

CLINICAL PRACTICE GUIDELINE

Prevention of acute and delayed chemotherapy-induced nausea and vomiting in pediatric cancer patients: A clinical practice guideline

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Abstract

This clinical practice guideline provides recommendations for preventing acute and delayed phase chemotherapy-induced nausea and vomiting (CINV) in pediatric patients. The recommendations are based on two systematic reviews of randomized controlled trials evaluating interventions to prevent (1) acute phase CINV and (2) delayed phase CINV. Recommendations for acute phase and delayed phase CINV prophylaxis are made for patients receiving chemotherapy of varying emetogenicity, as well as for patients not able to receive dexamethasone or a neurokinin-1

Abbreviations: (fos)aprepitant, IV fosaprepitant or oral aprepitant; (fos)netupitant, IV fosnetupitant or oral netupitant; 5HT₃RA, serotonin-3 receptor antagonist; CIN, chemotherapy-induced nausea; CINV, chemotherapy-induced nausea and vomiting; CIV, chemotherapy-induced vomiting; CPG, clinical practice guideline; HEC, highly emetogenic chemotherapy; HSCT, hematopoietic stem cell transplant; IV, intravenous; LEC, low emetogenic chemotherapy; MEC, moderately emetogenic chemotherapy; minEC, minimally emetogenic chemotherapy; NK1RA, neurokinin-1 receptor antagonist; POGO, Pediatric Oncology Group of Ontario; RCT, randomized controlled trial; SR, systematic review.

receptor antagonist. Evidence gaps, including antiemetic safety and optimal dosing, were identified.

KEYWORDS

chemotherapy-induced nausea and vomiting, guideline, pediatric oncology, supportive care

1 | INTRODUCTION

Chemotherapy-induced nausea and vomiting (CINV) are among the most common adverse effects related to cancer therapy and, when poorly controlled, impair patients' health and quality of life.^{1–7} Clinical practice guideline (CPG)-consistent CINV prophylaxis improves CINV control for both adult and pediatric patients.^{8–10}

This CPG is one of a series focused on CINV prevention and treatment in pediatric patients receiving cancer treatment or undergoing hematopoietic stem cell transplant (HSCT).^{11–13} Our objective was to provide evidence-based guidance on strategies for acute and delayed phase CINV prevention and thereby optimize the supportive care of children and adolescents with cancer or receiving chemotherapy for HSCT. This CPG will be of interest to health care professionals who care for patients up to 18 years of age with cancer or undergoing HSCT. It may also be useful for patients and their families, administrators, educators, supportive care researchers, and quality improvement leaders.

2 | METHODS

2.1 | CPG panel constitution

The panel included representatives from pediatric hematology/oncology, HSCT, nursing, pharmacy, and psychology; patient advocates; and CPG methodologists (Appendix SA1). Panel member selection was based upon expertise in CINV, pediatric supportive care, CPG methodology, and experience in managing CINV as a family caregiver. Invited panel members declared potential conflicts of interest; no panel member was excluded from participation due to a conflict (Appendix SA2).

This CPG was funded and developed through the Pediatric Oncology Group of Ontario (POGO) Guidelines Program. The development process and the CPG content are editorially independent from POGO.

2.2 | General approach to CPG development

The Appraisal of Guidelines for Research and Evaluation II¹⁴ framed CPG development. Eight virtual CPG panel meetings were held between February 2021 and April 2022 to formulate the approach and recommendations.

Key health questions are shown in Table 1. Panel members identified key outcomes and rated their importance by consensus.

Complete chemotherapy-induced vomiting (CIV) control, complete chemotherapy-induced nausea (CIN) control, complete CINV control, adverse effects of an intervention, and feasibility of intervention administration to children and adolescents were considered critical outcomes for both the acute and delayed phase.

The Grading of Recommendations Assessment, Development and Evaluation approach¹⁵ was used to rate the quality of evidence and formulate recommendations. Evidence quality was rated as high, moderate, low, or very low. The quality rating was lowered if there were study design flaws, inconsistent results, imprecision or if direct pediatric data were lacking. Strong or conditional recommendations were based on the panel's confidence in an intervention's effect, while also taking into consideration its safety profile. A strong recommendation was made when the benefit of an intervention clearly outweighed the potential harms. A conditional recommendation was made when the benefit or harm of an intervention were unclear or when the benefits and disadvantages were closely matched.

This CPG will be updated within 5 years or sooner if new evidence becomes available that would affect its recommendations.

2.3 | Evidence base formulation

Although originally planned as an update of the 2013 and 2017 acute CINV prevention CPGs,^{16,17} a new (rather than updated) acute phase CINV CPG was created so that recommendations for preventing both acute and delayed phase CINV could be developed as a single CPG using identical methodology. Two systematic reviews (SRs) were conducted to identify the evidence base that informed CPG recommendations (see Appendix SA3 for list of team members). Each SR included parallel arm randomized controlled trials (RCTs) evaluating interventions to prevent: (1) acute phase CINV or (2) delayed phase CINV. The complete methods for the SR evaluating acute phase CINV are published separately.¹⁸ The complete methods for the SR evaluating delayed phase CINV are presented in Appendix SA4. In brief, English-language RCTs published between January 1, 1989 (publication year of first ondansetron study) and January 21, 2022 that evaluated a strategy to prevent acute phase or delayed phase CINV were identified. RCTs conducted in patients of any age were included.

2.4 | Definitions

A chemotherapy block was defined as consecutive days of chemotherapy. The acute phase was defined as starting with administration of the

TABLE 1 Summary of health questions and recommendations for prevention of acute and delayed phase CINV in pediatric patients

Health questions and recommendations	Recommendation strength/evidence quality
1. In pediatric patients receiving highly emetogenic chemotherapy,	
1.1 what strategies are recommended to prevent acute phase CINV?	
a. Use a 5HT3RA + dexamethasone + (fos)aprepitant ^a	Strong/high
b. Use palonosetron + dexamethasone in patients unable to receive (fos)aprepitant ^a	Strong/moderate
c. Use palonosetron + (fos)aprepitant ^a in patients unable to receive dexamethasone	Strong/low
d. Use palonosetron in patients unable to receive dexamethasone + (fos)aprepitant ^a	Strong/moderate
e. Consider adding olanzapine to other CPG-consistent antiemetics	Conditional/moderate
1.2 what strategies are recommended to prevent delayed phase CINV?	
a. Use palonosetron in the acute phase as the preferred 5HT3RA in patients at high risk of delayed phase CINV	Strong/moderate
b. Use oral aprepitant in the delayed phase, if (fos)aprepitant ^a started in the acute phase	Strong/high
c. Add dexamethasone in the delayed phase in patients who received granisetron or ondansetron in the acute phase	Strong/moderate
d. Consider adding dexamethasone in the delayed phase in patients who received palonosetron in the acute phase	Conditional/moderate
e. Use dexamethasone in the delayed phase in patients unable to receive oral aprepitant	Strong/moderate
f. Continue olanzapine in the delayed phase, if started in the acute phase	Strong/moderate
g. Do not use 5HT3RAs in the delayed phase	Strong/low
2. In pediatric patients receiving moderately emetogenic chemotherapy,	
2.1 what strategies are recommended to prevent acute phase CINV?	
a. Use a 5HT3RA + dexamethasone	Strong/moderate
b. Use a 5HT3RA + (fos)aprepitant ^a in patients unable to receive dexamethasone	Strong/low
c. Use a 5HT3RA in patients unable to receive dexamethasone + (fos)aprepitant ^a	Strong/low
d. Consider using palonosetron as the preferred 5HT3RA in patients unable to receive dexamethasone + (fos)aprepitant ^a	Conditional/low
e. Consider adding olanzapine to other CPG-consistent antiemetics in patients unable to receive dexamethasone + (fos)aprepitant ^a	Conditional/low
2.2 what strategies are recommended to prevent delayed phase CINV?	
a. Consider using dexamethasone in the delayed phase	Conditional/low
b. Continue oral aprepitant in the delayed phase in patients receiving single-day chemotherapy who received (fos)aprepitant ^a in the acute phase	Strong/moderate
c. Consider not using oral aprepitant in the delayed phase in patients receiving multi-day chemotherapy (≥ 3 days) who received (fos)aprepitant ^a in the acute phase	Conditional/low
d. Continue olanzapine in the delayed phase, if started in the acute phase	Strong/low
3. In pediatric patients receiving low emetogenic chemotherapy,	
3.1 what strategies are recommended to prevent acute phase CINV?	
a. Use a 5HT3RA	Strong/low
3.2 what strategies are recommended to prevent delayed phase CINV?	
a. Do not use prophylaxis routinely in the delayed phase	Strong/very low
4. In pediatric patients receiving minimally emetogenic chemotherapy,	
4.1 what strategies are recommended to prevent acute phase CINV?	
a. Do not use prophylaxis routinely	Strong/very low
4.2 what strategies are recommended to prevent delayed phase CINV?	
a. Do not use prophylaxis routinely in the delayed phase	Strong/very low

CINV, chemotherapy-induced nausea and vomiting; 5HT3RA, serotonin-3 receptor antagonist.

