nausea, loss of appetite or stomach discomfort.* Complete control: granisetron + methylprednisolone: **80%** (16/20)
5-HT3 ANTAGONIST PLUS OTHER							
No study available							

Study	Antiemetic Agents Evaluated	Study Design	Number of Patients	Age Range (years)	Number of Patients who were Chemo Naïve	Method of Nausea Assessment	Response Definition and Results
5-HT3 ANTAGONIST ALONE							
Hachimi-Idrissi (1993)*	tropisetron	Prospective, observational	19 (169 antineo-plastic blocks; 5 patients received 11 antineo-plastic blocks of low emeto-genicity)	2-16	0	Not stated	*Complete control defined as: no nausea, no vomiting and no retching.* Complete control: tropisetron: **91%** (10/11)
Hirota T (1993)	granisetron vs granisetron + methylpredni-solone	Randomized, controlled, crossover	10 (20 antineo-plastic blocks; 12 highly emetogenic, 6 moderately emetogenic and 2 blocks of low emeto-genicity)	4-18	Not stated	Unvalidated scale	*Complete control defined as: no vomiting, nausea, loss of appetite or stomach discomfort.* Complete control: granisetron: **50%** (10/20)
Holdsworth (2006)* (supplementary data)	ondansetron	Prospective, descriptive	224 (1256 anti-neoplastic blocks; 11 patients received antineo-plastic blocks of low emeto-genicity)	0-19	Not stated	Validated retrospective survey	*Complete control defined as: no vomiting, no retching and no nausea.* Complete control: ondansetron: **82%** (9/11)
Koseoglu (1998)	ondansetron vs metoclopramide + diphen-hydramine	Randomized	46 antineo-plastic blocks	Mean age: 7.6	100%	Not stated	*Complete control defined as: no vomiting and non nausea.* Complete control: ondansetron: **91%** (21/23)

Study	Antiemetic Agents Evaluated	Study Design	Number of Patients	Age Range (years)	Number of Patients who were Chemo Naïve	Method of Nausea Assessment	Response Definition and Results
Ozkan (1999)	tropisetron	Prospective, observational	100 (23 patients received antineoplas-tic blocks of low to high emetogeni-city)	0.5-15	Not stated	Unvalidated scale	*Complete control defined as: no nausea and no vomiting.* Complete control: tropisetron: **60%** (14/23)
Sandoval (1999)	ondansetron: single dose vs multiple dose	Prospective, double-blind, randomized	31 (patients received antineoplas-tic blocks of low to high emetogeni-city)	0.25-18	31	Unvalidated scale	*Complete control defined as: no nausea or emesis* Complete control: single dose: **75%** (12/16) multiple dose: **60%** (9/15)
OTHER							
Koseoglu (1998)	ondansetron vs metoclopramide + diphen-hydramine	Randomized	18 antineo-plastic blocks	Mean age: 7.6	100%	Not stated	*Complete control defined as: no vomiting and non nausea.* Complete control: metoclopramide + diphen-hydramine: **74%** (17/23)

Table F4a: Summary of studies used to inform recommendation 2d: antineoplastic therapy of minimal emetic risk as ranked by study investigators where insufficient information available to assign emetogenic risk using the POGO Guideline for Classification of the Acute Emetogenic Potential of Antineoplastic Medication in Pediatric Cancer Patients

Study	Antiemetic Agents Evaluated	Study Design	Number of Patients	Age Range (years)	Number of Patients who were Chemo Naïve	Method of Nausea Assessment	Response Definition and Results
5-HT3 ANTAGONIST, CORTICOSTEROID PLUS APREPITANT							
No study available							
5-HT3 ANTAGONIST, CORTICOSTEROID PLUS OTHER							
No study available							
5-HT3 ANTAGONIST PLUS OTHER							
No study available							
5-HT3 ANTAGONIST ALONE							

Study	Antiemetic Agents Evaluated	Study Design	Number of Patients	Age Range (years)	Number of Patients who were Chemo Naïve	Method of Nausea Assessment	Response Definition and Results
Ozkan (1999)	tropisetron	Prospective, observational	100 (16 patients received antineoplas-tic blocks of minimal to high emetogeni-city)	0.5-15	Not stated	Unvalidated scale	*Complete control defined as: no nausea and no vomiting.* Complete control: tropisetron: **100%** (16/16)
OTHER							
No study available							

Table F.5: Summary of studies used to inform recommendation 4.

First Author (Year of Publication)	Antiemetic Agents Evaluated	Study Design	Number of Patients	Age Range (years)	Emetogenicity of Antineoplastic Therapy	Findings: Efficacy	Findings: Adverse Effects
5-HT3 ANTAGONIST, CORTICOSTEROID, APREPITANT PLUS OTHER							
Ouellet (2005)	ondansetron/ granisetron, dexamethasone, lorazepam, metoclopramide, prochlorproma-zine, diphenhyd-ramine + aprepitant	Case report	1 (10 antineo-plastic blocks)	15	High	*Complete control not defined.* Significant clinical reduction in vomiting and nausea severity and nausea duration with the addition of aprepitant. AINV control not quantified.	None reported.
5-HT3 ANTAGONIST, CORTICOSTEROID PLUS APREPITANT							

First Author (Year of Publication)	Antiemetic Agents Evaluated	Study Design	Number of Patients	Age Range (years)	Emetogenicity of Antineoplastic Therapy	Findings: Efficacy	Findings: Adverse Effects
Choi (2010)	ondansetron, aprepitant ± dexamethasone	Retrospec-tive review	32	2.7-18	Moderate to High	*Complete control not defined.* 59.4% of patients experienced "minimal to no" AINV. Note: results 'unknown' for 18.8% patients.	Hyperglycemia: 2/32
Coppola (2008)	aprepitant	Retrospec-tive chart review	33	< 18	Not provided	*Complete control not defined* 76.7% of patients experienced complete or major response.	Peripheral neuropathy: 6% attributed to antineoplastic agent – aprepitant interaction
Gore (2009)	ondansetron, dexamethasone + aprepitant vs ondansetron, dexamethasone + placebo	Rando-mized, double-blind, placebo-controlled trial (4 patients received open label aprepitant)	46	11-19	Unknown	*Complete response defined as: no vomiting and no use of rescue therapy* 60.7% of 32 patients who received ondansetron, dexamethasone + aprepitant experienced complete control.	Febrile neutropenia: aprepitant 25%; control 11.1%

First Author (Year of Publication)	Antiemetic Agents Evaluated	Study Design	Number of Patients	Age Range (years)	Emetogenicity of Antineoplastic Therapy	Findings: Efficacy	Findings: Adverse Effects
Hesketh (2003) and personal com-munication Pregent E, Merck Frosst Canada Ltd., March 14, 2007.	ondansetron, dexamethasone + placebo vs ondansetron, dexamethasone + aprepitant	Rando-mized, double-blind	3	12-18		*Complete control defined as: no vomiting and no use of breakthrough antiemetic agents* Complete control: 100% (3/3) patients who received ondansetron, dexamethasone + aprepitant experienced complete control.	None reported.
Smith (2005)	ondansetron, dexamethasone + aprepitant	Case reports	2 (3 anti-neoplastic blocks)	16 - 17	Patient 1: High Patient 2: Moderate	Patient 1: No vomiting, less nausea and decreased need for breakthrough antiemetic therapy when aprepitant given. Patient 2: No vomiting and no nausea when aprepitant given.	None reported.
Vianello (2005)	ondansetron, dexamethasone + aprepitant	Case reports	5	10-15	High	*Complete control defined as: a maximum of grade 1 nausea (able to eat) and vomiting (0-1 episode in 24 hrs)* 80% of patients experienced complete control	None reported.

Table F.6: Summary of studies used to inform recommendation 5

First Author (Year)	Antiemetic Agents Evaluated	Study Design	Number of Patients	Age Range (years)	Number of Patients who were Chemo Naïve	Method of Nausea Assessment	Response Definition and Results
CHLORPROMAZINE							
HIGHLY EMETOGENIC ANTINEOPLASTIC THERAPY							
Marshall (1989)	chlorpromazine + placebo vs metoclopramide, dexamethasone, benztropine, lorazepam + placebo	Randomized, double-blind crossover	26	4-15	3	Not assessed	*Complete control defined as: no vomiting.* Complete control: chlorpromazine + placebo: **19%** (5/26)
MODERATELY EMETOGENIC ANTINEOPLASTIC THERAPY							
Mehta (1986)	methylpred-nisolone vs chlorpromazine	Randomized, double-blind	20	2-22	Not stated	Not stated	*Complete control defined as: no vomiting and no nausea.* Complete control: chlorpromazine: **30%** (3/10)
METOCLOPRAMIDE							
HIGHLY EMETOGENIC ANTINEOPLASTIC THERAPY							
Koseoglu (1996)	ondansetron vs metoclopramide + diphenhydramine	Randomized	18 antineoplastic courses of highly emetogenic potential (unknown number of patients)	unknown	Not stated	Unvalidated scale	*Complete control defined as: no vomiting* Complete control: metoclopramide + diphenhydramine: **11%** (1/9)
Miyajima (1994)	granisetron vs metoclopramide + promethazine	Prospective, open, crossover	22	0.9-12	Not stated	Unvalidated scale	*Complete control defined as: no vomiting and no more than mild nausea.* Complete control: metoclopramide + promethazine: **0%** (0/22)

First Author (Year)	Antiemetic Agents Evaluated	Study Design	Number of Patients	Age Range (years)	Number of Patients who were Chemo Naïve	Method of Nausea Assessment	Response Definition and Results
ANTINEOPLASTIC THERAPY OF LOW EMETOGENIC POTENTIAL							
Koseoglu (1996)	ondansetron vs metoclopramide + diphenhydramine	Randomized	46 antineoplastic courses of low to moderate emetogenic potential (unknown number of patients)	unknown	Not stated	Unvalidated scale	*Complete control defined as: no vomiting.* Complete control: metoclopramide + diphenhydramine: **74%** (17/23)
NABILONE							
MODERATELY EMETOGENIC ANTINEOPLASTIC THERAPY							
Chan (1987)	nabilone vs prochlorperazine	Randomized, double-blind, crossover	30	3.5-17.8	0	Not assessed	*Complete control defined as: no vomiting and no retching.* Complete control: nabilone: **10% (**3/30)
PROCHLORPERAZINE							
MODERATELY EMETOGENIC ANTINEOPLASTIC THERAPY							
Chan (1987)	nabilone vs prochlorperazine	Randomized, double-blind, crossover	30	3.5-17.8	0	Not assessed	*Complete control defined as: no vomiting and no retching.* Complete control: prochlorperazine: **10%** (3/30)

Table F.7a: Summary of evidence to inform recommendation 6: Aprepitant Dose

Study	Study Design	Quality of Evidence	Aprepitant Dose	Route	Concurrent Antiemetic Agent(s)	Findings
HIGHLY EMETOGENIC ANTINEOPLASTIC AGENTS						
Choi (2010)	Retrospec-tive chart review	Very low	> 20 kg: Day 1: 125mg x 1 Day 2 & 3: 80mg daily < 20 kg: 80mg/day x 3 days < 15 kg: Day 1: 80mg x 1 Day 2 & 3: 40mg daily	PO	ondansetron +/- dexamethasone	*Complete control defined as: not stated.*
Coppola (2008)	Retrospec-tive chart review	Very low	Day 1: 80mg (approximately 2mg/kg x 1) Day 2 & 3: 40mg (approximately 1.5mg/kg daily)	PO	Not stated	*Complete control defined as: no emetic episodes.* <u>Complete control</u>: Highly emetogenic therapy: ~89% Moderately emetogenic therapy: ~67% 2 cases of peripheral neuropathy attributed to aprepitant-chemotherapy interaction

Study	Study Design	Quality of Evidence	Aprepitant Dose	Route	Concurrent Antiemetic Agent(s)	Findings
Hesketh (2003) and personal communi-cation Pregent E, Merck Frosst Canada Ltd., March 14, 2007.	Randomized, double-blind, placebo controlled	Very low	Day 1: 125mg x 1 Day 2 & 3: 80mg daily	PO	ondansetron + dexamethasone	*Complete control defined as: no vomiting and no use of breakthrough antiemetic agents.* <u>Complete control:</u> ondansetron, dexamethasone + aprepitant: **100%** (3/3)
Ouellet & Theriien (2005)	Case report	Very low	Day 1: 125mg x 1 Day 2 & 3: 80mg daily	PO	granisetron, dexamethasone, lorazepam, nabilone and dimenhydrinate	*Complete control defined as: not stated.* No vomiting in 5/11 blocks given with aprepitant.
Smith (2005)	Case reports (2)	Very low	Day 1: 125mg x 1 Day 2 & 3: 80mg daily	PO	ondansetron + dexamethasone	*Complete control defined as: not stated.* No vomiting in 2/2 and 1/1 blocks given with aprepitant.
EMETOGENICITY NOT ABLE TO BE DETERMINED						
Gore (2009)	Randomized, double-blind, placebo controlled	Very low	Day 1: 125mg x 1 Day 2 & 3: 80mg daily	PO	ondansetron + dexamethasone	*Complete control defined as: no vomiting and no use of breakthrough antiemetic agents.* <u>Complete control:</u> ondansetron, dexamethasone + aprepitant: **100%** (3/3)

Study	Study Design	Quality of Evidence	Aprepitant Dose	Route	Concurrent Antiemetic Agent(s)	Findings
Vianello (2005)	Case series	Very low	Day 1: 125mg x 1 Day 2 & 3: 80mg daily	PO	ondansetron + dexamethasone	*Complete control defined as: not stated.* No more than 1 vomiting episode in 24 hrs (NCI grade 1) observed in 7/8 blocks.