^aIV fosaprepitant or oral aprepitant.

first chemotherapy dose and ending 24 h after administration of the last chemotherapy dose of a chemotherapy block. The delayed phase was defined as starting at the end of the acute phase and continuing for 96 h or until another chemotherapy block began, whichever occurred first.

2.5 | Meta-analysis

The methods for synthesis of the acute phase data have been published elsewhere.¹⁸ The methods for meta-analysis of the delayed phase data were similar and are fully presented in Appendix SA4. Briefly, for the acute and delayed phase CINV SRs, synthesis was planned when three or more RCTs had the following characteristics: compared the same intervention against the same control, reported one of the designated key outcome measures and included chemotherapy of the same emetogenicity. Serotonin-3 receptor antagonists (5HT3RAs) and neurokinin-1 receptor antagonists (NK1RAs) were each evaluated as a group to evaluate class effects. For multi-arm studies, the two study arms of highest clinical interest that permitted synthesis were used; this decision was made by three authors (PP, PDR, and LLD) blinded to outcome data.

Three categories of studies were relevant to delayed phase CINV control: (1) RCTs where antiemetics given in the acute phase were the same in each study arm and randomization to different delayed phase antiemetics occurred; (2) RCTs where randomization to different antiemetics occurred in both the acute and delayed phase and where the randomized antiemetic was the same in both the acute and delayed phase; and (3) RCTs where randomization to different acute phase antiemetics occurred, delayed phase antiemetics were the same by study arm and delayed phase CINV control was evaluated. These categories are summarized with examples in Appendix SA5.

Intervention effects were described using the risk ratio (RR) with its 95% confidence interval (CI) and synthesis was conducted using the random effects model in Review Manager 5.4 (Cochrane Collaboration, Nordic Cochrane Centre, London, United Kingdom).¹⁹ A $RR > 1$ in analyses evaluating CIV, CIN, and CINV control suggests that the intervention improves patient outcomes (e.g., a higher proportion of patients receiving the intervention experienced complete CINV control versus the comparator). For the safety outcome of antiemetic discontinuation due to an antiemetic-related adverse effect, a $RR < 1$ suggests a benefit among patients receiving the intervention. In addition to evaluating antiemetic-related adverse effects, we narratively described adverse effects for antiemetics that were not included in the previous acute CINV CPG.

For the delayed phase meta-analysis, two stratified analyses were performed. First, we evaluated the effect of randomization to dexamethasone versus no dexamethasone in the delayed phase among those who systematically received a first-generation 5HT3RA (granisetron or ondansetron) or a second-generation 5HT3RA (palonosetron) in the acute phase (category 1). Second, we evaluated the effect of

randomization to palonosetron versus granisetron or ondansetron in the acute phase among those who systematically received dexamethasone or no dexamethasone in the delayed phase (category 3). We used the p value for interaction (p_{int}) to determine if heterogeneity in the effect of an intervention (e.g., 5HT3RA choice) could be explained by the use of another antiemetic (e.g., delayed phase dexamethasone).

Publication bias of meta-analyses was explored through visual examination of funnel plots when there were at least 10 studies included. When publication bias was suspected, "trim and fill" technique was to be applied to determine the impact of the potential bias. Outlying studies would be removed (trim) and hypothetical negative studies with equal weight would be added (fill).²⁰

3 | RESULTS

The literature search identified 65,172 citations, of which 744¹⁸ were retrieved for full-text screening for both the acute and delayed phase SRs. A total of 328 RCTs were included across both SRs. The characteristics of the RCTs included in the acute phase (296 RCTs) and delayed phase (212 RCTs) SRs are summarized in Appendix SA6. The study flow diagram for the acute phase SR has been published previously and the delayed phase SR study flow diagram can be found in Appendix SA7. The study-level data for the acute phase RCTs were previously published¹⁸ while the study-level data for the delayed phase RCTs are presented in Appendices SA8a and SA8b.

3.1 | Acute phase CINV

The acute phase CINV SR has been published.¹⁸ Few RCTs were conducted exclusively in pediatric patients (25 out of 296; 8%). Almost all RCTs consisted of patients with cancer (284 out of 296; 96%). Almost half (133 out of 296; 45%) of the RCTs studied chemotherapy-naïve patients and 58% (173 out of 296) studied patients receiving single-day chemotherapy. Most RCTs studied patients receiving HEC (167 out of 296; 56%). Table 2 summarizes the meta-analyses that informed recommendations for preventing acute phase CINV. More detailed analyses are available elsewhere.¹⁸

3.2 | Delayed phase CINV

Few RCTs were conducted exclusively in pediatric patients (14 out of 212; 7%). Most studied patients with cancer (210 out of 212; 99%) receiving single-day chemotherapy (145 out of 212; 68%) and approximately half evaluated CIV, CIN, or CINV control in chemotherapy-naïve patients (99 out of 212; 47%). Administered chemotherapy was classified as HEC or MEC in 184 (87%) and 27 (13%) RCTs, respectively.

TABLE 2 Summary of meta-analyses used to inform acute phase CINV prevention recommendations. More detailed tables have been published elsewhere.¹⁸ (RR > 1 favors intervention arm)

Comparison and outcomes	Number of studies	N	RR	95% CI	I ²	p
Highly emetogenic chemotherapy						
5HT3RA prophylaxis						
Granisetron vs ondansetron						
Granisetron vs ondansetron						
Complete acute phase CIV control	11	3202	1.00	0.94–1.07	24%	.91
Complete acute phase CIN control	7	2923	1.00	0.93–1.08	9%	.97
Complete acute phase CINV control	2	UTD	UTD	UTD	UTD	UTD
Granisetron + corticosteroid vs ondansetron + corticosteroid						
Complete acute phase CIV control	3	1047	0.99	0.93–1.06	0%	.84
Complete acute phase CIN control	2	UTD	UTD	UTD	UTD	UTD
Complete acute phase CINV control	2	UTD	UTD	UTD	UTD	UTD
Palonosetron vs granisetron/ondansetron						
Palonosetron vs granisetron/ondansetron						
Complete acute phase CIV control	6 ^b	1410	1.11	1.02–1.20	43%	.01
Complete acute phase CIN control	2 ^b	UTD	UTD	UTD	UTD	UTD
Complete acute phase CINV control	0	UTD	UTD	UTD	UTD	UTD
Palonosetron + dexamethasone vs granisetron/ondansetron + dexamethasone						
Complete acute phase CIV control	7 ^b	4985	1.10	1.02–1.18	79%	.01
Complete acute phase CIN control	3 ^b	1784	1.53	1.00–2.34	94%	.05
Complete acute phase CINV control	2 ^b	UTD	UTD	UTD	UTD	UTD
Palonosetron + dexamethasone + NK1RA vs granisetron/ondansetron + dexamethasone + NK1RA						
Complete acute phase CIV control	5 ^b	1301	1.01	0.97–1.05	15%	.71
Complete acute phase CIN control	2	UTD	UTD	UTD	UTD	UTD
Complete acute phase CINV control	1	UTD	UTD	UTD	UTD	UTD
Corticosteroid prophylaxis						
Corticosteroid vs no corticosteroid						
Corticosteroid + metoclopramide vs metoclopramide						
Complete acute phase CIV control	3	226	1.03	0.70–1.52	0%	.89
Complete acute phase CIN control	3	226	1.02	0.75–1.39	0%	.88
Complete acute phase CINV control	0	UTD	UTD	UTD	UTD	UTD
Corticosteroid + 5HT3RA vs 5HT3RA						
Complete acute phase CIV control	14	2410	1.32	1.18–1.47	78%	<.00001
Complete acute phase CIN control	8	1252	1.39	1.26–1.53	2%	<.00001
Complete acute phase CINV control	5	1301	1.36	1.23–1.50	15%	<.00001
Dexamethasone + 5HT3RA vs 5HT3RA						
Complete acute phase CIV control	10	1855	1.29	1.12–1.49	82%	.0003
Complete acute phase CIN control	5	783	1.46	1.28–1.67	0%	<.00001
Complete acute phase CINV control	4	993	1.35	1.18–1.55	34%	<.00001

(Continues)

TABLE 2 (Continued)

Comparison and outcomes	Number of studies	N	RR	95% CI	I^2	p
NK1RA prophylaxis						
NK1RA vs no NK1RA						
(Fos)aprepitant^c + ondansetron vs ondansetron						
Complete acute phase CIV control	3 ^b	371	1.20	1.00–1.44	0%	.06
Complete acute phase CIN control	0	UTD	UTD	UTD	UTD	UTD
Complete acute phase CINV control	0	UTD	UTD	UTD	UTD	UTD
NK1RA + 5HT3RA + corticosteroid vs 5HT3RA + corticosteroid						
Complete acute phase CIV control	28 ^b	11,767	1.11	1.08–1.14	68%	<.00001
Complete acute phase CIN control	14	5739	1.05	1.01–1.08	0%	.01
Complete acute phase CINV control	7	2906	1.07	1.01–1.13	0%	.02
NK1RA + 5HT3RA + dexamethasone vs 5HT3RA + dexamethasone						
Complete acute phase CIV control	27 ^b	11,666	1.11	1.07–1.14	69%	<.00001
Complete acute phase CIN control	13	5638	1.04	1.01–1.08	0%	.02
Complete acute phase CINV control	7	2906	1.07	1.01–1.13	0%	.02
(Fos)aprepitant^c + 5HT3RA + dexamethasone vs 5HT3RA + dexamethasone						
Complete acute phase CIV control	20 ^b	6376	1.13	1.08–1.18	70%	<.00001
Complete acute phase CIN control	7	2070	1.04	0.98–1.11	0%	.17
Complete acute phase CINV control	6	2322	1.07	1.00–1.14	0%	.04
Fosaprepitant vs oral aprepitant						
Fosaprepitant + 5HT3RA + dexamethasone vs oral aprepitant + 5HT3RA + dexamethasone						
Complete acute phase CIV control	3	3611	1.01	0.99–1.03	0%	.50
Complete acute phase CIN control	0	UTD	UTD	UTD	UTD	UTD
Complete acute phase CINV control	0	UTD	UTD	UTD	UTD	UTD
(Fos)netupitant^d vs (fos)aprepitant^c						
(Fos)netupitant^d + 5HT3RA + dexamethasone vs (fos)aprepitant^c + 5HT3RA + dexamethasone						
Complete acute phase CIV control	4	2653	1.00	0.97–1.02	0%	.70
Complete acute phase CIN control	2	UTD	UTD	UTD	UTD	UTD
Complete acute phase CINV control	1	UTD	UTD	UTD	UTD	UTD
Olanzapine prophylaxis						
Olanzapine vs no olanzapine						
Olanzapine (+/- any concomitant antiemetics^a) vs no olanzapine (+/- any concomitant antiemetics^a)						
Complete acute phase CIV control	7 ^b	1659	1.23	1.05–1.44	91%	.01
Complete acute phase CIN control	7 ^b	1660	1.34	1.10–1.62	87%	.003
Complete acute phase CINV control	3	909	1.29	0.95–1.77	74%	.10

(Continues)

TABLE 2 (Continued)

Comparison and outcomes	Number of studies	N	RR	95% CI	I^2	p
Olanzapine + NK1RA + 5HT3RA + dexamethasone vs NK1RA + 5HT3RA + dexamethasone						
Complete acute phase CIV control	5 ^b	1520	1.25	0.99–1.57	93%	.06
Complete acute phase CIN control	5 ^b	1521	1.36	1.06–1.75	90%	.02
Complete acute phase CINV control	2	UTD	UTD	UTD	UTD	UTD
Olanzapine vs NK1 receptor antagonist						
Olanzapine + 5HT3RA + dexamethasone vs NK1RA + 5HT3RA + dexamethasone						
Complete acute phase CIV control	4	500	1.07	0.98–1.15	19%	.13
Complete acute phase CIN control	3	481	1.00	0.91–1.10	12%	.98
Complete acute phase CINV control	0	UTD	UTD	UTD	UTD	UTD
Moderately emetogenic chemotherapy						
5HT3RA prophylaxis						
Palonosetron vs granisetron/ondansetron						
Palonosetron + dexamethasone vs granisetron/ondansetron + dexamethasone						
Complete acute phase CIV control	3 ^b	193	0.94	0.86–1.02	0%	.15
Complete acute phase CIN control	1	UTD	UTD	UTD	UTD	UTD
Complete acute phase CINV control	0	UTD	UTD	UTD	UTD	UTD
Corticosteroid prophylaxis						
Corticosteroid vs no corticosteroid						
Dexamethasone + 5HT3RA vs 5HT3RA						
Complete acute phase CIV control	3	1002	1.29	1.21–1.39	0%	<.00001
Complete acute phase CIN control	2	UTD	UTD	UTD	UTD	UTD
Complete acute phase CINV control	1	UTD	UTD	UTD	UTD	UTD
NK1RA prophylaxis						
NK1RA vs no NK1RA						
(fos)aprepitant^c + 5HT3RA vs 5HT3RA						
Complete acute phase CIV control	3 ^b	344	1.15	0.96–1.37	80%	.12
Complete acute phase CIN control	2	UTD	UTD	UTD	UTD	UTD
Complete acute phase CINV control	0	UTD	UTD	UTD	UTD	UTD
(fos)aprepitant^c + 5HT3RA + dexamethasone vs 5HT3RA + dexamethasone						
Complete acute phase CIV control	11	2916	1.03	1.00–1.07	76%	.07
Complete acute phase CIN control	4	595	1.02	0.91–1.16	37%	.70
Complete acute phase CINV control	0	UTD	UTD	UTD	UTD	UTD

N, number of patients included in analysis; RR, risk ratio; CI, confidence interval; I^2 , statistic describing percentage of variation across studies that is due to heterogeneity rather than chance; CIV, chemotherapy-induced vomiting; CIN, chemotherapy-induced nausea; CINV, chemotherapy-induced nausea and vomiting; UTD, unable to determine; OLZ, olanzapine; HEC, highly emetogenic chemotherapy; MEC, moderately emetogenic chemotherapy; LEC, low emetogenic chemotherapy; NR, not reported; 5HT3RA, serotonin-3 receptor antagonist; NK1RA, neurokinin-1 receptor antagonist.

^aConcomitant antiemetics identical in both study arms.

^bAt least one pediatric study included.

^cIV fosaprepitant or oral aprepitant.

^dIV fosnetupitant or oral netupitant.

Table 3 summarizes the meta-analyses that informed recommendations for delayed phase CINV prevention. Detailed versions of this table are provided in Appendices SA9 and SA10. The results of the stratified analyses are presented in Appendix SA11. Details of RCTs included in meta-analyses of studies involving HEC and MEC are presented in Appendices SA12 and SA13. Sensitivity analyses undertaken for the meta-analyses where publication bias was suggested by visual inspection of funnel plots did not change the interpretation of the base analyses (Appendix SA14).

3.3 | Safety

Synthesis of antiemetic discontinuation due to an antiemetic-related adverse effect was possible for one comparison in the acute phase SR¹⁸ and for none in the delayed phase most studies either did not report these data (176 out of 328; 54%) or had zero events in both study arms (70 out of 328; 21%). (Appendix SA15)

Fosaprepitant and olanzapine were the only antiemetics included in the recommendations of this CPG that had not appeared in earlier pediatric CPGs on acute phase CINV prevention. Therefore, more detailed information regarding the adverse effects reported in the 11 and 19 included RCTs evaluating fosaprepitant and olanzapine, respectively, was abstracted. These are presented in Appendix SA16 and SA17.

For fosaprepitant, the most commonly reported adverse effects and the incidence rates reported were: anorexia/decreased appetite (eight RCTs: 2–52%), constipation (10 RCTs: 3–40%), diarrhea (eight RCTs: 4–60%), dyspepsia/abdominal discomfort (seven RCTs: 0–17%), fatigue/asthenia (eight RCTs: 2–64%), headache (eight RCTs: 0–47%), and hiccups (six RCTs: 1–32%). Two patients in two separate RCTs experienced anaphylaxis or hypersensitivity. Four RCTs described infusion-related reactions; the incidence of these reactions ranged from 1 to 24%.

For olanzapine, rates of sedation or drowsiness were reported in 14 of the included RCTs and ranged from 0 to 100%. Few studies reported rates of dyslipidemia (two RCTs: 5 and 10%), extrapyramidal symptoms (four RCTs: 0–18%), hyperglycemia (five RCTs: 0–6%), or increased appetite (two RCTs: 2 and 13%). Descriptions of these adverse effects, when reported in included RCTs, are presented in Appendix SA17. No RCT described ECG changes. Two RCTs reported the rate of olanzapine dose reduction due to toxicity (0 and 20%).

4 | RECOMMENDATIONS

Recommendations are summarized in Table 1 and Figure 1. The rationales for each recommendation are presented below and are summarized in Appendix SA18. Note that all references to aprepitant refer to oral administration. (Fos)aprepitant refers to intravenous (IV) fosaprepitant or oral aprepitant.

4.1 | Health Question 1.1: In pediatric patients receiving HEC, what strategies are recommended to prevent acute phase CINV?

4.1.1 | Recommendation 1.1a: Use a 5HT3RA + dexamethasone + (fos)aprepitant

Strong recommendation, high-quality evidence

Rationale: In making this recommendation, the panel considered a meta-analysis of 27 RCTs (four pediatric) that demonstrated benefit in giving triple-agent prophylaxis (5HT3RA + dexamethasone + NK1RA) versus dual-agent prophylaxis (5HT3RA + dexamethasone) for complete acute phase CIV control (RR 1.11, 95% CI: 1.07–1.14). Benefits in complete acute phase CIN and CINV control were also observed (RR 1.04, 95% CI: 1.01–1.08; RR 1.07, 95% CI: 1.01–1.13, respectively).