Table F.7b: Summary of studies used to inform recommendation 6: Chlorpromazine Dose

Study	Study Design	Quality of Evidence	Chlorpro-mazine Dose	Route	Concurrent Antiemetic Agent(s)	Findings
HIGHLY EMETOGENIC ANTINEOPLASTIC AGENTS						
Marshall (1989)	Randomized, double-blind crossover	Low	0.825 mg/kg/dose pre-therapy x 1 and q6h x 3	IV	none	*Complete control defined as: no vomiting.* Complete control: chlorpromazine + placebo: **19%**
MODERATELY EMETOGENIC ANTINEOPLASTIC AGENTS						
Hahlen (1995)	Randomized, single-blinded	Low	0.5mg/kg/dose pre-therapy x 1 and q4-6h OR 0.3mg/kg/dose pre-therapy x 1 and 0.3-0.5mg/kg/dose q4-6h	IV	dexamethasone	*Complete control defined as: no worse than mild nausea, no vomiting and no rescue antiemetic agents required.* Complete control: chlorpromazine + dexamethasone: **9.5%** (4/42) Chlorpromazine dose reduced due to excessive sedation.
Mehta (1986)	Randomized, double-blind	Low	0.5mg/kg/dose pre-therapy x 1 and another dose 6 hours later if needed	IV	none	*Complete control defined as: no vomiting and no nausea.* Complete control: chlorpromazine: **30%** (3/10)
EMETOGENICITY NOT ABLE TO BE DETERMINED						
Graham-Pole (1986)	Randomized, double blind, prospective	Moderate	0.5mg/kg/dose pre-therapy x 1 and q3h x 5	IV	none	*Complete control defined as: not stated.* Reduced number of vomits in children receiving chlorpromazine compared to metoclopramide

Study	Study Design	Quality of Evidence	Chlorpro-mazine Dose	Route	Concurrent Antiemetic Agent(s)	Findings
Relling (1993)	Randomized, double-blind prospective	Moderate	30mg/m^2/dose (approx 1mg/kg/dose) pre-therapy x 1 and 4 hours later x 1	IV	+/-lorazepam	*Complete control defined as: not stated.* No benefit of adding lorazepam to chlorpromazine.
Zeltzer (1984)	Post hoc analysis	Very low	25-100mg/dose pre-therapy x 1 and q4-6h	IV	none	*Complete control defined as: not stated.* Use of phenothiazines may increase nausea and vomiting.

Table F.7c: Summary of studies used to inform recommendation 6: Dexamethasone Dose

First Author (Year)	Study Design	Study Population	Interventions	Dexamethasone Dose & Route	Definition Used for Complete Control	% Complete Control
Highly emetogenic antineoplastic therapy						
Alvarez (1995)	Randomized double blind, placebo controlled, crossover trial	▪ Children with solid tumours receiving highly emetogenic chemotherapy ▪ Median age 9 yrs; range 3 to 18 yrs ▪ Naive to antineoplastic therapy: 49%	Randomized to G1 or G2 then crossover for 2nd antineoplastic block. G1: ondansetron + placebo G2: ondansetron + dexamethasone	Varied by hospital: 8 mg/m^2/dose pre-therapy x 1 then 4 mg/m^2/dose q6h IV (24 mg/m^2/day) (site A) or 8 mg/m^2/dose pre-therapy x 1 dose then q4h x 2 doses IV (24 mg/m^2/day)(site B)	No vomiting or retching	G1: 23% (7/30) G2: 61% (17/28) 25/33 pts enrolled completed 2 study blocks
Hesketh* (2003)	Random allocation of 6 adolescents to treatment arms of a Phase III randomized, double-blind, placebo controlled adult trial	▪ A site-specific amendment allowed pts ≥12 years but <18 years and ≥40kg to be randomized to a Phase III RCT of pts with solid tumours ≥18 yrs receiving cisplatin ≥70mg/m^2 for the first time ▪ Naive to antineoplastic therapy: 0%	G1: ondansetron, dexamethasone + placebo G2: ondansetron, dexamethasone + aprepitant	G1: Day 1: 20mg x 1 Day 2 - 4: 8mg once daily PO G2: Day 1: 12mg x 1 Day 2 - 4: 8mg once daily PO	No vomiting and no use of breakthrough antiemetic agents	G1: 67% (2/3) G2: 100% (3/3)

First Author (Year)	Study Design	Study Population	Interventions	Dexamethasone Dose & Route	Definition Used for Complete Control	% Complete Control
Holdsworth** (2006)	Prospective, descriptive	▪ Children with cancer receiving antineoplastic therapy requiring antiemetic prophylaxis ▪ Naive to antineoplastic therapy: 100%	ondansetron + dexamethasone	G1: 10 mg/m^2/dose once daily IV G2: 10 mg/m^2/dose q12h or q24h IV	No vomiting, no retching and no nausea	G1: 48% (62/129) G2: 75% (6/8)
Marshall (1989)	Randomized, double blind placebo controlled crossover trial	▪ Children with cancer receiving antineoplastic therapy ▪ Median age: 7 yrs; range 4 to 15 yrs ▪ Naive to antineoplastic therapy: 12%	Randomized to G1 or G2 then crossover for second antineoplastic block G1:chlorpromazine + placebo G2: metoclopramide, dexamethasone, benztropine, lorazepam + placebo	0.7 mg/kg/dose (approximately 21 mg/m^2/dose) pre-therapy x 1 IV	No vomiting	G1: 19% (5/26) G2: 46% (12/26)
Sumer (1988)	Randomized trial	▪ Children receiving cisplatin therapy ▪ Age range: 1.3 to 5.4 yrs ▪ Naive to antineoplastic therapy: 45%	Randomized to G1 or G2 then G2 given every second cisplatin block G1: no antiemetic G2: dexamethasone	1 mg/m^2/dose IV 6 hrs before cisplatin and then every 4 hrs x 10 doses (approximately 6 mg/m^2/day)	No vomiting	G1: 0% (0/11) G2: 27% (3/11)
Moderately emetogenic antineoplastic therapy						
Dick (1995)	Randomized, double blind comparison	▪ Children with leukemia ▪ Age range: 1.5 to 15 yrs ▪ Naive to antineoplastic therapy: 0%	G1: ondansetron G2: metoclopramide, dexamethasone + procyclidine	4mg/m^2/dose pre-therapy IV x 1 dose then 2mg/m^2/dose three times daily IV or PO	No vomiting or retching	G1: 73% (11/15) G2: 20% (3/15)
Hahlen (1995)	Single blinded, randomized comparison	▪ Children receiving ifosfamide +/- other antineoplastic agents ▪ Mean age: 9.5 yrs	G1: granisetron G2: chlorpromazine + dexamethasone	2mg/m^2/dose pre-therapy IV and q8h x 2	No worse than mild nausea, no vomiting, no rescue antiemetics required	G1: 21.7% (10/46) G2: 9.5% (4/42)
White (2000)	Randomized, double-blind, placebo controlled parallel group	▪ Children receiving moderately/highly emetogenic antineoplastic therapy ▪ Mean age: 8 yrs; range: 1 to 17 yrs	G1: ondansetron IV + dexamethasone G2: ondansetron PO + dexamethasone	2 to 4 mg/dose pre-therapy PO, 6 to 8 hrs later and then twice daily BSA ≤ 0.6m^2: 2 mg/dose BSA > 0.6m^2: 4 mg/dose	No vomiting or retching	G1: 81% (172/212) G2: 78% (168/216)

First Author (Year)	Study Design	Study Population	Interventions	Dexamethasone Dose & Route	Definition Used for Complete Control	% Complete Control
Antineoplastic therapy of unknown emetogenicity						
Basade (1996)	Randomized, single-blind, cross-over	▪ Children with cancer receiving cyclophosphamide ≥ 600mg/m^2 +/- other antineoplastic agents ▪ Median age: 7 yrs; range: 3 to 14 yrs	G1: dexamethasone G2: metoclopramide	8mg/m^2/dose pre-therapy IV	No emetic episodes	G1: 62% (16/26) G2: 30% (8/27)
Gore[£] (2009)	Randomized, double-blind, placebo-controlled (4 patients received open label aprepitant)	▪ Children receiving antineoplastic therapy ▪ Age range: 11 to 19 yrs	G1: ondansetron, dexamethasone + aprepitant G2:ondansetron, dexamethasone + placebo	G1: Day 1: 8mg as a single daily dose PO; Days 2 -4: 4mg as a single daily dose PO G2: Day 1: 16mg as a single daily dose PO; Days 2-4: 8mg as a single daily dose PO	No vomiting and no use of rescue therapy	G1: 60.7% (19/32) G2: 38.9% (7/18)
Kusnierczyk (2002)	Prospective descriptive	▪ 25 children receiving conditioning for haematopoietic stem cell transplant ▪ Median age: 8.5 yrs; range: 0.6 to 16 yrs	ondansetron every 8 or 12 hrs + dexamethasone	8mg/m^2/dose (max: 20mg/dose) pre-therapy IV and q12h	No vomiting or retching	74% of days

G1: group 1, G2: group 2
*With supplemental data obtained from personal communication with Pregent E, Merck Frost Canada Ltd., March 14, 2007.
**With supplemental data obtained from personal communication with Mark Holdsworth, March 28, 2011
[£]With supplemental appendix

Table F.7d: Summary of studies used to inform recommendation 6: Granisetron Dose

First Author (Year)	Study Design	Study Population	Interventions	Granisetron Dose & Route	Definition Used for Complete Control	% Complete Control
Highly emetogenic antineoplastic therapy						
Komada (1999)	Randomized, crossover	▪ Children receiving cytarabine 3 g/m^2	granisetron + dexamethasone	G1: 20 mcg/kg/dose pre-therapy IV x 1 G2: 40 mcg/kg/dose pre-therapy IV x 1	No emetic episodes	G1: 100% (13/13) G2: 100% (13/13)
Miyajima (1994)	Prospective, open, crossover	▪ Children receiving antineoplastic therapy ▪ Median age: 5 yrs; range: 0.9 to 12 yrs	G1: granisetron G2: metoclopramide + promethazine	40 mcg/kg/dose pre-therapy IV x 1. Dose was repeated in the event of uncontrolled AINV.	No vomiting and no more than mild nausea	G1: 59% (13/22); no repeat doses were given G2: 0% (0/22); 20 patients were given repeat doses
Moderately emetogenic antineoplastic therapy						
Aksoylar (2001)	Randomized	▪ Children receiving antineoplastic therapy ▪ Median age: 6.5 yrs; range: 1 to 17 yrs ▪ Naïve to antineoplastic therapy: 25%	G1: granisetron G2: tropisetron	40 mcg/kg/dose (maximum: 3 mg/dose) pre-therapy IV daily	No vomiting and no nausea	G1: 32% (7/22) G2: 30% (8/27)
Craft (1995)	Prospective, observational	▪ Children receiving antineoplastic therapy ▪ Age range: 2 to 16 yrs ▪ Naïve to chemotherapy: 100%	granisetron	40 mcg/kg/dose pre-therapy IV x 1	No nausea, vomiting or retching	11/40 (28%)
Hahlen (1995)	Single blinded, randomized	▪ Children receiving ifosfamide ≥ 3g/m^2/day ± other antineoplastic agents ▪ Mean age: 9.5 yrs	G1: granisetron G2: chlorproperazine + dexmethasone	20 mcg/kg/dose pre-therapy IV x 1 then 20 mcg/kg/dose IV post therapy if needed up to twice in 24 hrs	No vomiting, no worse than mild nausea and no rescue antiemetic agents	G1: 22% (10/46) G2: 10% (4/42)
Jaing (2004)	Randomized, open-label, crossover	▪ Children receiving antineoplastic therapy ▪ Mean age: 7.8 ± 4.9 yrs; range: 3 to 18 yrs	G1: granisetron G2: ondansetron	Based on patient actual body weight: 25 – 50 kg: 0.5 mg ≥ 50 kg: 1 mg pre-therapy PO x 1	No emetic episodes and no need for rescue medication	G1: 61% (20/33) G2: 45.5% (15/33)
Komada (1999)	Randomized, crossover	▪ Children receiving methotrexate 3 g/m^2 + vincristine	granisetron	G1: 20 mcg/kg/dose pre-therapy IV x 1 G2: 40 mcg/kg/dose pre-therapy IV x 1	No emetic episodes	G1: 81% (29/36) G2: 94% (34/36)