Granisetron, ondansetron, and palonosetron were the 5HT3RAs studied in the RCTs that were included in the above-mentioned meta-analyses demonstrating the benefit of triple-agent prophylaxis. Among five RCTs (one pediatric) that compared palonosetron versus granisetron/ondansetron in patients also receiving dexamethasone + NK1RA, no benefit of palonosetron was observed with respect to acute phase CIV control (RR 1.01, 95% CI: 0.97–1.05).

Synthesis of three RCTs in adults receiving HEC comparing oral aprepitant to IV fosaprepitant in combination with a 5HT3RA and dexamethasone showed comparable acute phase CIV control (RR 1.01, 95% CI: 0.99–1.03), suggesting either NK1RA may be used.

Thus, among patients receiving triple-agent prophylaxis, the choice of which 5HT3RA to use (granisetron, ondansetron, or palonosetron) and which NK1RA to use (IV fosaprepitant or oral aprepitant) should be based on institutional resources, feasibility, and patient preference. The choice of palonosetron over other 5HT3RAs may also be influenced by delayed phase CINV risk (see Recommendation 1.2a).

4.1.2 | Recommendation 1.1b: Use palonosetron + dexamethasone in patients unable to receive (fos)aprepitant

Strong recommendation, moderate-quality evidence

Rationale: In the meta-analysis of seven RCTs (two pediatric) evaluating palonosetron + dexamethasone versus granisetron/ondansetron + dexamethasone in patients receiving HEC, palonosetron improved acute phase CIV control (RR 1.10, 95% CI: 1.02–1.18). A meta-analysis of the three RCTs (one pediatric) reporting acute phase CIN control demonstrated that palonosetron also benefits acute phase CIN control compared with granisetron/ondansetron (RR 1.53, 95% CI: 1.00–2.34). These analyses suggest that patients who are unable to receive fos(aprepitant) should receive palonosetron and dexamethasone.

TABLE 3 Summary of meta-analyses used to inform delayed phase CINV prevention recommendations (RR > 1 favors intervention arm)

Comparison and delayed phase outcomes	Number of studies	N	RR	95% CI	I ²	p
Highly emetogenic chemotherapy						
Category 1: Meta-analyses where acute phase antiemetics were the same in each study arm and randomization to different delayed phase antiemetics occurred						
Delayed phase 5HT3RA prophylaxis						
5HT3RA vs no 5HT3RA						
Granisetron/ondansetron (+/- any concomitant antiemetics^a) vs no granisetron/ondansetron (+/- any concomitant antiemetics^a)						
Complete delayed phase CIV control	4	1642	1.03	0.97–1.10	15%	.39
Complete delayed phase CIN control	3	1226	0.98	0.84–1.14	0%	.76
Complete delayed phase CINV control	1	UTD	UTD	UTD	UTD	UTD
5HT3RA vs metoclopramide						
Granisetron/ondansetron + corticosteroid vs metoclopramide + corticosteroid						
Complete delayed phase CIV control	3	744	1.01	0.92–1.10	0%	.89
Complete delayed phase CIN control	2	UTD	UTD	UTD	UTD	UTD
Complete delayed phase CINV control	2	UTD	UTD	UTD	UTD	UTD
Delayed phase corticosteroid prophylaxis						
Corticosteroid vs no corticosteroid						
Dexamethasone (+/- any concomitant antiemetics^a) vs no dexamethasone (+/- any concomitant antiemetics^a)						
Complete delayed phase CIV control	11	2980	1.11	1.02–1.20	74%	.01
Complete delayed phase CIN control	6	2050	1.22	1.10–1.35	22%	.0001
Complete delayed phase CINV control	3	1195	1.38	1.11–1.72	55%	.004
Category 2: Meta-analyses where randomization to different antiemetics occurred in both the acute and delayed phase and where the antiemetic randomized was the same in both the acute and delayed phase						
Acute and delayed phase oral aprepitant prophylaxis						
Oral aprepitant vs no oral aprepitant						
Oral aprepitant (+/- any concomitant antiemetics^a) vs no oral aprepitant (+/- any concomitant antiemetics^a)						
Complete delayed phase CIV control	11 ^b	2818	1.44	1.29–1.61	65%	<.00001
Complete delayed phase CIN control	5	1958	1.29	1.12–1.48	40%	.0003
Complete delayed phase CINV control	4	1858	1.34	1.14–1.56	42%	.0003
Acute and delayed phase olanzapine prophylaxis						
Olanzapine vs no olanzapine						
Olanzapine (+/- any concomitant antiemetics^a) vs no olanzapine (+/- any concomitant antiemetics^a)						
Complete delayed phase CIV control	6 ^b	1507	1.53	1.25–1.89	76%	<.00001
Complete delayed phase CIN control	5 ^b	825	1.70	1.45–1.99	0%	<.00001
Complete delayed phase CINV control	3	889	1.19	0.70–2.05	82%	.52
Olanzapine vs oral aprepitant						
Olanzapine + dexamethasone vs oral aprepitant + dexamethasone						
Complete delayed phase CIV control	3	259	1.04	0.93–1.18	0%	.48
Complete delayed phase CIN control	2	UTD	UTD	UTD	UTD	UTD
Complete delayed phase CINV control	0	UTD	UTD	UTD	UTD	UTD
Category 3: Meta-analyses where randomization to different acute phase antiemetics occurred and delayed phase antiemetics were the same in each study arm						

(Continues)

TABLE 3 (Continued)

Comparison and delayed phase outcomes	Number of studies	N	RR	95% CI	I ²	p
Delayed phase 5HT3RA prophylaxis						
Delayed phase: impact of day 1 5HT3RA						
Palonosetron D1 (+/- any concomitant antiemetics^a) vs granisetron/ondansetron D1 (+/- any concomitant antiemetics^a)						
Complete delayed phase CIV control	10	4010	1.26	1.11–1.43	81%	.0004
Complete delayed phase CIN control	5	1684	1.68	1.16–2.43	74%	.006
Complete delayed phase CINV control	1	UTD	UTD	UTD	UTD	UTD
Delayed phase NK1RA prophylaxis						
Delayed phase: impact of day 1 NK1RA						
NK1RA D1 (+/- any concomitant antiemetics^a) vs no NK1RA D1 (+/- any concomitant antiemetics^a)						
Complete delayed phase CIV control	9 ^b	5792	1.21	1.14–1.29	67%	<.00001
Complete delayed phase CIN control	6	3726	1.17	1.09–1.25	0%	<.00001
Complete delayed phase CINV control	3	1104	1.24	1.06–1.46	0%	.0009
Moderately emetogenic chemotherapy						
Category 1: Meta-analyses where acute phase antiemetics were the same in each study arm and randomization to different delayed phase antiemetics occurred						
Delayed phase oral aprepitant prophylaxis						
Dexamethasone vs no dexamethasone						
Dexamethasone (+/- any concomitant antiemetics^a) vs no dexamethasone (+/- any concomitant antiemetics^a)						
Complete delayed phase CIV control	4	313	1.13	0.99–1.28	0%	.06
Complete delayed phase CIN control	1	UTD	UTD	UTD	UTD	UTD
Complete delayed phase CINV control	3	245	1.15	0.91–1.44	0%	.25
Category 2: Meta-analyses where randomization to different antiemetics occurred in both the acute and delayed phase and where the antiemetic randomized was the same in both the acute and delayed phase						
Acute and delayed phase oral aprepitant prophylaxis						
Oral aprepitant vs no oral aprepitant						
Oral aprepitant (+/- any concomitant antiemetics^a) vs no oral aprepitant (+/- any concomitant antiemetics^a)						
Complete delayed phase CIV control	8	1801	1.20	1.12–1.29	29%	<.00001
Complete delayed phase CIN control	2	UTD	UTD	UTD	UTD	UTD
Complete delayed phase CINV control	0	UTD	UTD	UTD	UTD	UTD
Category 3: Meta-analyses where randomization to different acute phase antiemetics occurred and delayed phase antiemetics were the same in each study arm						
Delayed phase NK1RA prophylaxis						
Delayed phase: impact of oral aprepitant in acute phase						
Oral aprepitant (+/- any concomitant antiemetics^a) vs no oral aprepitant (+/- any concomitant antiemetics^a) in acute phase						
Complete delayed phase CIV control	3 ^b	319	1.31	0.97–1.78	55%	.08
Complete delayed phase CIN control	1	UTD	UTD	UTD	UTD	UTD
Complete delayed phase CINV control	0	UTD	UTD	UTD	UTD	UTD

N, number of patients included in analysis; RR, risk ratio; CI, confidence interval; I², statistic describing percentage of variation across studies that is due to heterogeneity rather than chance; CIV, chemotherapy-induced vomiting; CIN, chemotherapy-induced nausea; CINV, chemotherapy-induced nausea and vomiting; UTD, unable to determine; HEC, highly emetogenic chemotherapy; 5HT3RA, serotonin-3 receptor antagonist; NK1RA, neurokinin-1 receptor antagonist.

^aConcomitant antiemetics identical in both study arms

^bAt least one pediatric study included.

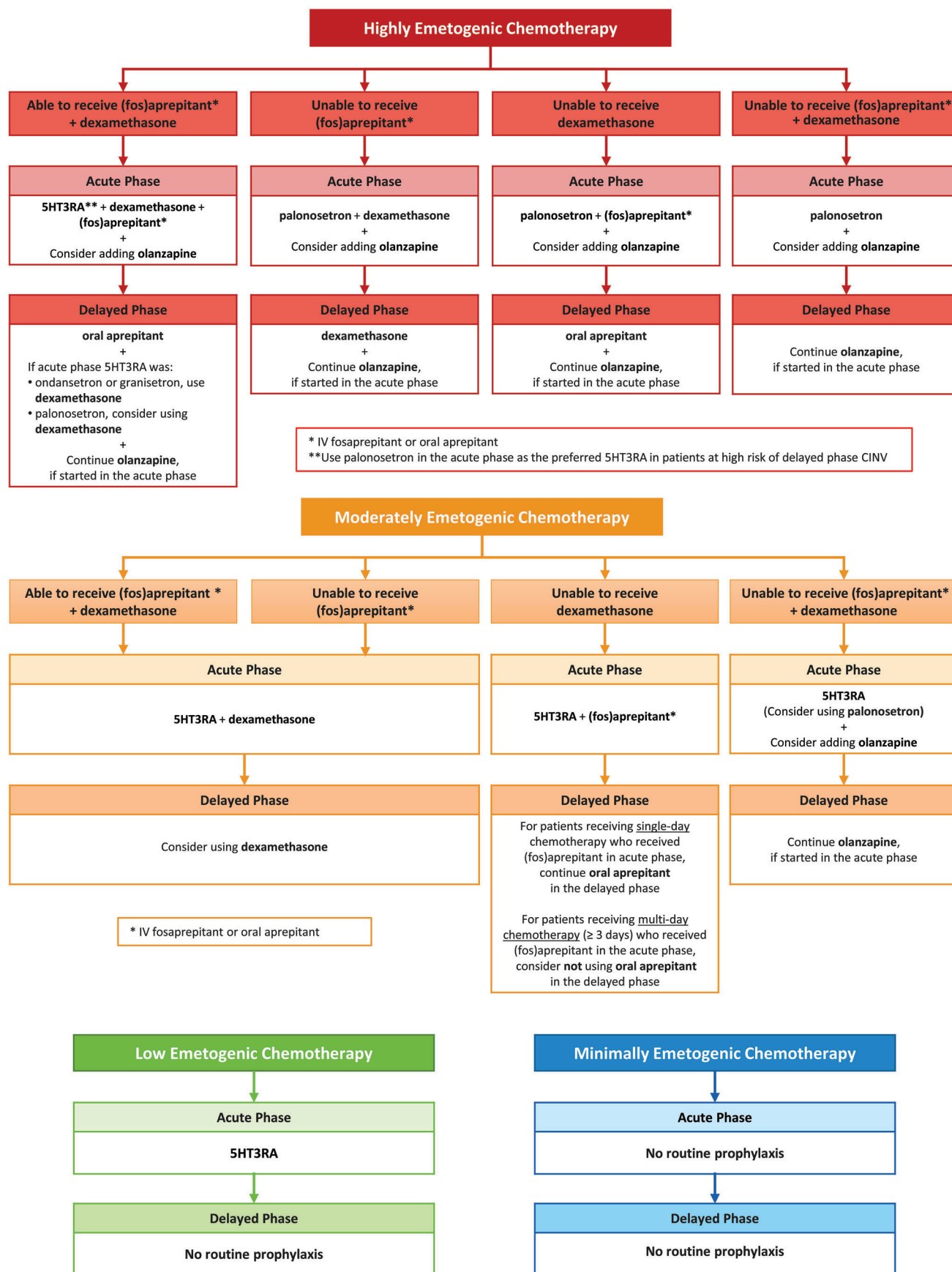


FIGURE 1 Algorithm for the prevention of acute and delayed CINV in pediatric patients

4.1.3 | Recommendation 1.1c: Use palonosetron + (fos)aprepitant in patients unable to receive dexamethasone

Strong recommendation, low-quality evidence

Rationale: Synthesis of three RCTs evaluating ondansetron + (fos)aprepitant versus ondansetron alone in patients receiving HEC (three pediatric) showed RR 1.20; 95% CI 1.00–1.44, suggesting benefit of (fos)aprepitant when added to a 5HT3RA regimen. Given the benefit of palonosetron versus granisetron/ondansetron when used in addition to dexamethasone (see Recommendation 1.1b) and the benefit of palonosetron versus granisetron/ondansetron when 5HT3RA monotherapy is used (see Recommendation 1.1d), the panel specifically recommended the 5HT3RA palonosetron plus fos(aprepitant) in patients unable to receive dexamethasone.

4.1.4 | Recommendation 1.1d: Use palonosetron in patients unable to receive dexamethasone + (fos)aprepitant

Strong recommendation, moderate-quality evidence

Rationale: This recommendation is based on a meta-analysis of six RCTs (one pediatric) evaluating palonosetron versus granisetron/ondansetron single-agent prophylaxis that demonstrated improved acute phase CIV complete control with the use of palonosetron (RR 1.11, 95% CI: 1.02–1.20).

4.1.5 | Recommendation 1.1e: Consider adding olanzapine to other CPG-consistent antiemetics

Conditional recommendation, moderate-quality evidence

Rationale: Meta-analyses of seven RCTs (one pediatric) demonstrated that when olanzapine versus no olanzapine was evaluated in combination with any concomitant antiemetics, olanzapine improved acute phase CIV control (RR 1.23, 95% CI: 1.05–1.44) and CIN control (RR 1.34, 95% CI: 1.10–1.62). Improved acute phase CIN control was seen in the subset of five RCTs (one pediatric) evaluating the addition of olanzapine versus no olanzapine to a 5HT3RA, dexamethasone, and an NK1RA. This is a conditional recommendation since the panel acknowledged uncertainty regarding olanzapine adverse effects (e.g.,

cardiotoxicity, metabolic toxicity, and neurotoxicity) in children and adolescents receiving chemotherapy.

4.2 | Health Question 1.2: In pediatric patients receiving HEC, what strategies are recommended to prevent delayed phase CINV?

4.2.1 | Recommendation 1.2a: Use palonosetron in the acute phase as the preferred 5HT3RA in patients at high risk of delayed phase CINV

Strong recommendation, moderate-quality evidence

Rationale: Synthesis of 10 RCTs (0 pediatric) that evaluated the influence of the acute phase 5HT3RA administered on delayed phase CIV control showed benefit of palonosetron versus granisetron/ondansetron (RR 1.26, 95% CI: 1.11–1.43) (Table 3). Benefit of palonosetron on delayed phase CIN control compared with granisetron/ondansetron (RR 1.68, 95% 1.16–2.43) was also seen on meta-analysis of five RCTs (0 pediatric). This is a strong recommendation due to the clear impact that palonosetron administration in the acute phase has on delayed phase CINV control. Given the uncertainty regarding the prevalence of delayed phase CINV in pediatric patients, this recommendation applies to patients at high risk of delayed phase CINV.

4.2.2 | Recommendation 1.2b: Use oral aprepitant in the delayed phase, if (fos)aprepitant started in the acute phase

Strong recommendation, high-quality evidence

Rationale: Among 11 included RCTs (two pediatric) where patients were randomized to oral aprepitant versus no oral aprepitant for the acute and delayed phase (category 2), patients receiving an aprepitant-containing regimen had improved delayed phase CIV control (RR 1.44, 95% CI: 1.29–1.61), CIN control (RR 1.29; 95% CI: 1.12–1.48), and CINV control (RR 1.34, 95% CI: 1.14–1.56). Oral aprepitant was given for a total of three or 5 consecutive days in the included RCTs. No RCTs were identified that evaluated delayed phase IV fosaprepitant administration. In the context of the acute phase recommendations, the panel made a strong recommendation to use oral aprepitant in the delayed phase in addition to (fos)aprepitant in the acute phase based upon the consistent benefit of delayed phase oral aprepitant and direct pediatric evidence.

4.2.3 | Recommendation 1.2c: Add dexamethasone in the delayed phase in patients who received granisetron or ondansetron in the acute phase

Strong recommendation, moderate-quality evidence

4.2.4 | Recommendation 1.2d: Consider adding dexamethasone in the delayed phase in patients who received palonosetron in the acute phase

Conditional recommendation, moderate-quality evidence

Rationale: Among 11 RCTs where acute phase antiemetics were identical and there was randomization between dexamethasone versus no dexamethasone in the delayed phase (category 1), dexamethasone significantly improved delayed phase CIV control (RR 1.11, 95% CI: 1.02–1.20), delayed phase CIN control (RR 1.22, 95% CI: 1.10–1.35), and delayed phase CINV control (RR 1.38, 95% CI: 1.11–1.72).