First Author (Year)	Study Design	Study Population	Interventions	Granisetron Dose & Route	Definition Used for Complete Control	% Complete Control
Lemerle (1991)	Open-label, prospective	▪ Children receiving antineoplastic therapy ▪ Mean age: 6.4 yrs; range: 3 to 15 yrs ▪ Naïve to antineoplastic therapy: 21%	granisetron ± chlorpromazine	G1: 10 mcg/kg/dose pre-therapy IV x 1 G2: 20 mcg/kg/dose pre-therapy IV x 1 G3: 40 mcg/kg/dose pre-therapy IV x 1	No nausea, no retching, no vomiting	G1: 25% (2/8) G2: 50% (4/8) G3: 63% (5/8)
Mabro (2000)	Randomized, double blind	▪ Children receiving antineoplastic therapy ▪ Mean age: 7.8 yrs; range: 1 to 16 yrs ▪ Naïve to antineoplastic therapy: 64%	G1: granisetron dose 1 G2: granisetron dose 2	G1: 20 mcg/kg/dose PO pre-therapy x 1 and again 6 to 12 hrs after the start of therapy G2: 40 mcg/kg/dose PO pre-therapy x 1 and again 6 to 12 hrs after the start of therapy	No nausea, no vomiting	G1: 51% (73/143) G2: 53% (80/151)
Antineoplastic therapy of low emetogenicity						
Aksoylar (2001)	Randomized	▪ Children receiving antineoplastic therapy ▪ Median age: 6.5 yrs; range: 1 to 17 yrs ▪ Naïve to antineoplastic therapy: 25%	G1: granisetron G2: tropisetron	40 mcg/kg/dose (maximum: 3 mg/dose) pre-therapy IV daily	No vomiting and no nausea	G1: 67% (30/45) G2: 28% (11/39)
Hirota (1993)	Randomized, controlled, crossover	▪ Children receiving antineoplastic therapy ▪ Mean age: 10.8 yrs; range: 4 to 18 yrs	G1: granisetron G2: granisetron + methylprednisolone	40 mcg/kg/dose IV pre-therapy IV x 1	No vomiting, no nausea, no loss of appetite, no stomach discomfort	G1: 50% (10/20) G2: 80% ((16/20)
Antineoplastic therapy of unknown emetogenicity						
Fujimoto (1996)	Randomized crossover	▪ Children receiving antineoplastic therapy ▪ Mean age: 7.5 yrs; range: 1 to 15 yrs	granisetron	G1: 20 mcg/kg/dose pre-therapy IV x 1 G2: 40 mcg/kg/dose pre-therapy IV x 1	No emetic episodes	G1: 58% (23/40) G2: 55% (22/40) p=0.991
Jacobson (1994)	Open-label, prospective with option to continue to receive granisetron with subsequent courses	▪ Children receiving antineoplastic therapy with a history of poor AINV control ▪ Mean age: 10 yrs; range: 3 to 18 yrs ▪ Naïve to antineoplastic therapy: 0%	granisetron	20 mcg/kg/dose pre-therapy IV x 1 then 20 mcg/kg/dose IV post therapy if needed up to twice in 24 hrs	No nausea, no vomiting, no receipt of antiemetic agents other than granisetron	39% (26/66)

First Author (Year)	Study Design	Study Population	Interventions	Granisetron Dose & Route	Definition Used for Complete Control	% Complete Control
Tsuchida (1999)	Randomized, crossover	▪ Children with solid tumors ▪ Mean age: 4.9 yrs; range: 0.75 to 13 yrs ▪ Naïve to antineoplastic therapy: 0%	granisetron	G1: 20 mcg/kg/dose pre-therapy IV x 1 G2: 40 mcg/kg/dose pre-therapy IV x 1	No vomiting	G1: 44% (18/41) G2: 61% (27/44)

G1: group 1, G2: group 2

Table F.7e: Summary of studies used to inform recommendation 6: Metoclopramide Dose

First Author (Year)	Study Design	Study Population	Interventions	Metoclopramide Dose & Route	Definition Used for Complete Control	% Complete Control
Moderately emetogenic antineoplastic therapy						
Dick (1995)	Randomized, double blind comparison	▪ Children with leukemia ▪ Age range: 1.5 to 15 yrs ▪ Naive to antineoplastic therapy: 0%	G1: ondansetron G2: metoclopramide, dexamethasone + procyclidine	10 mg/m^2/dose IV pre-therapy x 1 then every 6 hours for at least 3 days	No vomiting or retching	G1: 73% (11/15) G2: 20% (3/15)
Antineoplastic therapy of low emetogenicity						
Koseoglu (1996)	Randomized	▪ Children with cancer receiving non-cisplatin antineoplastic therapy of low to moderate emetogenicity ▪ 46 antineoplastic blocks	G1: ondansetron G2: metoclopramide + diphenhydramine	1 mg/kg/dose IV pre-therapy x 1 then 0.15 mg/kg/day PO divided into 4 daily doses	No vomiting	G1: 91% (21/23) G2: 74% (17/23)
Antineoplastic therapy of unknown emetogenicity						
Basade (1996)	Randomized, single-blind, cross-over	▪ Children with cancer receiving cyclophosphamide ≥ 600mg/m^2 +/- other antineoplastic agents ▪ Median age: 7 yrs; range: 3 to 14 yrs	G1: dexamethasone G2: metoclopramide	1.5 mg/kg/dose IV pre-therapy x 1	No emetic episodes	G1: 62% (16/26) G2: 30% (8/27)

G1: group 1, G2: group 2

Table F.7f: Summary of studies used to inform recommendation 6: Nabilone Dose

First Author (Year)	Study Design	Study Population	Interventions	Nabilone Dose & Route	Definition Used for Complete Control	% Complete Control
MODERATELY EMETOGENIC ANTINEOPLASTIC THERAPY						
Chan (1987)	Randomized, double-blind, crossover	▪ Children receiving antineoplastic therapy ▪ Mean age: 11.8 yrs; range: 3.5 to 17.8 yrs ▪ Naïve to antineoplastic therapy: 0%	G1: nabilone G2: prochlorperazine	Dose 1: Body weight: 18 to 27 kg: 1 mg twice daily PO 27.1 to 36 kg: 1 mg three times daily PO > 36 kg: 2 mg twice daily PO Dose 2: Body weight: < 18 kg: 0.5 mg twice daily PO 18 to 30 kg: 1 mg twice daily PO > 30 kg: 1 mg three times daily PO	No vomiting and no retching	G1: 10% (3/30) G2: 10% (3/30)

Table F.7g: Summary of primary evidence to inform recommendation 6: Ondansetron Dose

First Author (Year)	Study Design	Study Population	Interventions	Ondansetron Dose & Route	Definition Used for Complete Control	% Complete Control
Highly emetogenic antineoplastic therapy						
Alvarez (1995)	Randomized double blind, placebo controlled, crossover trial	▪ Children with solid tumours receiving highly emetogenic antineoplastic therapy ▪ Median age 9 yrs; range 3 to 18 yrs ▪ Naive to antineoplastic therapy: 49%	Randomized to G1 or G2 then crossover for 2nd antineoplastic block. G1: ondansetron + placebo G2: ondansetron + dexamethasone	0.15 mg/kg/dose pre-therapy IV x 1 then q4h x 2 doses	No vomiting or retching	G1: 23% (7/30) G2: 61% (17/28) 25/33 pts enrolled completed 2 study blocks
Brock P (1996)	Randomized, double blind , parallel group	▪ Children receiving highly emetogenic chemotherapy ▪ Mean age: G1: 8.4 yrs; G2: 8.5 yrs; age range: 1.9 to 16.7 yrs ▪ Naïve to antineoplastic therapy: 100%	G1: ondansetron without loading dose G2: ondansetron with loading dose	G1: 5 mg/m^2/dose IV pre-therapy x 1 then q8h IV x 2 doses G2: 10mg/m^2/dose pre-therapy IV x 1 then 5mg/m^2/dose q8h IV x 2 doses	No vomiting and no retching	G1: 44% (35/79) G2: 42% (33/79)

First Author (Year)	Study Design	Study Population	Interventions	Ondansetron Dose & Route	Definition Used for Complete Control	% Complete Control
Cohen (1995)	Prospective, open-label study	▪ Children receiving cisplatin-containing or ifosfamide plus etoposide multiple day antineoplastic therapy	ondansetron	IV pre-therapy x 1 then every 8 hrs IV or PO IV: BSA ≤ 1.2 m^2: 5 mg BSA > 1.2 m^2: 8 mg PO: BSA: < 0.6 m^2: 2 mg BSA 0.6 to 1.2 m^2: 4 mg BSA > 1.2 m^2: 8 mg	No emetic episodes	31% (5/13)
Hesketh* (2003)	Random allocation of 6 adolescents to treatment arms of a Phase III randomized, double-blind, placebo controlled adult trial	▪ A site-specific amendment allowed pts ≥12 years but <18 years and ≥40kg to be randomized to a Phase III RCT of pts with solid tumours ≥18 yrs receiving cisplatin ≥70mg/m^2 for the first time ▪ Naive to antineoplastic therapy: 0%	G1: ondansetron, dexamethasone + placebo G2: ondansetron, dexamethasone + aprepitant	32 mg/dose IV pre-therapy x 1	No vomiting and no use of breakthrough antiemetic agents	G1: 67% (2/3) G2: 100% (3/3)
Hewitt (1993)	Open, non-comparative, prospective	▪ Children receiving antineoplastic therapy ▪ Mean age: 8.8 yrs; range: 0.9 to 18 yrs	ondansetron	5 mg/m^2/dose (maximum 8 mg/dose) IV pre-therapy x 1 then PO q8h starting 2 hrs after IV dose PO dosing regimen: BSA < 0.6 m^2: 2 mg/dose BSA 0.6 to 1.2 m^2: 4 mg/dose BSA > 1.2 m^2: 8 mg/dose	No vomiting or retching	12% (3/25)
Holdsworth (1995)	Prospective, observational	▪ Children receiving antineoplastic therapy ▪ Mean age: 6.2 ± 3.72 yrs; range: 2 to 15 yrs	ondansetron	0.15 mg/kg/dose IV pre-therapy x 1 and then 2 to 3 hrs later x 1	No vomiting	80% (51/64)
Holdsworth (2000)	Prospective, observational with retrospective comparison	▪ Children receiving antineoplastic therapy ▪ Median age: 11 and 9 yrs	G1: ondansetron + methylprednisolone G2: ondansetron + dexamethasone	G1: 0.15 mg/kg/dose IV pre-therapy x 1 then q4h x 2 doses G2: 0.45 mg/kg/dose IV pre-therapy	No nausea and no vomiting	G1: 19.2% (72/376) G2: 39.2% (60/153)

First Author (Year)	Study Design	Study Population	Interventions	Ondansetron Dose & Route	Definition Used for Complete Control	% Complete Control
Holdsworth** (2006)	Prospective, observational	▪ Children with cancer receiving antineoplastic therapy requiring antiemetic prophylaxis ▪ Naive to antineoplastic therapy: 100%	G1: ondansetron + dexamethasone G2: high-dose ondansetron G3: low-dose ondansetron	G1: 0.45 mg/kg/dose once daily IV G2: 0.3 to 0.45 mg/kg/dose once daily IV G3: 0.3 mg/kg/dose once daily IV	No vomiting, no retching and no nausea	G1: 53% (61/116) G2: 33% (7/21) G3: 53% (16/30)
Pinkerton (1990)	Prospective, observational	▪ Children with solid tumors ▪ Mean age: 9.5 yrs; range: 2 to 16 yrs ▪ Naïve to antineoplastic therapy: 39%	ondansetron	5 mg/m^2/dose IV pre-therapy x 1 then PO q8h PO dosing regimen: BSA < 0.3 m^2: 1 mg/dose BSA 0.3 to 0.6 m^2: 2 mg/dose BSA 0.6 to 1 m^2: 3 mg/dose BSA > 1 m^2: 4 mg/dose	No vomiting	71% (22/31)
Moderately emetogenic antineoplastic therapy						
Corapcioglu (2005)	Randomized trial	▪ Children receiving antineoplastic therapy ▪ Median age: 9.4 yrs; range: 3 to 17 yrs ▪ Naïve to antineoplastic therapy: 45%	G1: ondansetron oral dissolving tablet G2: IV ondansetron	G1: BSA ≤ 0.8 m^2: 4 mg/dose PO q12h BSA > 0.8 m^2: 8 mg/dose PO q12h G2: 5 mg/m^2/dose IV q12h	No vomiting or retching	G1: 80% (19/24) G2: 75% (24/32) (p=0.931)
Dick (1995)	Randomized, double blind comparison	▪ Children with leukemia ▪ Age range: 1.5 to 15 yrs ▪ Naive to antineoplastic therapy: 0%	G1: ondansetron G2: metoclopramide, dexamethasone + procyclidine	Pre-therapy IV x 1 dose: BSA < 1.2 m^2: 3 mg/m^2/dose BSA > 1.2 m^2: 8 mg/dose Then q12h IV/PO: BSA < 0.6 m^2: 3 mg/m^2 or 2 mg BSA 0.6 to 1.2 m^2: 3 mg/m^2 or 4 mg BSA > 1.2 m^2: 8 mg	No vomiting or retching	G1: 73% (11/15) G2: 20% (3/15)
Hewitt (1993)	Open, non-comparative, prospective	▪ Children receiving antineoplastic therapy ▪ Mean age: 8.8 yrs; range: 0.9 to 18 yrs	ondansetron	5 mg/m^2/dose (maximum 8 mg/dose) IV pre-therapy x 1 then PO q8h starting 2 hrs after IV dose PO dosing regimen: BSA < 0.6 m^2: 2 mg/dose BSA 0.6 to 1.2 m^2: 4 mg/dose BSA > 1.2 m^2: 8 mg/dose	No vomiting or retching	28% (11/40)