In a stratified analysis of studies that randomized patients to dexamethasone versus no dexamethasone in the delayed phase (category 1) (Appendix SA10), the effect of dexamethasone on delayed phase CIV control was significantly different depending on the 5HT3RA received (nonrandomly) in the acute phase (p int <.0001). Specifically, the benefit of dexamethasone compared with no dexamethasone in delayed phase CIV control among patients who received palonosetron in the acute phase was RR 1.04 (95% CI: 1.00–1.08) while among those who received granisetron/ondansetron in the acute phase, it was RR 1.31 (95% CI: 1.20–1.44). In a second stratified analysis (Appendix SA11), the effect of receiving dexamethasone (nonrandomly) in the delayed phase differed depending on receipt (randomized) of palonosetron in the acute phase versus granisetron/ondansetron (p int <.006) (category 3). Thus, the benefit of using dexamethasone in the delayed phase on delayed phase CIV control may be larger in patients receiving granisetron/ondansetron compared with palonosetron in the acute phase.

The panel made a strong recommendation to use dexamethasone in the delayed phase when granisetron/ondansetron had been administered in the acute phase. A conditional recommendation was made to use dexamethasone in the delayed phase when palonosetron had been administered in the acute phase since the potential benefit in delayed phase CINV control and the risks associated with dexamethasone use may be finely balanced.

4.2.5 | Recommendation 1.2e: Use dexamethasone in the delayed phase in patients unable to receive oral aprepitant

Strong recommendation, moderate-quality evidence

Rationale: This recommendation is based on the meta-analysis of 11 RCTs described in recommendations 1.2c and 1.2d that demonstrated benefit of dexamethasone on delayed phase CINV control. Patients unable to receive an NK1RA are at higher risk of experiencing delayed phase CIV, CIN, and CINV. Thus, dexamethasone should be given in

the delayed phase regardless of the 5HT3RA administered in the acute phase.

4.2.6 | Recommendation 1.2f: Continue olanzapine in the delayed phase, if started in the acute phase

Strong recommendation, moderate-quality evidence

Rationale: The panel valued the results of the meta-analysis of six RCTs (one pediatric) that demonstrated improved delayed phase CIV control in patients who received olanzapine versus no olanzapine starting in the acute phase and continued in the delayed phase (RR 1.53, 95% CI: 1.25–1.89), regardless of the concomitant antiemetics. A benefit in delayed phase CIN control (RR 1.70, 95% CI: 1.45–1.99) was also noted. The panel reasoned that once a decision is taken to add olanzapine in the acute phase based on a risk:benefit assessment, the benefits of continuing olanzapine in the delayed phase should outweigh the risks for most patients. Thus, the panel made a strong recommendation for its continued use in the delayed phase.

4.2.7 | Recommendation 1.2g: Do not use 5HT3RAs in the delayed phase

Strong recommendation, low-quality evidence

Rationale: Recognizing that 5HT3RA use during the delayed phase is a common practice in many pediatric oncology centers, the CPG panel evaluated their contribution to delayed phase CINV control in a meta-analysis involving four RCTs (0 pediatric) among patients receiving HEC. No benefit on delayed phase CIV control (RR 1.03, 95% CI: 0.97–1.10) or delayed phase CIN was seen (RR 0.98, 95% CI: 0.84–1.13). The recommendation not to use ondansetron or granisetron in the delayed phase after HEC administration was generalized to palonosetron.

4.3 | Health Question 2.1: In pediatric patients receiving MEC, what strategies are recommended to prevent acute phase CINV?

4.3.1 | Recommendation 2.1a: Use a 5HT3RA + dexamethasone

Strong recommendation, moderate-quality evidence

Rationale: This recommendation is based on a meta-analysis of three RCTs (0 pediatric), which demonstrated benefit in acute phase CIV control when a 5HT3RA and dexamethasone were given compared with a 5HT3RA alone (RR 1.29, 95% CI: 1.21–1.39). In addition, a meta-analysis of 11 RCTs (0 pediatric) observed no benefit of triple-agent (5HT3RA, dexamethasone, and (fos)aprepitant) compared with dual-agent (5HT3RA and dexamethasone) prophylaxis in acute phase CIV control (RR 1.03, 95% CI: 1.00–1.07) or acute phase CIN control (RR 1.02, 95% CI: 0.91–1.16).

With respect to 5HT3RA choice, a meta-analysis of three RCTs (one pediatric) showed no difference in acute phase CIV control with palonosetron + dexamethasone versus granisetron or ondansetron + dexamethasone (RR 0.94, 95% CI: 0.86–1.02). Hence, 5HT3RA choice (granisetron, ondansetron, or palonosetron) should be based on institutional resources, feasibility, and patient preference.

4.3.2 | Recommendation 2.1b: Use a 5HT3RA + (fos)aprepitant in patients unable to receive dexamethasone

Strong recommendation, low-quality evidence

Rationale: Based on recommendation 2.1a, the panel believed single-agent 5HT3RA prophylaxis was likely to be inadequate for patients receiving MEC. While the meta-analysis of three RCTs (one pediatric) evaluating (fos)aprepitant + 5HT3RA versus 5HT3RA monotherapy did not show a significant difference in CIV control (RR 1.15, 95% CI: 0.96–1.37), the panel valued a pediatric RCT that demonstrated a 30% improvement in CIV control with the addition of oral aprepitant to ondansetron.²¹ In making this strong recommendation, the panel also generalized from the demonstrated efficacy of NK1RAs in pediatric patients receiving HEC and their favorable adverse effect profile.

4.3.3 | Recommendation 2.1c: Use a 5HT3RA in patients unable to receive dexamethasone + (fos)aprepitant

Strong recommendation, low-quality evidence

4.3.4 | Recommendation 2.1d: Consider using palonosetron as the preferred 5HT3RA in patients unable to receive dexamethasone + (fos)aprepitant

Conditional recommendation, low-quality evidence

Rationale: To formulate these recommendations, the panel relied on the individual study arm data of included RCTs that described CIN V control in patients who received single-agent 5HT3RA prophylaxis. In these RCTs, complete CIV control was reported in 29–92% of patients receiving single-agent 5HT3RA prophylaxis. In recommending palonosetron as the preferred 5HT3RA, the panel drew on the evidence supporting recommendation 1.1d and the results of delayed phase meta-analyses and stratified analyses in patients receiving HEC showing that giving palonosetron in the acute phase leads to improved delayed phase CIV control. While use of a 5HT3RA is strongly recommended, use of palonosetron specifically is a conditional recommendation since the acute phase vomiting risk associated with MEC is wide (30–90%) and the risk of delayed phase vomiting is uncertain.

4.3.5 | Recommendation 2.1e: Consider adding olanzapine to other CPG-consistent antiemetics in patients unable to receive dexamethasone + (fos)aprepitant

Conditional recommendation, low-quality evidence

Rationale: Synthesis was not possible to address olanzapine use in patients receiving MEC. This recommendation generalizes from the evidence supporting olanzapine use in patients receiving HEC (see recommendation 1.1e). It is a conditional recommendation based on the same safety concerns described previously, the wide range of emetic risk associated with MEC and the lack of direct pediatric evidence.

4.4 | Health Question 2.2: In pediatric patients receiving MEC, what strategies are recommended to prevent delayed phase CIN V?

4.4.1 | Recommendation 2.2a: Consider using dexamethasone in the delayed phase

Conditional recommendation, low-quality evidence

Rationale: In making this recommendation, the panel considered the results of a meta-analysis of four RCTs (0 pediatric) where acute phase antiemetics were the same in each study arm and use of dexamethasone versus no dexamethasone in the delayed phase was randomized (category 1). This effect of delayed phase dexamethasone on CIN and CIN V control was RR 1.13, 95% CI: 0.99–1.28 and RR 1.15, 95% CI: 0.91–1.44, respectively. In considering these results and the evidence supporting recommendations 1.2c and 1.2d, the panel made a conditional recommendation to use dexamethasone in the delayed phase.

4.4.2 | Recommendation 2.2b: Continue oral aprepitant in the delayed phase in patients receiving single-day chemotherapy who received (fos)aprepitant in the acute phase

Strong recommendation, moderate-quality evidence

Rationale: A meta-analysis of eight RCTs (0 pediatric) (category 2) demonstrated a benefit in delayed phase CIV control when oral aprepitant was continued in the delayed phase once started in the acute phase versus no aprepitant (RR 1.20, 95% CI: 1.12–1.29). Seven of the eight included RCTs gave oral aprepitant on days 2 and 3 following single-day chemotherapy; one included RCT continued oral aprepitant until day 4 following 2-day chemotherapy. In making this strong recommendation, the panel considered the evidence supporting recommendation 2.1b, the preponderance of evidence in patients receiving single-day chemotherapy and the benefit of continuing oral aprepitant in the delayed phase for CIV control. The panel acknowledged that for patients receiving fosaprepitant in the acute phase, oral

aprepitant administration in the delayed phase may vary depending on dosing approved by jurisdictional regulatory bodies (Appendix SA19).