First Author (Year)	Study Design	Study Population	Interventions	Ondansetron Dose & Route	Definition Used for Complete Control	% Complete Control
Holdsworth (1995)	Prospective, descriptive	▪ Children receiving antineoplastic therapy ▪ Mean age: 6.2 ± 3.72 yrs; range: 2 to 15 yrs	ondansetron	0.15 mg/kg/dose IV pre-therapy x 1 and then 2 to 3 hrs later x 1	No vomiting	Carmustine: 80% (12/15) Cyclophospha-mide 600 mg/m^2/dose: 56% (10/18)
Holdsworth (1998)	Prospective, observational	▪ Children receiving intrathecal antineoplastic therapy ▪ Mean age: 7.6 yrs; range: 1 to 17 yrs	G1: no antiemetic agent G2: ondansetron IV G3: ondansetron PO	G2: 0.15 mg/kg/dose IV pre-therapy x 1 and after therapy x 1 G3: 3 to 11 yrs: 4 mg/dose PO pre-therapy x 1 and after therapy x 1 ≥ 12 yrs: 8 mg/dose PO pre-therapy x 1 and after therapy x 1	No nausea, vomiting or retching	G1: 22.2% (8/37) G2: 40% (14/35) G3: 25% (4/16)
Holdsworth** (2006)	Prospective, descriptive	▪ Children with cancer receiving antineoplastic therapy requiring antiemetic prophylaxis ▪ Naive to antineoplastic therapy: 100%	ondansetron	0.3 mg/kg/dose IV pre-therapy x 1	No nausea, vomiting or retching	74% (126/171)
Jaing (2004)	Randomized, open-label, crossover	▪ Children receiving antineoplastic therapy ▪ Mean age: 7.8 ± 4.9 yrs; range: 3 to 18 yrs	G1: granisetron G2: ondansetron	0.15 mg/kg/dose IV pre-therapy and then q4h x 2. Last dose given PO.	No emetic episodes and no need for rescue medication	G1: 61% (20/33) G2: 45.5% (15/33)
Parker (2001)	Randomized, double-blind, placebo-controlled, cross-over trial	▪ Children receiving intrathecal antineoplastic therapy ▪ Mean age: 6 yrs; range: 2 to 17 yrs	G1: placebo G2: low dose ondansetron G3: high dose ondansetron	G2: 0.15 mg/kg/dose IV pre-therapy G3: 0.45 mg/kg/dose IV pre-therapy	No vomiting	G1: 37% (19/51) G2: 72% (34/47) G3: 85% (41/48)
Stevens (1991)	Open, non-comparative	▪ Children receiving antineoplastic therapy ▪ Mean age: 9.2 yrs; range: 4 to 18 yrs	ondansetron	3 or 5 mg/m^2/dose IV pre-therapy x 1 and 3 or 4 mg/dose PO x 1 pre-therapy then 3 or 4 mg/dose 3 times daily PO starting with the IV dose	No vomiting and no retching	87%
White (2000)	Randomized, double-blind, placebo controlled parallel group	▪ Children receiving moderately/highly emetogenic antineoplastic therapy ▪ Mean age: 8 yrs; range: 1 to 17 yrs	G1: ondansetron IV + dexamethasone G2: ondansetron PO + dexamethasone	G1: 5 mg/m^2/dose IV pre-therapy x 1 then 4 mg PO 6 to 8 hrs later G2: 8 mg PO pre-therapy x 1 then 4 mg PO 6 to 8 hrs later	No vomiting or retching	G1: 81% (172/212) G2: 78% (168/216)

First Author (Year)	Study Design	Study Population	Interventions	Ondansetron Dose & Route	Definition Used for Complete Control	% Complete Control
Antineoplastic therapy of low emetogenicity						
Holdsworth (2006)**	Prospective, descriptive	▪ Children with cancer receiving antineoplastic therapy requiring antiemetic prophylaxis ▪ Naive to antineoplastic therapy: 100%	ondansetron	0.3mg/kg/dose IV pre-therapy x 1	No nausea, vomiting or retching	82% (9/11)
Sandoval (1999)	Randomized, double blind	▪ Children with cancer receiving antineoplastic therapy ▪ Median age: 4.0 or 4.5 yrs ; range: 0.25 to 18 yrs ▪ Naïve to antineoplastic therapy: 100%	ondansetron	G1: 0.6 mg/kg/dose (max: 32 mg/dose) IV pre-therapy x 1 G2: 0.15 mg/kg/dose (max: 8 mg/dose) IV pre-therapy x 1 and then q4h x 3 doses	No nausea or emesis	G1: 75% (12/16) G2: 60% (9/15)
Antineoplastic therapy of unknown emetogenicity						
Gore (2009)	Randomized, double-blind, placebo-controlled (4 patients received open label aprepitant)	▪ Children receiving antineoplastic therapy ▪ Mean age: 15 yrs; range: 11 to 19 yrs	G1: ondansetron, dexamethasone + aprepitant G2:ondansetron, dexamethasone + placebo	0.15 mg/kg/dose IV pre-therapy and then q4h x 2 doses (maximum total daily dose: 32 mg)	No vomiting and no use of rescue therapy	G1: 60.7% (19/32) G2: 38.9% (7/18)
Sepulveda-Vildosola (2008)	Randomized	▪ Children with brain or solid tumors receiving highly emetogenic antineoplastic therapy ▪ Naïve to antineoplastic therapy: 14%	G1: ondansetron G2: palonosetron	8 mg/m^2/dose IV pre-therapy x 1 and then q8h	No emesis	G1: 72% (36/50) G2: 92% (46/50)

G1: group 1, G2: group 2

*With supplemental data obtained from personal communication with Pregent E, Merck Frost Canada Ltd., March 14, 2007.

[t] Data includes those presented in Hewitt et al 1991

Appendix G: Forest Plots of Studies Evaluating Complete AINV Control In Children.

Note that squares indicate percentages with horizontal lines representing 95% confidence intervals. Diamonds represent overall percentages form the meta-analysis with corresponding 95% confidence intervals.

I. Forest plots supporting recommendation 2a

Figure Ia: All studies included in the analysis

Study or Subgroup	Proportion	SE	Weight	Proportion IV, Random, 95% CI
Aksoylar 2001	0.2962963	0.08787719	3.9%	0.30 [0.12, 0.47]
Aksoylar_b 2001	0.31818182	0.0993026	3.8%	0.32 [0.12, 0.51]
Alvarez 1995	0.6	0.09797959	3.8%	0.60 [0.41, 0.79]
Alvarez_b 1995	0.24	0.08541663	3.9%	0.24 [0.07, 0.41]
Berberoglu 1995	0.53333333	0.12881224	3.6%	0.53 [0.28, 0.79]
Brock 1996	0.44303798	0.05588815	4.1%	0.44 [0.33, 0.55]
Brock_b 1996	0.41772152	0.05548751	4.1%	0.42 [0.31, 0.53]
Cappelli 2005	0.85344828	0.03283636	4.2%	0.85 [0.79, 0.92]
Hachimi-Idrissi 1993	0.76344086	0.04406726	4.2%	0.76 [0.68, 0.85]
Hesketh 2003	0.875	0.19094065	3.0%	0.88 [0.50, 1.25]
Hesketh_b 2003	0.66666667	0.27216553	2.2%	0.67 [0.13, 1.20]
Hewitt 1993	0.12	0.06499231	4.1%	0.12 [-0.01, 0.25]
Holdsworth 2006	0.4890511	0.04270764	4.2%	0.49 [0.41, 0.57]
Holdsworth_b 2006	0.53333333	0.09108401	3.9%	0.53 [0.35, 0.71]
Koseoglu	0.55555556	0.16563466	3.2%	0.56 [0.23, 0.88]
Koseoglu_b	0.11111111	0.10475656	3.8%	0.11 [-0.09, 0.32]
Marshall 1989	0.19230769	0.07729202	4.0%	0.19 [0.04, 0.34]
Marshall_b 1989	0.46153846	0.09776752	3.8%	0.46 [0.27, 0.65]
Miyajima 1994	0.59090909	0.10482356	3.8%	0.59 [0.39, 0.80]
Miyajima_b 1994	0.02173913	0.03109117	4.3%	0.02 [-0.04, 0.08]
Otten 1994	0.69565217	0.04797194	4.2%	0.70 [0.60, 0.79]
Ozkan 1999	0.44827586	0.09234953	3.9%	0.45 [0.27, 0.63]
Ozkan_b 1999	0.5	0.1118034	3.7%	0.50 [0.28, 0.72]
Pinkerton 1990	0.73076923	0.08698929	3.9%	0.73 [0.56, 0.90]
Rosso 1994	0.7	0.10246951	3.8%	0.70 [0.50, 0.90]
Uysal 1999	0.68992248	0.02879555	4.3%	0.69 [0.63, 0.75]
Total (95% CI)			**100.0%**	**0.49 [0.37, 0.60]**

Heterogeneity: Tau² = 0.08; Chi² = 550.73, df = 25 (P < 0.00001); I² = 95%
Test for overall effect: Z = 8.27 (P < 0.00001)

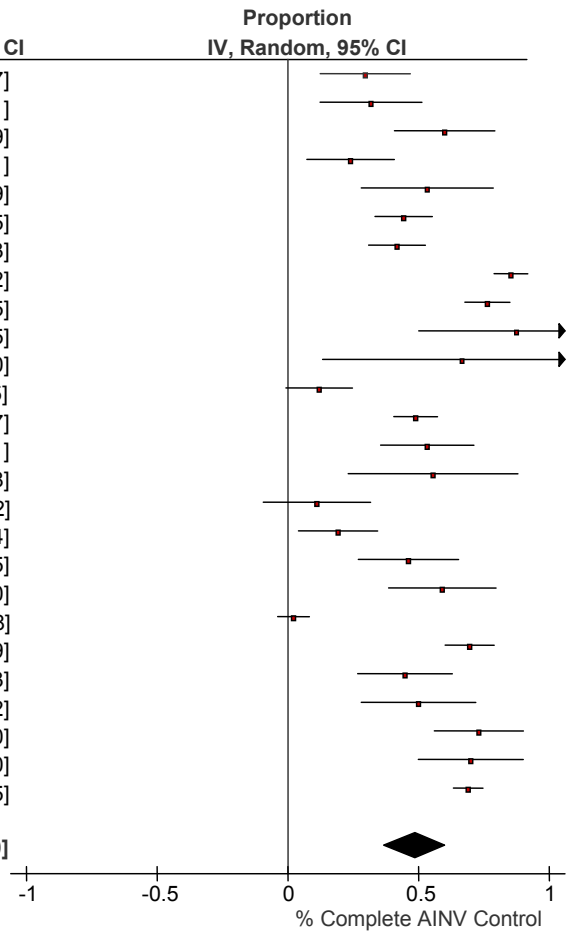


Figure Ib: Studies evaluating a 5-HT3 antagonist plus a corticosteroid

Study or Subgroup	Proportion	SE	Weight	Proportion IV, Random, 95% CI
Alvarez 1995	0.6	0.09797959	13.3%	0.60 [0.41, 0.79]
Hesketh_b 2003	0.66666667	0.27216553	1.7%	0.67 [0.13, 1.20]
Holdsworth 2006	0.4890511	0.04270764	70.0%	0.49 [0.41, 0.57]
Ozkan 1999	0.44827586	0.09234953	15.0%	0.45 [0.27, 0.63]
Total (95% CI)			**100.0%**	**0.50 [0.43, 0.57]**

Heterogeneity: Tau² = 0.00; Chi² = 1.80, df = 3 (P = 0.62); I² = 0%
Test for overall effect: Z = 14.01 (P < 0.00001)

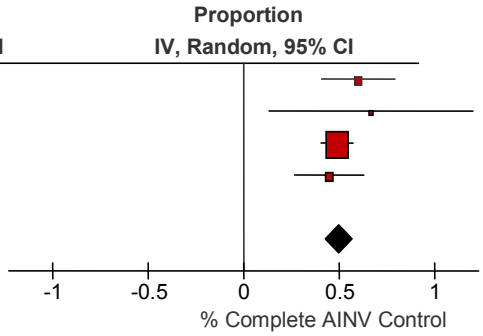


Figure Ic: Studies evaluating a 5-HT3 antagonist alone

Study or Subgroup	Proportion	SE	Weight	Proportion IV, Random, 95% CI
Aksoylar 2001	0.2962963	0.08787719	6.1%	0.30 [0.12, 0.47]
Aksoylar_b 2001	0.31818182	0.0993026	5.8%	0.32 [0.12, 0.51]
Alvarez_b 1995	0.24	0.08541663	6.1%	0.24 [0.07, 0.41]
Berberoglu 1995	0.53333333	0.12881224	5.2%	0.53 [0.28, 0.79]
Brock 1996	0.44303798	0.05588815	6.7%	0.44 [0.33, 0.55]
Brock_b 1996	0.41772152	0.05548751	6.7%	0.42 [0.31, 0.53]
Cappelli 2005	0.85344828	0.03283636	7.0%	0.85 [0.79, 0.92]
Hachimi-Idrissi 1993	0.76344086	0.04406726	6.9%	0.76 [0.68, 0.85]
Hewitt 1993	0.12	0.06499231	6.5%	0.12 [-0.01, 0.25]
Holdsworth_b 2006	0.53333333	0.09108401	6.0%	0.53 [0.35, 0.71]
Miyajima 1994	0.59090909	0.10482356	5.7%	0.59 [0.39, 0.80]
Otten 1994	0.69565217	0.04797194	6.8%	0.70 [0.60, 0.79]
Ozkan_b 1999	0.5	0.1118034	5.6%	0.50 [0.28, 0.72]
Pinkerton 1990	0.73076923	0.08698929	6.1%	0.73 [0.56, 0.90]
Rosso 1994	0.7	0.10246951	5.8%	0.70 [0.50, 0.90]
Uysal 1999	0.68992248	0.02879555	7.0%	0.69 [0.63, 0.75]
Total (95% CI)			**100.0%**	**0.53 [0.42, 0.64]**

Heterogeneity: Tau² = 0.04; Chi² = 199.17, df = 15 (P < 0.00001); I² = 92%
Test for overall effect: Z = 9.55 (P < 0.00001)

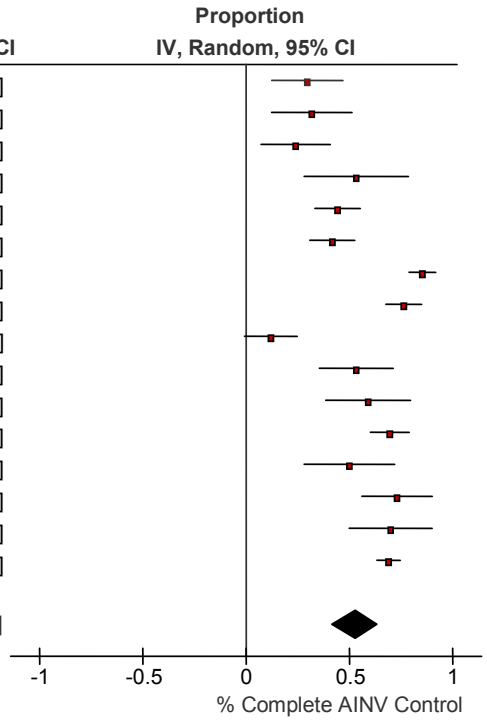
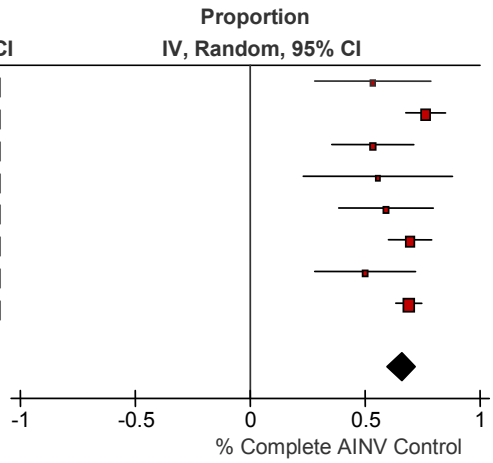


Figure Id: Studies evaluating a 5-HT3 antagonist alone with antineoplastic emetogenicity determined by the POGO guideline and the definition of complete AINV control including nausea control

Study or Subgroup	Proportion	SE	Weight	Proportion IV, Random, 95% CI
Berberoglu 1995	0.53333333	0.12881224	5.0%	0.53 [0.28, 0.79]
Hachimi-Idrissi 1993	0.76344086	0.04406726	21.3%	0.76 [0.68, 0.85]
Holdsworth_b 2006	0.53333333	0.09108401	8.8%	0.53 [0.35, 0.71]
Koseoglu	0.55555556	0.16563466	3.2%	0.56 [0.23, 0.88]
Miyajima 1994	0.59090909	0.10482356	7.1%	0.59 [0.39, 0.80]
Otten 1994	0.69565217	0.04797194	19.8%	0.70 [0.60, 0.79]
Ozkan_b 1999	0.5	0.1118034	6.4%	0.50 [0.28, 0.72]
Uysal 1999	0.68992248	0.02879555	28.4%	0.69 [0.63, 0.75]
Total (95% CI)			**100.0%**	**0.66 [0.60, 0.72]**

Heterogeneity: Tau² = 0.00; Chi² = 11.55, df = 7 (P = 0.12); I² = 39%
Test for overall effect: Z = 21.35 (P < 0.00001)



II. Forest plots supporting recommendation 2b

Figure IIa: All studies evaluating antiemetic agents in children receiving moderately emetogenic antineoplastic agents.

Study or Subgroup	Proportion	SE	Weight	Proportion IV, Random, 95% CI
Cappelli 2005	0.80357143	0.05309096	3.7%	0.80 [0.70, 0.91]
Chan 1987	0.1	0.05477226	3.7%	0.10 [-0.01, 0.21]
Chan_b 1987	0.1	0.05477226	3.7%	0.10 [-0.01, 0.21]
Coppes 1999a	0.66666667	0.13608276	3.3%	0.67 [0.40, 0.93]
Coppes 1999b	0.5	0.15811388	3.2%	0.50 [0.19, 0.81]
Corapcioglu 2005	0.79166667	0.08289817	3.6%	0.79 [0.63, 0.95]
Corapcioglu_b 2005	0.75	0.07654655	3.6%	0.75 [0.60, 0.90]
Craft 1995	0.275	0.07060011	3.6%	0.28 [0.14, 0.41]
Dick 1995	0.73333333	0.11417984	3.4%	0.73 [0.51, 0.96]
Dick_b 1995	0.2	0.10327956	3.5%	0.20 [-0.00, 0.40]
Hachimi-Idrissi 1993	0.78125	0.05167483	3.7%	0.78 [0.68, 0.88]
Hahlen 1995	0.2173913	0.06081553	3.6%	0.22 [0.10, 0.34]
Hahlen_b 1995	0.0952381	0.04529475	3.7%	0.10 [0.01, 0.18]
Hewitt 1993	0.275	0.07060011	3.6%	0.28 [0.14, 0.41]
Holdsworth 1998	0.4	0.08280787	3.6%	0.40 [0.24, 0.56]
Holdsworth 2006	0.74269006	0.03342982	3.7%	0.74 [0.68, 0.81]
Holdsworth_b 1998	0.02173913	0.03645763	3.7%	0.02 [-0.05, 0.09]
Mabro	0.01612903	0.01053429	3.7%	0.02 [-0.00, 0.04]
Mabro_b	0.01612903	0.01025144	3.7%	0.02 [-0.00, 0.04]
Mehta 1986	0.4	0.15491933	3.2%	0.40 [0.10, 0.70]
Mehta_b 1986	0.3	0.14491377	3.2%	0.30 [0.02, 0.58]
Nadaraja 2012	0.841	0.03116174	3.7%	0.84 [0.78, 0.90]
Ozkan 1999	0.3	0.14491377	3.2%	0.30 [0.02, 0.58]
Parker 2001	0.49180328	0.06400984	3.6%	0.49 [0.37, 0.62]
Parker_b 2001	0.85416667	0.05094236	3.7%	0.85 [0.75, 0.95]
Stevens 1991	0.72340426	0.06524757	3.6%	0.72 [0.60, 0.85]
White 2000	0.81132076	0.02687141	3.7%	0.81 [0.76, 0.86]
White_b 2000	0.77777778	0.0282875	3.7%	0.78 [0.72, 0.83]
Total (95% CI)			**100.0%**	**0.46 [0.33, 0.60]**

Heterogeneity: Tau² = 0.13; Chi² = 2937.36, df = 27 (P < 0.00001); I² = 99%
Test for overall effect: Z = 6.55 (P < 0.00001)

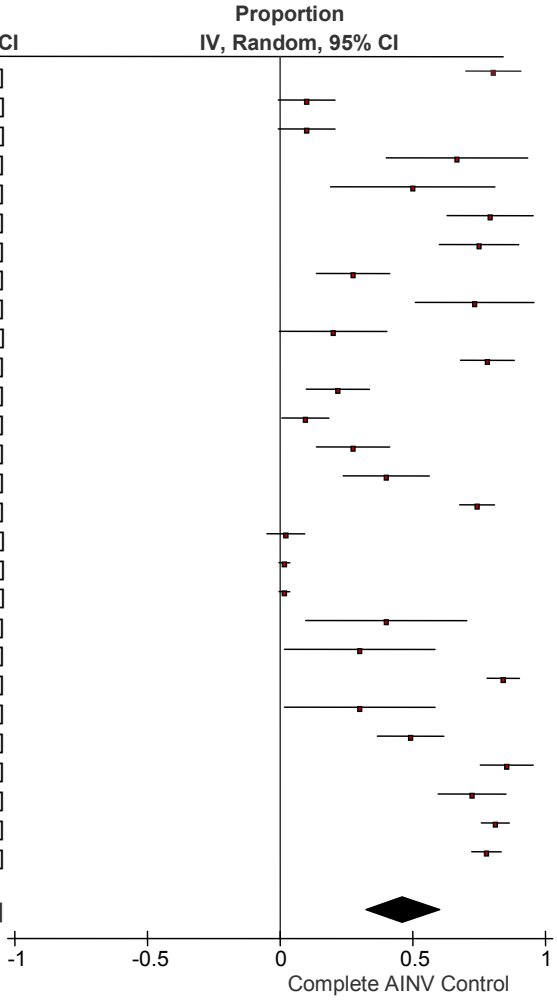


Figure IIb: Studies evaluating a 5HT3 antagonist alone, palonosetron excluded

Study or Subgroup	Proportion	SE	Weight	Proportion IV, Random, 95% CI
Cappelli 2005	0.80357143	0.05309096	5.4%	0.80 [0.70, 0.91]
Coppes 1999a	0.66666667	0.13608276	4.7%	0.67 [0.40, 0.93]
Coppes 1999b	0.5	0.15811388	4.4%	0.50 [0.19, 0.81]
Corapcioglu 2005	0.79166667	0.08289817	5.2%	0.79 [0.63, 0.95]
Corapcioglu_b 2005	0.75	0.07654655	5.2%	0.75 [0.60, 0.90]
Craft 1995	0.275	0.07060011	5.3%	0.28 [0.14, 0.41]
Dick 1995	0.73333333	0.11417984	4.9%	0.73 [0.51, 0.96]
Hachimi-Idrissi 1993	0.78125	0.05167483	5.4%	0.78 [0.68, 0.88]
Hahlen 1995	0.2173913	0.06081553	5.4%	0.22 [0.10, 0.34]
Hewitt 1993	0.275	0.07060011	5.3%	0.28 [0.14, 0.41]
Holdsworth 1998	0.4	0.08280787	5.2%	0.40 [0.24, 0.56]
Holdsworth 2006	0.74269006	0.03342982	5.5%	0.74 [0.68, 0.81]
Holdsworth_b 1998	0.02173913	0.03645763	5.5%	0.02 [-0.05, 0.09]
Mabro	0.01612903	0.01053429	5.6%	0.02 [-0.00, 0.04]
Mabro_b	0.01612903	0.01025144	5.6%	0.02 [-0.00, 0.04]
Ozkan 1999	0.49180328	0.06400984	5.3%	0.49 [0.37, 0.62]
Parker 2001	0.85416667	0.05094236	5.4%	0.85 [0.75, 0.95]
Parker_b 2001	0.72340426	0.06524757	5.3%	0.72 [0.60, 0.85]
Stevens 1991	0.85555556	0.05299662	5.4%	0.86 [0.75, 0.96]
Total (95% CI)			**100.0%**	**0.52 [0.37, 0.66]**

Heterogeneity: Tau² = 0.10; Chi² = 1608.30, df = 18 (P < 0.00001); I² = 99%
Test for overall effect: Z = 6.97 (P < 0.00001)

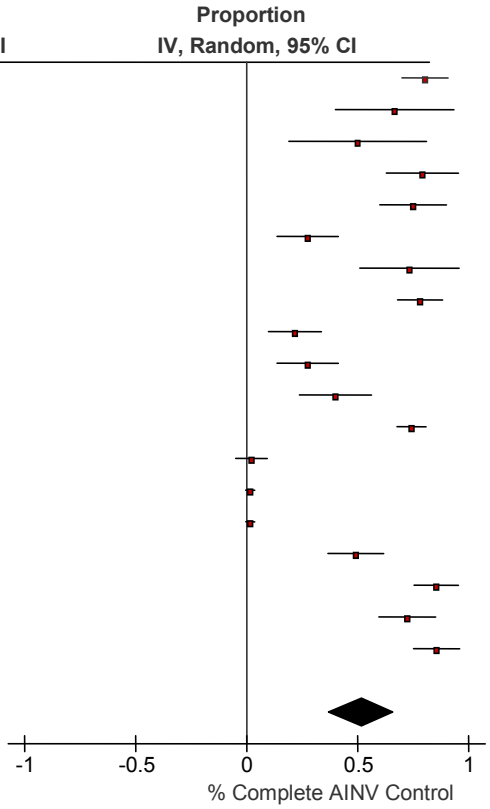


Figure IIc: Studies evaluating a 5-HT3 antagonist alone, palonosetron included

Study or Subgroup	Proportion	SE	Weight	Proportion IV, Random, 95% CI
Cappelli 2005	0.80357143	0.05309096	5.1%	0.80 [0.70, 0.91]
Coppes 1999a	0.66666667	0.13608276	4.5%	0.67 [0.40, 0.93]
Coppes 1999b	0.5	0.15811388	4.3%	0.50 [0.19, 0.81]
Corapcioglu 2005	0.79166667	0.08289817	4.9%	0.79 [0.63, 0.95]
Corapcioglu_b 2005	0.75	0.07654655	5.0%	0.75 [0.60, 0.90]
Craft 1995	0.275	0.07060011	5.0%	0.28 [0.14, 0.41]
Dick 1995	0.73333333	0.11417984	4.7%	0.73 [0.51, 0.96]
Hachimi-Idrissi 1993	0.78125	0.05167483	5.1%	0.78 [0.68, 0.88]
Hahlen 1995	0.2173913	0.06081553	5.1%	0.22 [0.10, 0.34]
Hewitt 1993	0.275	0.07060011	5.0%	0.28 [0.14, 0.41]
Holdsworth 1998	0.4	0.08280787	4.9%	0.40 [0.24, 0.56]
Holdsworth 2006	0.74269006	0.03342982	5.2%	0.74 [0.68, 0.81]
Holdsworth_b 1998	0.02173913	0.03645763	5.2%	0.02 [-0.05, 0.09]
Mabro	0.01612903	0.01053429	5.2%	0.02 [-0.00, 0.04]
Mabro_b	0.01612903	0.01025144	5.2%	0.02 [-0.00, 0.04]
Nadaraja 2012	0.84057971	0.03116174	5.2%	0.84 [0.78, 0.90]
Ozkan 1999	0.49180328	0.06400984	5.1%	0.49 [0.37, 0.62]
Parker 2001	0.85416667	0.05094236	5.1%	0.85 [0.75, 0.95]
Parker_b 2001	0.72340426	0.06524757	5.0%	0.72 [0.60, 0.85]
Stevens 1991	0.85555556	0.05299662	5.1%	0.86 [0.75, 0.96]
Total (95% CI)			**100.0%**	**0.54 [0.38, 0.69]**