4.4.3 | Recommendation 2.2c: Consider not using oral aprepitant in the delayed phase in patients receiving multi-day chemotherapy (≥ 3 days) who received (fos)aprepitant in the acute phase

Conditional recommendation, low-quality evidence

Rationale: This recommendation was based on a meta-analysis of three RCTs (one pediatric; category 3) evaluating receipt of oral aprepitant only in the acute phase versus no aprepitant in patients receiving multi-day chemotherapy (≥ 3 days), regardless of concomitant antiemetics. Oral aprepitant receipt for three or 5 days of the acute phase did not improve delayed phase CIV control (RR 1.31, 95% CI: 0.97–1.78). However, CIN control based on timing of oral aprepitant administration (acute phase versus acute phase plus delayed phase) was not a primary endpoint of any included RCT. The panel balanced the uncertainty regarding the risk of delayed phase CIN in pediatric patients receiving MEC against the potential for improved delayed phase CIV and made a conditional recommendation to consider not giving oral aprepitant in the delayed phase in pediatric patients receiving MEC blocks 3 days or longer.

4.4.4 | Recommendation 2.2d: Continue olanzapine in the delayed phase, if started in the acute phase

Strong recommendation, low-quality evidence

Rationale: This recommendation generalizes from the evidence and rationale supporting recommendation 1.2f.

4.5 | Health Question 3.1: In pediatric patients receiving low emetogenic chemotherapy (LEC), what strategies are recommended to prevent acute phase CIN?

4.5.1 | Recommendation 3.1a: Use a 5HT3RA

Strong recommendation, low-quality evidence

Rationale: Given the lack of direct evidence evaluating acute CIV, CIN, and CIN control in patients receiving LEC, the panel drew from evidence regarding CIN prophylaxis during HEC and MEC to make this recommendation. Since CIV risk associated with LEC in the absence of prophylaxis is 10–30%, the panel deemed that CIN prophylaxis was warranted. The panel made a strong recommendation to use a 5HT3RA for CIN prophylaxis in patients receiving LEC based on the extensive pediatric experience with 5HT3RAs, their proven benefit in preventing acute phase CIN in patients receiving HEC and MEC and their favorable adverse effect profile.

4.6 | Health Question 3.2: In pediatric patients receiving LEC, what strategies are recommended to prevent delayed phase CIN?

4.6.1 | Recommendation 3.2a: Do not use prophylaxis routinely in the delayed phase

Strong recommendation, very low-quality evidence

Rationale: We identified no RCTs to inform this question. The panel deemed that, given the low risk of vomiting in the acute phase for patients receiving LEC and the uncertainty regarding the risk of delayed phase CIN following LEC, routine delayed phase CIN prophylaxis is not warranted.

4.7 | Health Question 4.1: In pediatric patients receiving minimally emetogenic chemotherapy (minEC), what strategies are recommended to prevent acute phase CIN?

4.7.1 | Recommendation 4.1a: Do not use prophylaxis routinely in the acute phase

Strong recommendation, very low-quality evidence

Rationale: There were no RCTs identified that evaluated CIV, CIN, or CIN control in patients receiving minEC. Since acute phase CIV risk following minEC is less than 10% in the absence of prophylaxis, the panel deemed that routine acute phase prophylaxis is not warranted.

4.8 | Health Question 4.2: In pediatric patients receiving minEC, what strategies are recommended to prevent delayed phase CIN?

4.8.1 | Recommendation 4.2a: Do not use prophylaxis routinely in the delayed phase

Strong recommendation, very low-quality evidence

Rationale: No RCTs were identified that evaluated acute phase CIN prophylaxis in patients receiving minEC. Since the risk of acute phase CIV during minEC is low and the incidence of delayed phase CIN following minEC is unknown, the panel deemed that routine delayed phase CIN prophylaxis is not warranted.

5 | DISCUSSION

We have developed a comprehensive CPG to provide recommendations for acute and delayed phase CIN prevention in pediatric patients. Recommendations were based on SRs that encompassed the experience of both pediatric and adult patients. This is the first CPG to make recommendations for delayed phase CIN prevention in pediatric patients.

TABLE 4 Evidence gaps regarding acute and delayed phase CINV prevention in pediatric patients

What nonpharmacological interventions to prevent acute phase and delayed phase CINV are effective and safe?
What chemotherapy is associated with risk of delayed phase CINV?
What is the optimal dosing frequency of palonosetron for patients receiving multi-day chemotherapy?
What is the effective and safe oral palonosetron dose?
What is the optimal dose of dexamethasone?
What is the optimal duration of oral aprepitant in patients receiving multi-day chemotherapy?
What is the optimal fosaprepitant dose and dosing frequency?
Is it necessary to follow fosaprepitant with oral aprepitant?
What are the safety concerns with olanzapine use?
What adverse effect monitoring, if any, is required for patients receiving olanzapine?
What is the optimal olanzapine dose for prevention of acute and delayed CINV?
Can olanzapine be given safely to patients <5 years old?
What patient-related factors increase the risk for acute and delayed phase CINV?

CINV, chemotherapy-induced nausea and vomiting.

Recommendations for CINV prophylaxis are provided for patients who are unable to receive dexamethasone or (fos)aprepitant. Cancer treatment or cellular therapy protocols or patient-specific concerns such as history of fungal infection or adverse effects may preclude dexamethasone use.^{22–24} Patient age, concerns regarding its effect on chemotherapy clearance, and unintended increases in chemotherapy dose intensity or increasing risk of chemotherapy toxicity may preclude (fos)aprepitant use.²⁵ In most situations, the quality of evidence supporting alternate CINV prophylaxis regimens for patients who are unable to receive dexamethasone or (fos)aprepitant is moderate to low. Clinicians are encouraged to critically evaluate patients' ability to receive these agents since their omission will likely increase risk of uncontrolled CINV.

Compared with the 2017 CPG on acute phase CINV prevention, fosaprepitant and olanzapine are newly recommended interventions. High-quality evidence supports the interchangeability of IV fosaprepitant and oral aprepitant. Preference will be driven by feasibility issues (e.g., IV access, ability to take oral medications, funding models). Conditional recommendations to consider olanzapine signal the need to carefully weigh the risk:benefit for individual patients in consideration of patient-related risk factors for CIV such as older age, long chemotherapy block duration, history of motion sickness, and inability to receive an NK1RA.^{26,27} It is notable that the included pediatric RCT evaluating olanzapine excluded patients <5 years old.

Our chosen proxy for safety, rates of antiemetic discontinuation due to toxicity, was not helpful to identify antiemetic-related adverse effects. Nevertheless, 5HT3RAs, dexamethasone, and oral aprepitant are associated with a low incidence of adverse effects which are usually of minor clinical significance.²⁸ The adverse effects reported in included RCTs of IV fosaprepitant are similar to those associated with oral aprepitant, with the exception of infusion-related reactions. While the safety profile of olanzapine is acceptable among pediatric patients with mental health conditions, some potential adverse effects may be serious (e.g., metabolic effects, QTc prolongation, and extra-pyramidal

reactions)^{29,30} and the risk:benefit assessment may not be favorable in all pediatric patients receiving chemotherapy. The prospective safety monitoring incorporated into RCTs evaluating olanzapine does not allow a full appreciation of its safety profile in pediatric cancer patients; thus, optimal monitoring strategies are unknown.

The strengths of this CPG relate to the rigorous methods applied to its development: comprehensive SRs; international, interprofessional, and patient advocate representation on the panel; and integration of the acute phase and delayed phase CINV recommendations. Our work is limited by the quality of the published evidence. Definitions of the acute phase and delayed phase and reporting completeness, especially in the delayed phase, lack consistency. Many included RCTs omitted CIN measurement and, when included, many did not use a validated tool. This was especially common in pediatric RCTs. No included pediatric RCT stratified enrollment based on known risk factors for acute phase CIV. Reporting of safety outcomes was inadequate in most studies.

Despite the number of studies included in our SRs, evidence gaps are plentiful and continue to be barriers to ensuring that pediatric patients experience complete CINV control. Among the most fundamental of the evidence gaps listed in Table 4 are the lack of RCTs examining nonpharmacological interventions, absence of strategies using pharmacogenomic data to inform initial CINV prophylaxis selection, scarcity of information regarding risk of delayed phase CINV associated with specific chemotherapies and lack of pediatric antiemetic dosing strategies applicable to multi-day chemotherapy blocks.

5.1 | Implementation Considerations

Integration of these recommendations into clinical care will require intentional and systematic implementation. Obstacles may include intervention cost, lack of dosage forms appropriate for children in some jurisdictions, and clinician and patient resistance to deimplementation

of 5HT3RAs in the delayed phase. Cost of recommended antiemetics was not weighed highly by the CPG panel since drug costs vary widely between jurisdictions and over time. As well, the cost of the intervention itself may be outweighed by reductions in costs of interventions to treat uncontrolled CINV (e.g., breakthrough antiemetics) or manage the effects of uncontrolled CINV (e.g., hospital admission, nutrition support). Pediatric-friendly formulations are marketed in most jurisdictions or extemporaneous formulations are available for all recommended antiemetics except for oral olanzapine and oral palonosetron.