Heterogeneity: Tau² = 0.12; Chi² = 2105.28, df = 19 (P < 0.00001); I² = 99%
Test for overall effect: Z = 6.75 (P < 0.00001)

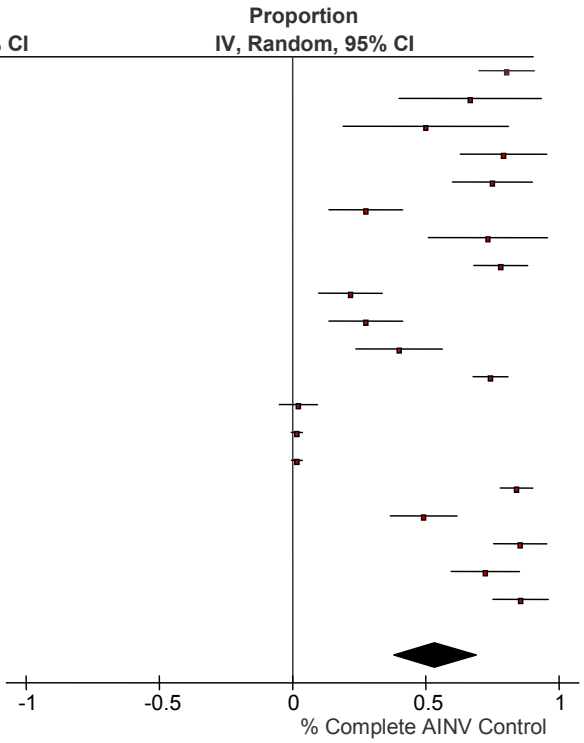
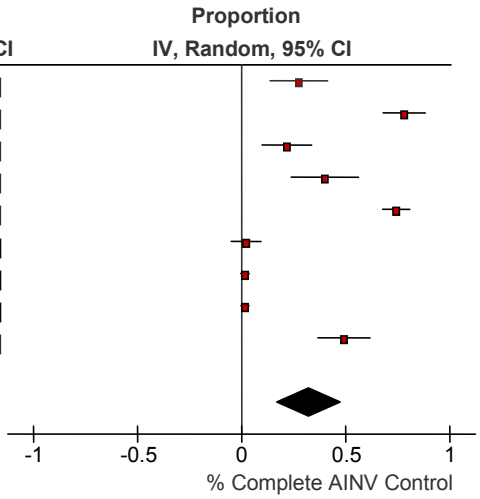


Figure IId: Studies evaluating a 5HT3 antagonist alone, where emetogenicity of the antineoplastic agents administered was able to be determined using the POGO guideline and where nausea was included in the definition of complete AINV control.

Study or Subgroup	Proportion	SE	Weight	Proportion IV, Random, 95% CI
Craft 1995	0.275	0.07060011	10.7%	0.28 [0.14, 0.41]
Hachimi-Idrissi 1993	0.78125	0.05167483	11.1%	0.78 [0.68, 0.88]
Hahlen 1995	0.2173913	0.06081553	10.9%	0.22 [0.10, 0.34]
Holdsworth 1998	0.4	0.08280787	10.3%	0.40 [0.24, 0.56]
Holdsworth 2006	0.74269006	0.03342982	11.4%	0.74 [0.68, 0.81]
Holdsworth_b 1998	0.02173913	0.03645763	11.4%	0.02 [-0.05, 0.09]
Mabro	0.01612903	0.01053429	11.6%	0.02 [-0.00, 0.04]
Mabro_b	0.01612903	0.01025144	11.6%	0.02 [-0.00, 0.04]
Ozkan 1999	0.49180328	0.06400984	10.8%	0.49 [0.37, 0.62]
Total (95% CI)			**100.0%**	**0.33 [0.17, 0.48]**

Heterogeneity: Tau² = 0.05; Chi² = 723.28, df = 8 (P < 0.00001); I² = 99%

Test for overall effect: Z = 4.11 (P < 0.0001)



III. Forest plots supporting recommendation 2c

Figure IIIa: All studies evaluating antiemetic agents in children receiving antineoplastic agents of low emetogenicity.

Study or Subgroup	Proportion	SE	Weight	Proportion IV, Random, 95% CI
Hachimi-Idrissi 1993	0.90909091	0.08667842	12.3%	0.91 [0.74, 1.08]
Hirota 1993	0.8	0.08944272	12.0%	0.80 [0.62, 0.98]
Hirota_b 1993	0.5	0.1118034	9.8%	0.50 [0.28, 0.72]
Holdsworth 2006	0.81818182	0.1162913	9.4%	0.82 [0.59, 1.05]
Koseoglu	0.91304348	0.05875338	15.5%	0.91 [0.80, 1.03]
Koseoglu_b	0.73913044	0.09156054	11.7%	0.74 [0.56, 0.92]
Ozkan 1999	0.60869565	0.10176385	10.7%	0.61 [0.41, 0.81]
Sandoval 1999	0.75	0.10825318	10.1%	0.75 [0.54, 0.96]
Sandoval_b 1999	0.6	0.12649111	8.5%	0.60 [0.35, 0.85]
Total (95% CI)			**100.0%**	**0.75 [0.66, 0.85]**

Heterogeneity: Tau² = 0.01; Chi² = 18.90, df = 8 (P = 0.02); I² = 58%

Test for overall effect: Z = 15.42 (P < 0.00001)

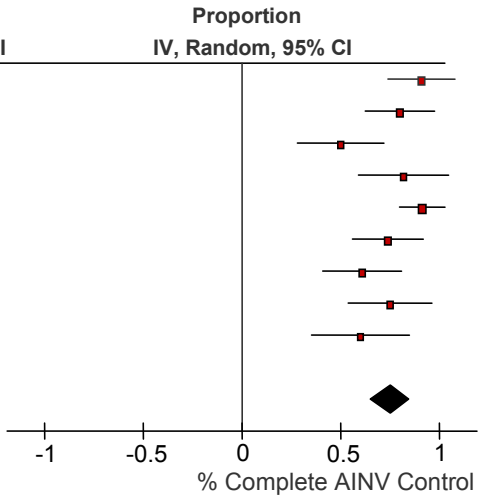
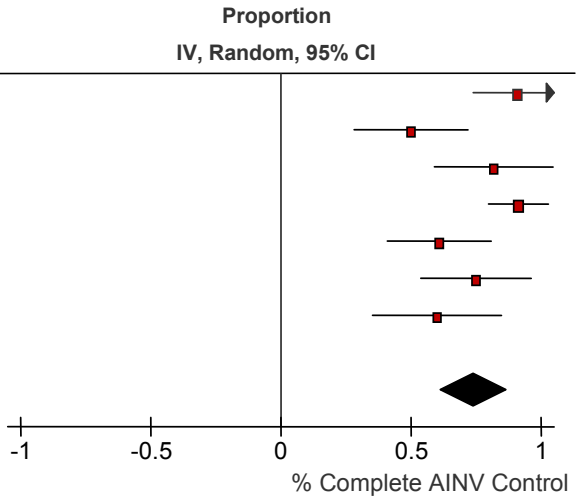


Figure IIIb: Studies evaluating a 5HT3 antagonist alone, where emetogenicity of the antineoplastic agents administered was able to be determined using the POGO guideline and where nausea was included in the definition of complete AINV control.

Study or Subgroup	Proportion	SE	Weight	Proportion IV, Random, 95% CI
Hachimi-Idrissi 1993	0.90909091	0.08667842	15.7%	0.91 [0.74, 1.08]
Hirota_b 1993	0.5	0.1118034	13.2%	0.50 [0.28, 0.72]
Holdsworth 2006	0.81818182	0.1162913	12.8%	0.82 [0.59, 1.05]
Koseoglu	0.91304348	0.05875338	18.5%	0.91 [0.80, 1.03]
Ozkan 1999	0.60869565	0.10176385	14.2%	0.61 [0.41, 0.81]
Sandoval 1999	0.75	0.10825318	13.6%	0.75 [0.54, 0.96]
Sandoval_b 1999	0.6	0.12649111	11.9%	0.60 [0.35, 0.85]
Total (95% CI)			**100.0%**	**0.74 [0.62, 0.87]**

Heterogeneity: Tau² = 0.02; Chi² = 18.62, df = 6 (P = 0.005); I² = 68%

Test for overall effect: Z = 11.47 (P < 0.00001)



Appendix H: Table of Antineoplastic Agents Known or Suspected to Interact With Aprepitant/Fosaprepitant

Table H.1: Summary of reports of aprepitant - antineoplastic agent interactions

ANTINEOPLASTIC AGENT	NATURE OF INTERACTION
Cyclophosphamide[1,2]	Inhibition of bioactivation of cyclophosphamide resulted in mean 5% decreased exposure to 4-hydroxycyclophosphamide.[1] No statistically significant differences in mean cyclophosphamide, hydroxycyclophosphamide or carboxyethylphosphoramide mustard area under the curve though considerable interindividual variability observed (coefficient of variation: 57%).[2]
Docetaxel[3]	No statistically significant differences in docetaxel mean area under the curve, mean maximum plasma concentration or mean plasma clearance.
Ifosfamide[4, 5,6,7]	Possible association with increased risk of neurotoxicity. Mechanism not determined.
Melphalan[8]	No statistically significant differences in mean elimination half-life, maximum concentration, area under the curve, volume of distribution, total body clearance, or residence time.
Thiotepa[1]	Mean clearance of thiotepa to tepa 33% lower resulting in a mean 15% higher total thiotepa exposure and mean 20% lower tepa exposure.
Vinorelbine[9]	No statistically significant differences in mean area under the curve.

Table H.2: List of antineoplastic agents whose dose intensity has the potential to be altered when given together with aprepitant.[10,11] Aprepitant is a weak inhibitor of CYP1A2, 2C8, 2C9, 2C19 and 2E1; a moderate inhibitor of CYP3A4; a weak inducer of CYP3A4 and a mild inducer of CYP2C9. Note: this list is not exhaustive.

ANTINEOPLASTIC AGENT	RATIONALE FOR POTENTIAL INTERACTION
Bortezomib	CYP3A4, CYP2C9 and CYP2C19 substrate
Busulfan	CYP3A4 substrate
Dasatinib	CYP3A4 substrate
Daunorubicin	CYP3A4 substrate
Doxorubicin	CYP3A4 substrate
Etoposide	CYP3A4 substrate
Imatinib	CYP3A4, CYP2C9 and CYP2C19 substrate; CYP3A4 inhibitor
Irinotecan	CYP3A4 substrate and inhibitor
Lapatinib	CYP3A4 substrate
Nilotinib	CYP3A4 substrate
Paclitaxel	CYP3A4 and CYP2C9 substrate
Sorafenib	CYP3A4 substrate
Sutinib	CYP3A4 substrate
Tamoxifen	CYP3A4 and CYP2C9 substrate
Teniposide	CYP 3A4, CYP3A5 and CYP 2C19 substrate
Vinblastine	CYP3A4 substrate and inhibitor
Vincristine	CYP3A4 substrate and inhibitor
Vinorelbine	CYP3A4 substrate and inhibitor

References

1. de Jong ME, Huitema ADR, Holtkamp MJ, van Dam SM, Beijnen JH, Rodenhuis S. Aprepitant inhibits cyclophosphamide bioactivation and thiotepa metabolism. Cancer Chemother pharmacol 2005; 56: 370-8.

2. Bubalo JS, Cherala G, McCune JS, Munar MY, Tse S, Maziarz R. Aprepitant pharmacokinetics and assessing the impact of aprepitant on cyclophosphamide metabolism in cancer patients undergoing hematopoietic stem cell transplantation. J Clin Pharmacol DOI: 10.1177/0091270011398243.

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6. Ho H, Yuen C. Aprepitant-associated ifosfamide neurotoxicity. J Oncol Pharm Practice 2010; 16: 137-8.

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11. Zhou S-F, Changli X, Yu X-Q, Li C, Wang G. Clinically important drug interactions potentially involving mechanism-based inhibition of cytochrome P450 3A4 and the role of therapeutic drug monitoring. Ther Drug Monit 2007; 29:687-710.