The panel chose not to develop antiemetic dosing recommendations. To assist implementation, the pediatric doses of the antiemetics with approved pediatric labels in Canada, the United States, and European Union are presented in Appendix SA19. No optimal pediatric dexamethasone dose for acute phase CINV prophylaxis has been identified.³¹ While the oral olanzapine dose used in the single included pediatric RCT was 0.14 mg/kg/dose po daily (max: 10 mg),³² others have suggested doses of 0.05–0.2 mg/kg/dose (max: 5 or 10 mg).^{33,34}

6 | CONCLUSION

Based on current literature, control of CINV during the acute and delayed phases in pediatric patients can be optimized. While antiemetic selection is initially based on chemotherapy emetogenicity, CINV prophylaxis should be adjusted from one chemotherapy block to the next based on each patient's history of CINV control. Research to address critical evidence gaps will ensure continued progress toward achieving complete CINV control for all pediatric patients.

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CONFLICT OF INTEREST

L. L. D. has received a research grant from Heron Therapeutics for work outside of this CPG. A. O. owns Pfizer stock. No other author has relevant financial or nonfinancial interests to disclose.

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REFERENCES

- Sommariva S, Pongiglione B, Tarricone R. Impact of chemotherapy-induced nausea and vomiting on health-related quality of life and resource utilization: A systematic review. *Crit Rev Oncol Hematol* 2016;99:13-36.
- Peoples AR, Roscoe JA, Block RC, et al. Nausea and disturbed sleep as predictors of cancer-related fatigue in breast cancer patients: a multicenter NCORP study. *Support Care Cancer* 2017;25(4):1271-1278.
- Neymark N, Crott R. Impact of emesis on clinical and economic outcomes of cancer therapy with highly emetogenic chemotherapy regimens: a retrospective analysis of three clinical trials. *Support Care Cancer* 2005;13(10):812-818.
- Schwartzberg LS, Navari RM, Ruddy KJ, et al. Work loss and activity impairment due to duration of nausea and vomiting in patients with breast cancer receiving CINV prophylaxis. *Journal of Clinical Oncology* 2020;38(15_suppl):e24133-e24133.
- Flink J, Sparavalo J, Vol H, et al. The burden of chemotherapy-induced nausea and vomiting in children receiving hematopoietic stem cell transplantation conditioning: a prospective study. *Bone Marrow Transplant* 2017;52(9):1294-1299.
- Hendricks CB. Improving adherence with oral antiemetic agents in patients with breast cancer receiving chemotherapy. *J Oncol Pract* 2015;11(3):216-218.
- Tang N, Kovacevic A, Zupanec S, et al. Perceptions of parents of pediatric patients with acute lymphoblastic leukemia on oral chemotherapy administration: A qualitative analysis. *Pediatr Blood Cancer* 2022;69(1):e29329.
- Aapro M, Caprariu Z, Chilingirov P, et al. Assessing the impact of antiemetic guideline compliance on prevention of chemotherapy-induced nausea and vomiting: Results of the nausea/emesis registry in oncology (NERO). *Eur J Cancer* 2022;166:126-133.
- Farhangi H, GHasemi A, Bahari M, et al. The role of clinical guidelines for the management of chemotherapy-induced nausea and vomiting in children with cancer. *Iranian journal of Pediatric Hematology and Oncology* 2022;12(1):17-24.
- L. Sandblom RFBK, M. Temkit and A. Walsh. Adherence to standardized guidelines improves control of vomiting in pediatric patients with cancer: ABSTRACT. *Pediatric Blood & Cancer* 2022;69(S2):e29735.
- Patel P, Robinson PD, Devine KA, et al. Prevention and treatment of anticipatory chemotherapy-induced nausea and vomiting in pediatric cancer patients and hematopoietic stem cell recipients: clinical practice guideline update. *Pediatric Blood & Cancer* 2021;68(5):e28947.
- Flink J, Robinson PD, Holdsworth M, et al. Guideline for the treatment of breakthrough and the prevention of refractory chemotherapy-induced nausea and vomiting in children with cancer. *Pediatr Blood Cancer* 2016;63(7):1144-1151.
- Paw Cho Sing E, Robinson PD, Flink J, et al. Classification of the acute emetogenicity of chemotherapy in pediatric patients: a clinical practice guideline. *Pediatr Blood Cancer* 2019;66(5):e27646.
- Brouwers MC, Kho ME, Browman GP, et al. Development of the AGREE II, part 1: performance, usefulness and areas for improvement. *Cmaj* 2010;182(10):1045-1052.
- Guyatt GH, Oxman AD, Vist GE, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *Bmj* 2008;336(7650):924-926.
- Dupuis LL, Boodhan S, Holdsworth M, et al. Guideline for the prevention of acute nausea and vomiting due to antineoplastic medication in pediatric cancer patients. *Pediatr Blood Cancer* 2013;60(7):1073-1082.
- Patel P, Robinson PD, Thackray J, et al. Guideline for the prevention of acute chemotherapy-induced nausea and vomiting in pediatric cancer patients: A focused update. *Pediatr Blood Cancer* e26542, 2017;64(10).
- Patel P, Robinson PD, Wahib N, et al. Interventions for the prevention of acute phase chemotherapy-induced nausea and vomiting in adult and pediatric patients: a systematic review and meta-analysis. *Support Care Cancer* 2022. <https://doi.org/10.1007/s00520-022-07287-w>
- The Nordic Cochrane Centre, The Cochrane Collaboration: RevMan (computer program). Version 5.4. <https://training.cochrane.org/online-learning/coresoftware-cochrane-reviews/revman/revman-5-download>

20. Higgins J.P.T., Green S., Cochrane handbook for systematic reviews of interventions version 5.1.0 [updated March 2011]. The Cochrane Collaboration; 2011. Available from: www.cochrane-handbook.org
21. Sharma A, Ganguly S, C SK, et al. Addition of aprepitant improves acute emesis control in children and adolescents receiving induction chemotherapy for acute myeloid leukaemia: a randomised, open-label trial. *BMJ supportive & palliative care* 2020;29:29.
22. Dix D, Cellot S, Price V, et al. Association between corticosteroids and infection, sepsis, and infectious death in pediatric acute myeloid leukemia (AML): results from the Canadian infections in AML research group. *Clin Infect Dis* 2012;55(12):1608-1614.
23. Wong ET, Swanson KD. Dexamethasone-Friend or Foe for Patients With Glioblastoma? *JAMA Neurol* 2019;76(3):247-248.
24. Gregoriou K, Craigie I, Gibson B, Mason A, Shaikh MG. Risk factors and management of corticosteroid-induced hyperglycaemia in paediatric acute lymphoblastic leukaemia. *Pediatr Blood Cancer* 2020;67(2):e28085.
25. Patel P, Leeder JS, Piquette-Miller M, Dupuis LL. Aprepitant and fosaprepitant drug interactions: a systematic review. *Br J Clin Pharmacol* 2017;83(10):2148-2162.
26. Dupuis LL, Tomlinson GA, Pong A, Sung L, Bickham K. Factors associated with chemotherapy-induced vomiting control in pediatric patients receiving moderately or highly emetogenic chemotherapy: a pooled analysis. *J Clin Oncol* 2020;38(22):2499-2509.
27. Eliassen A, Kornholt J, Mathiasen R, et al. Background sensitivity to chemotherapy-induced nausea and vomiting and response to antiemetics in paediatric patients: a genetic association study. *Pharmacogenet Genomics* 2022;32(2):72-78.
28. Patel P, Paw Cho Sing E, Dupuis LL. Safety of clinical practice guideline-recommended antiemetic agents for the prevention of acute chemotherapy-induced nausea and vomiting in pediatric patients: a systematic review and meta-analysis. *Expert Opin Drug Saf* 2019;18(2):97-110.
29. Flank J, Sung L, Dvorak CC, Spettigue W, Dupuis LL. The safety of olanzapine in young children: a systematic review and meta-analysis. *Drug Saf* 2014;37(10):791-804.
30. Samsel C, Kearney J, Meadows AL, Abrams A, Hirst JM, Muriel AC. Olanzapine for chemotherapy-induced nausea: lessons learned from child and adolescent psychiatry. *Pediatr Blood Cancer* 2018;65(10):e27289.
31. Patel P, Olteanu A, Cabral S, Santesso N, Robinson PD, Dupuis LL. Dexamethasone dosing for prevention of acute chemotherapy-induced vomiting in pediatric patients: A systematic review. *Pediatr Blood Cancer* 2020;67(12):e28716.
32. Naik RD, Sreenivas V, Singh V, Pillai AS, Dhawan D, Bakhshi S. Olanzapine for prevention of vomiting in children and adolescents receiving highly emetogenic chemotherapy: investigator-initiated, randomized, open-label trial. *Journal of Clinical Oncology* 2020;38(32):3785-3793.
33. Radhakrishnan V, Pai V, Rajaraman S, et al. Olanzapine versus metoclopramide for the treatment of breakthrough chemotherapy-induced vomiting in children: An open-label, randomized phase 3 trial. *Pediatric Blood & Cancer* 2020;67(9):e28532.
34. Flank J, Schechter T, Gibson P, et al. Olanzapine for prevention of chemotherapy-induced nausea and vomiting in children and adolescents: a multi-center, feasibility study. *Support Care Cancer* 2018;26(2):549-555.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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