Appendix I: Table of Antiemetic Doses Recommended for Acute AINV Prophylaxis in Adult Cancer Patients

ANTIEMETIC AGENT	RECOMMENDED PEDIATRIC DOSE	RECOMMENDED ADULT DOSE[11, 13]
Aprepitant	12 years of age and older: Day 1: 125 mg PO x 1; Days 2 and 3: 80 mg PO once daily	Day 1: 125 mg PO x 1; Days 2 and 3: 80 mg PO once daily
Chlorpromazine	0.5 mg/kg/dose IV q6h	Not included in guideline
Dexamethasone	Highly emetogenic antineoplastic therapy:	
	6 mg/m^2/dose IV/PO q6h If given concurrently with aprepitant, reduce dexamethasone dose by half.	20 mg IV/PO pre-therapy once daily If given concurrently with aprepitant, reduce dexamethasone dose to 12 mg IV/PO.
	Moderately emetogenic antineoplastic therapy:	
	≤ 0.6 m^2: 2 mg/dose IV/PO q12h > 0.6 m^2: 4 mg/dose IV/PO q12h If given concurrently with aprepitant, reduce dose by half.	8 mg IV/PO pre-therapy once daily If given concurrently with aprepitant, use dosing provided for highly emetogenic antineoplastic therapy.
Granisetron	Highly emetogenic antineoplastic therapy:	
	40 mcg/kg/dose IV as a single daily dose	2 mg PO pre-therapy once daily OR 1 mg (0.01mg/kg/dose) IV pre-therapy once daily
	Moderately emetogenic antineoplastic therapy:	
	40 mcg/kg/dose IV as a single daily dose OR 40 mcg/kg/dose PO q12h	2 mg PO pre-therapy once daily OR 1 mg (0.01mg/kg/dose) IV pre-therapy once daily
	Antineoplastic therapy of low emetogenicity:	
	40 mcg/kg/dose IV as a single daily dose OR 40 mcg/kg/dose PO as q12h	Not included in guideline
Metoclopramide	Highly emetogenic antineoplastic therapy:	
	2 mg/kg/dose IV pre-therapy x 1 then at 2, 6 and 12 hours after. Give diphenhydramine or benztropine concurrently.	Not included in guideline
	Moderately emetogenic antineoplastic therapy:	
	1 mg/kg/dose IV pre-therapy x 1 then 0.0375 mg/kg/dose PO q6h Give diphenhydramine or benztropine concurrently.	Not included in guideline
Nabilone	< 18 kg: 0.5 mg/dose PO twice daily 18 to 30 kg: 1 mg/dose PO twice daily > 30 kg: 1 mg/dose PO three times daily Maximum: 0.06 mg/kg/day	Not included in guideline
Ondansetron	Highly emetogenic antineoplastic therapy:	
	5 mg/m^2/dose (0.15 mg/kg/dose) IV/PO pre-therapy x 1 and then q8h	8 mg PO twice daily 8 mg (0.15 mg/kg/dose) IV twice daily
	Moderately emetogenic antineoplastic therapy:	
	5 mg/m^2/dose (0.15 mg/kg/dose) IV/PO pre-therapy x 1 and then q12h	8 mg PO twice daily 8 mg (0.15 mg/kg/dose) IV pre-therapy once daily
	Antineoplastic therapy of low emetogenicity:	
	10 mg/m^2/dose (0.3 mg/kg/dose; maximum 24 mg/dose) IV/PO pre-therapy x 1	Not included in guideline

Appendix J: Content Expert Reviewers' Survey

Feedback Questionnaire:
POGO Guideline for the Prevention of Acute Nausea and Vomiting due to Antineoplastic Medication in Pediatric Cancer Patients

The purpose of this survey is to obtain feedback from recognized experts in the field. After reviewing the draft Pediatric Oncology Group of Ontario (POGO) *Guideline for the Prevention of Acute Nausea and Vomiting due to Antineoplastic Medication in Pediatric Cancer Patients* that accompanied this survey, we ask you to complete the questions below. Your feedback, along with that from other reviewers, will be used to revise the guideline report and refine the recommendations.

1. What is your role in the care of patients with cancer?

   ❑ Pediatric Oncologist ❑ Pediatric Hematologist ❑ Pediatric Pharmacist ❑Pediatric Nurse

   ❑ Adult Oncologist ❑ Adult Hematologist ❑ Adult Pharmacist ❑ Adult Nurse

   ❑ Other (*please specify*): _____

2. Do you currently follow a practice guideline for prevention of acute nausea and vomiting?

   ❑ No

   ❑ Yes → Which guideline? _____

3. For each item below, please check the box that most adequately reflects your opinion:

Items	Strongly agree	Agree	Neither agree nor disagree	Disagree	Strongly disagree
a. The rationale for developing a guideline, as stated in the "*Introduction*" and "*Scope and Purpose*" sections of the draft guideline report, is clear.					
b. There is a need for a practice guideline on this topic.					
c. The literature search described in the draft report is complete (no key studies or guidelines were missed).					
d. The evidence described in the draft report is relevant.					
e. I agree with the methods used to summarize the evidence included in the draft report.					
f. The results of the studies described in the draft report are interpreted according to my understanding of the data.					
g. The draft recommendations are clear.					
h. I agree with the draft recommendations as stated.					
i. I would feel comfortable having these recommendations applied in my hospital.					

This questionnaire is based on a feedback questionnaire developed by the Cancer Care Ontario Program in Evidence-base Care.

4. How likely would you be to use the guideline recommendations in your own practice?

Likely	Unsure	Not likely	Not applicable
☐	☐	☐	☐

If you answered "Not likely", why not? _____

_____

_____

Please feel free to add comments below. Among other issues, you may wish to comment on the clarity and completeness of the report, the wording of specific recommendations, the links between the available evidence and the recommendations, and any significant gaps in the recommendations.

_____

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When you have completed the questionnaire, please return it by fax or e-mail to:

Linda Brown
Administrative Assistant to Clinical Programs and Selected Initiatives
Email: LBrown@pogo.ca
Fax: 416-592-1285

Thank you for contributing to the development of this POGO guideline.

This questionnaire is based on a feedback questionnaire developed by the Cancer Care Ontario Program in Evidence-base Care.

Stakeholder Feedback Survey
POGO Guideline for the Prevention of Acute Nausea and Vomiting due to Antineoplastic Medication in Pediatric Cancer Patients

The purpose of this survey is to obtain feedback from the pediatric oncology Ontario stakeholder community. After reviewing the draft Pediatric Oncology Group of Ontario (POGO) *Guideline for the Prevention of Acute Nausea and Vomiting due to Antineoplastic Medication in Pediatric Cancer Patients* that accompanied this survey, we ask you to complete the questions below.

1. What is your role in the care of patients?

☐ Oncologist ☐ Hematologist ☐ Pediatrician ☐ Nurse Practitioner
☐ Pharmacist ☐ Administrator ☐ Nurse Educator ☐ Advanced Practice Nurse
☐ Nurse ☐ Other (*please specify*):_____

2. At which institution do you work?

☐ Children's Hospital of Eastern Ontario
☐ Children's Hospital, London Health Sciences Centre
☐ Credit Valley Hospital
☐ Grand River Hospital
☐ Hospital for Sick Children
☐ Kingston General Hospital
☐ McMaster Children's Hospital, Hamilton Health Sciences
☐ Orillia Soldier's Memorial Hospital
☐ Rouge Valley Health System
☐ Southlake Regional Health Centre
☐ Northeast Cancer Centre, Health Sciences North
☐ Windsor Regional Hospital

3. Do you currently follow a practice guideline for prevention of acute nausea and vomiting?

☐ No
☐ Yes → Which guideline? _____

4. For each item below, please check the box that most adequately reflects your opinion:

Items	Strongly agree	Agree	Neither agree nor disagree	Disagree	Strongly disagree
There is a need for a practice guideline on this topic.					
The literature search described in the report is complete (no key studies were missed).					
The results of the studies described in the report are interpreted according to my understanding of the data.					
The recommendations are clear.					
I agree with the recommendations as stated.					
I would feel comfortable having these recommendations applied in my hospital.					
The recommendations are likely to be supported by a majority of my colleagues.					
Which do you foresee may be obstacles to implementing these recommendations at your institution?					
a) Concern to dose antiemetics as recommended					
b) Reluctance to standardize practice					
c) The recommendations conflict with current institutional policies					
d) Existing pre-printed and electronic order sets would need to be changed					
I see myself playing an active role in contributing towards the implementation of this guideline.					

5. How likely would you be to use the guideline recommendations in your own practice?

Likely	Unsure	Not likely	Not applicable
❒	❒	❒	❒

If you answered **"Not likely"**, why not? _____

_____

_____

6. For the information of the guideline development panel, please answer the following questions:

a) Is dexamethasone currently used as an antiemetic for prevention of AINV at your institution?

☐ Yes
☐ No

If you answered **"No"**, why not? _____

_____

_____

b) At your institution, aprepitant is: *(Please check all that apply)*

☐ Not used as an antiemetic for pediatric oncology patients
☐ Limited to adolescents
☐ Limited to patients receiving cisplatin
☐ Limited to patients who have failed standard antiemetic therapy
☐ No limitations to use for pediatric oncology patients
☐ Other (*please specify*):_____

Please feel free to add comments below. Among other issues, you may wish to comment on the clarity of the wording of specific recommendations and additional barriers or potential facilitators to use of these recommendations at your institution.

_____

_____

_____

_____

_____

When you have completed the questionnaire, please return it by fax or e-mail to:

Paula Robinson
Guideline Methodologist
Email: PRobinson@pogo.ca
Fax: 416-592-1285

Thank you for contributing to the development of this POGO guideline.

This questionnaire is based on a feedback questionnaire developed by the Cancer Care Ontario Program in Evidence-base Care.

Quick Review Summary

Guideline for the Prevention of Acute Nausea and Vomiting due to Antineoplastic Medication in Pediatric Cancer Patients

The purpose of this guideline is to provide health care providers with an approach to the prevention of acute antineoplastic-induced nausea and vomiting (AINV) in children who are receiving antineoplastic medication. The scope is limited to the prevention of AINV in the acute phase (within 24 hours of administration of an antineoplastic agent). Recommended antiemetic strategies are limited to those available in Canada at the time of guideline development.

The Pediatric Oncology Group of Ontario (POGO) AINV Guideline Development Panel included inter-disciplinary representation from several POGO institutions as well as content and methodological expertise. Using established methods, ADAPTE and CAN-IMPLEMENT, the scope of the guideline was determined and existing guidelines were identified for adaptation to the POGO context. A library scientist-guided literature search was undertaken and the source guidelines were updated and reframed based on a systematic review of pediatric evidence. The quality of evidence was assessed and the strength of each recommendation was determined. The guideline development process included an extensive two-stage external review: first by international experts in adult and pediatric AINV and then by Ontario health care provider stakeholders.

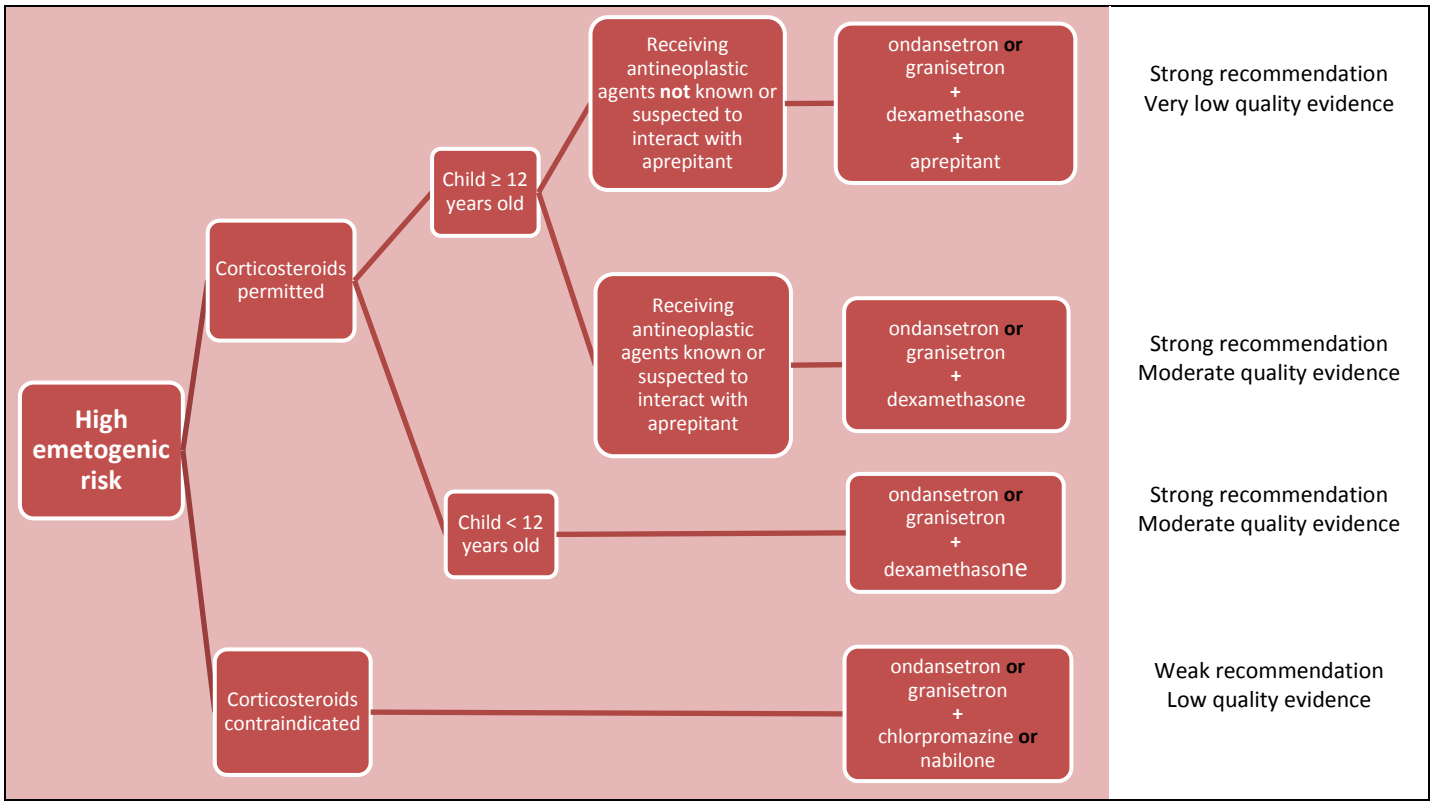
This guideline represents the second in a series of guidelines to address the need for, and the selection of, antiemetic prophylaxis in children with cancer receiving antineoplastic therapy. The first, the *POGO Guideline for the Classification of the Acute Emetogenic Potential of Antineoplastic Medication in Pediatric Cancer Patients,* provides evidence-based recommendations on the assessment of a regimen's emetogenicity. Since appropriate antiemetic selection for acute AINV prophylaxis begins with an assessment of the intrinsic emetogenicity of the antineoplastic therapy to be given, this Quick Review Summary will reference both guidelines.

The focus of this Quick Review Summary is on providing a summary of the recommended pharmacological interventions. It is intended to be used in conjunction with the complete guidelines which are available at http://www.pogo.ca/healthcare/practiceguidelines. These guidelines provide a standardized, evidence-based approach to the prevention of AINV in children receiving antineoplastic agents. They offer a platform upon which individual clinicians and institutions may frame local recommendations. Each institution is encouraged to adapt them to their local context.

Recommended citation: Dupuis LL, Boodhan S, Holdsworth M, Robinson PD, Hain R, Portwine C, O'Shaughnessy E and Sung L. *Guideline for the Prevention of Acute Nausea and Vomiting due to Antineoplastic Medication in Pediatric Cancer Patients*. Pediatric Oncology Group of Ontario; Toronto. 2012.

Disclaimer: This summary and the full guideline were developed by health care professionals using evidence-based or best practice references available at the time of its creation. The content of the guideline will change as it will be reviewed and revised on a periodic basis. Care has been taken to ensure accuracy of the information. However, every health care professional using this guideline is responsible for providing care according to their best professional judgement and the policies and standards in place at their institution.

Prevention of Acute AINV in Pediatric Cancer Patients



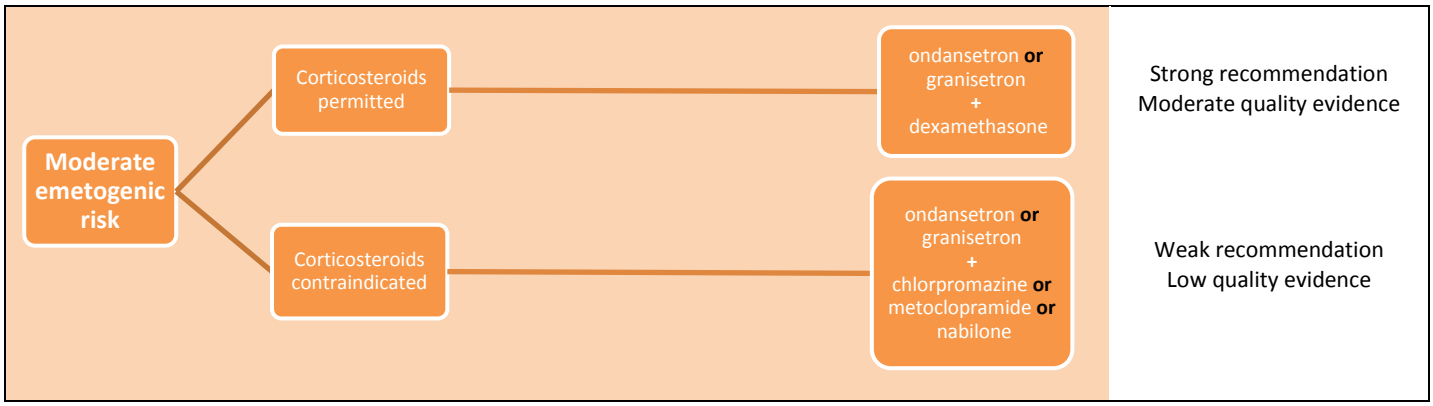
Antineoplastic Agents with HIGH Emetic Risk > 90% frequency of emesis in absence of prophylaxis	
Single agent antineoplastic therapy	
Altretamine Carboplatin Carmustine > 250 mg/m^2 Cisplatin Cyclophosphamide ≥1 g/m^2 Cytarabine 3 g/m^2/dose Dacarbazine	Dactinomycin Mechlorethamine Methotrexate ≥ 12 g/m^2 Procarbazine (oral) Streptozocin Thiotepa ≥ 300 mg/m^2
Multiple agent antineoplastic therapy	
With the exceptions listed below, emetogenicity is classified based on the most highly emetogenic agent. The following are also classified as high emetic risk: Cyclophosphamide + anthracycline Cyclophosphamide + doxorubicin Cyclophosphamide + epirubicin Cyclophosphamide + etoposide Cytarabine 150-200 mg/m^2 + daunorubicin Cytarabine 300 mg/m^2 + etoposide Cytarabine 300 mg/m^2 + teniposide Doxorubicin + ifosfamide Doxorubicin + methotrexate 5 g/m^2 Etoposide + ifosfamide	
Multi-day antineoplastic therapy	
Emetogenicity is classified based on the most highly emetogenic agent on each day of therapy.	

Antiemetic Dosage Recommendations for Children receiving HIGHLY Emetogenic Antineoplastic Therapy		**GRADE**
Drug	**Dose**	
Aprepitant	Day 1: 125 mg PO x 1 Days 2 and 3: 80mg PO once daily	Strong recommendation Moderate quality evidence
Dexamethasone	6 mg/m^2/dose IV/PO q6h If given concurrently with aprepitant, reduce dexamethasone dose by half.	Weak recommendation Low quality evidence
Granisetron	40 mcg/kg/dose IV as a single daily dose	Strong recommendation Low quality evidence
Ondansetron	5 mg/m^2/dose (0.15 mg/kg/dose) IV/PO pre-therapy x 1 and then q8h	Strong recommendation Moderate quality evidence
Chlorpromazine	0.5mg/kg/dose IV q6h	Strong recommendation Low quality evidence
Nabilone	< 18 kg: 0.5 mg/dose PO twice daily 18 to 30 kg: 1 mg/dose PO twice daily > 30 kg: 1 mg/dose PO three times daily Maximum: 0.06 mg/kg/day	Weak recommendation Low quality evidence

Refer to the complete POGO guidelines, available at http://www.pogo.ca/healthcare/practiceguidelines for further details:

- Guideline for the Prevention of Acute Nausea and Vomiting due to Antineoplastic Medication in Pediatric Cancer Patients. See page 36 and Appendix I for information regarding maximum antiemetic doses.
- Guideline for the Classification of the Acute Emetogenic Potential of Antineoplastic Medication in Pediatric Cancer Patients

Prevention of Acute AINV in Pediatric Cancer Patients



Antineoplastic Agents with MODERATE Emetic Risk 30-90% frequency of emesis in absence of prophylaxis
Single agent antineoplastic therapy
Aldesleukin > 12 to 15 million units/m^2 Amifostine > 300 mg/m^2 Arsenic trioxide Azacitidine Bendamustine Busulfan Carmustine ≤ 250 mg/m^2 Clofarabine Cyclophosphamide < 1 g/m^2 Cyclophosphamide (oral) Cytarabine > 200 mg to < 3 g/m^2 Daunorubicin Doxorubicin Epirubicin Etoposide (oral) Idarubicin Ifosfamide Imatinib (oral) Intrathecal therapy (methotrexate, hydrocortisone & cytarabine) Irinotecan Lomustine Melphalan > 50 mg/m^2 Methotrexate ≥ 250 mg to < 12 g/m^2 Oxaliplatin > 75 mg/m^2 Temozolomide (oral) Vinorelbine (oral)
Multiple agent antineoplastic therapy
With the exceptions listed under high emetic risk, emetogenicity is classified based on the most highly emetogenic agent.
Multi-day antineoplastic therapy
Emetogenicity is classified based on the most highly emetogenic agent on each day of therapy.

Antiemetic Dosage Recommendations for Children receiving MODERATELY Emetogenic Antineoplastic Therapy		GRADE
Drug	**Dose**	
Dexamethasone	**≤ 0.6m^2:** 2mg/dose IV/PO q12h **> 0.6m^2:** 4mg/dose IV/PO q12h If given concurrently with aprepitant, reduce dexamethasone dose by half	Strong recommendation Low quality evidence
Granisetron	40 mcg/kg/dose IV as a single daily dose **or** 40 mcg/kg/dose PO q12h	**IV:** Strong recommendation Moderate quality evidence **PO:** Weak recommendation Low quality evidence
Ondansetron	5 mg/m^2/dose (0.15 mg/kg/dose; maximum 8 mg/dose) IV/PO pre-therapy x 1 and then q12h	Strong recommendation Moderate quality evidence
Chlorpromazine	0.5mg/kg/dose IV q6h	Strong recommendation Low quality evidence
Metoclopramide	1 mg/kg/dose IV pre-therapy x 1 then 0.0375 mg/kg/dose PO q6h Give diphenhydramine or benztropine concurrently.	Strong recommendation Low quality evidence
Nabilone	< 18 kg: 0.5 mg/dose PO twice daily 18 to 30 kg: 1 mg/dose PO twice daily > 30 kg: 1 mg/dose PO three times daily Maximum: 0.06 mg/kg/day	Weak recommendation Low quality evidence

Refer to the complete POGO guidelines, available at http://www.pogo.ca/healthcare/practiceguidelines for further details:

- Guideline for the Prevention of Acute Nausea and Vomiting due to Antineoplastic Medication in Pediatric Cancer Patients. See page 36 and Appendix I for information regarding maximum antiemetic doses.
- Guideline for the Classification of the Acute Emetogenic Potential of Antineoplastic Medication in Pediatric Cancer Patients

Prevention of Acute AINV in Pediatric Cancer Patients

Low emetogenic risk	ondansetron **or** granisetron	Strong recommendation Moderate quality evidence

Antineoplastic Agents with LOW Emetic Risk 10% to <30% frequency of emesis in absence of prophylaxis	
Single agent antineoplastic therapy	
Amifostine ≤300 mg/m^2 Amsacrine Bexarotene Busulfan (oral) Capecitabine Cytarabine ≤200 mg/m^2 Docetaxel Doxorubicin (liposomal) Etoposide Fludarabine (oral) 5-Fluorouracil Gemcitabine Ixabepilone	Methotrexate >50 mg/m^2 to <250mg/m^2 Mitomycin Mitoxantrone Nilotinib Paclitaxel Paclitaxel-albumin Pemetrexed Teniposide Thiotepa <300 mg/m^2 Topotecan Vorinostat
Multiple agent antineoplastic therapy	
With the exceptions listed under high emetic risk, emetogenicity is classified based on the most highly emetogenic agent.	
Multi-day antineoplastic therapy	
Emetogenicity is classified based on the most highly emetogenic agent on each day of therapy.	

Antiemetic Dosage Recommendations for Children receiving LOW Emetic Risk Antineoplastic Therapy		**GRADE**
Drug	**Dose**	
Granisetron	40 mcg/kg/dose IV as a single daily dose or 40 mcg/kg/dose PO q12h	**IV:** Strong recommendation Low quality evidence **PO:** Weak recommendation Low quality evidence
Ondansetron	10 mg/m^2/dose (0.3 mg/kg/dose; Maximum 16 mg/dose IV 24 mg/dose PO pre-therapy x 1	Strong recommendation Low quality evidence

Refer to the complete POGO guidelines for further details:

- Guideline for the Prevention of Acute Nausea and Vomiting due to Antineoplastic Medication in Pediatric Cancer Patients
- Guideline for the Classification of the Acute Emetogenic Potential of Antineoplastic Medication in Pediatric Cancer Patients

Available at http://www.pogo.ca/healthcare/practiceguidelines

Minimal emetogenic risk	no routine prophylaxis	Strong recommendation Very low quality evidence

Antineoplastic Agents with MINIMAL Emetic Risk <10% frequency of emesis in absence of prophylaxis		
Single agent antineoplastic therapy		
Alemtuzumab Alpha interferon Aspagarinase (IM or IV) Bevacizumab Bleomycin Bortezomib Cetuximab Chlorambucil (oral) Cladribine (2-chlorodeoxyadenosine) Dasatinib Decitabine Denileukin diftitox Dexrazoxane	Erlotinib Fludarabine Gefitinib Gemtuzumab ozogamicin Hydroxyurea (oral) Lapatinib Lenalidomide Melphalan (oral low-dose) Mercaptopurine (oral) Methotrexate ≤ 50 mg/m^2 Nelarabine Panitumumab Pentostatin	Rituximab Sorafenib Sunitinib Temsirolimus Thalidomide Thioguanine (oral) Trastuzumab Valrubicin Vinblastine Vincristine Vindesine Vinorelbine
For multiple agent and multi-day antineoplastic therapy – Please refer to recommendations in Low emetic risk table.		

Appendix M: Relative Acquisition Costs of Recommended Antiemetic Agents in Ontario at the Time of Guideline Development

Drug	Dose	Formulation	Relative Daily Cost *
Aprepitant	Day 1: 125mg PO x 1; Days 2 and 3: 80mg PO once daily	capsule	$$$$
Dexamethasone	6mg/m^2/dose IV q6h 4mg/dose PO q12h	injection tablet	$$ $
Granisetron	40mcg/kg/dose PO q12h 40mcg/kg/dose IV daily	tablet injection	$$$$$ $
Ondansetron	5mg/m^2/dose IV/PO q8h	tablet oral dissolving tablet oral liquid injection	$$$ $$ $$$$$ $
Chlorpromazine	0.5mg/kg/dose IV q6h	injection	$
Metoclopramide	1mg/kg/dose IV then 0.0375mg/kg po q6h	injection + tablet injection + oral liquid	$ $
Nabilone	1mg po q12h	capsule	$$$

*based on a patient with body weight of 30kg and body surface area of 1m^2;
$: < $1; $$: 5-10; $$$: 10 – 20; $$$$: 20-35; $$$$$: 35-50.