BC Cancer Guidelines for Prevention and Treatment of
Chemotherapy-Induced Nausea and Vomiting in Adults

Protocol Code
SCNAUSEA

Tumour group
SUPPORTIVE CARE

Physician Contact
Dr. Paul Hoskins

ELIGIBILITY

• Adults receiving chemotherapy.

• Drug acquisition: Antiemetics are considered supportive treatment. These agents are not BC Cancer benefit drugs and are not covered by any BC Cancer program. Patients being treated with these agents should have prescriptions filled at a community pharmacy and must arrange their own payment for the drugs.

EXCLUSION CRITERIA

• Pediatric patients.

• Radiation-induced nausea and vomiting.

APPROACH TO TREATMENT

• The goal is NO nausea or vomiting.1-3

• It is far easier to prevent nausea and vomiting than to treat it.1,2

• Anticipatory nausea and vomiting is a conditioned response, and can only happen after a negative past experience.1,2

• Ensure optimal antiemetic therapy for every cycle of chemotherapy.

• Use of guidelines: This is a general reference based upon best available evidence and is not intended to replace the clinical judgment of individual practitioners caring for individual patients.
PROPHYLACTIC ANTIEMETIC REGIMENS FOR IV AND COMBINED IV / ORAL CHEMOTHERAPY

- For multiple days of chemotherapy, repeat antiemetics *before each* treatment (*Exception:* netupitant-palonosetron is dosed on day 1 only).
- See comment below table for ORAL chemotherapy regimens.
- For prophylaxis after prior treatment failures, refer to Figure 1.

<table>
<thead>
<tr>
<th>EMETOGENICITY</th>
<th>PRE-CHEMOTHERAPY</th>
<th>POST-CHEMOTHERAPY</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>High (HEC)</strong></td>
<td>dexamethasone§ 8 to 12 mg PO¹⁻³ PLUS NK₁ and 5-HT₃ ANTAGONIST</td>
<td>dexamethasone§ 4 mg PO evening of chemo,⁷ then BID x 2 to 4 days²³</td>
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<tr>
<td></td>
<td>• netupitant-palonosetron 300 mg-0.5 mg† PO¹⁸ OR</td>
<td>• No post-chemotherapy netupitant-palonosetron OR</td>
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<tr>
<td></td>
<td>• aprepitant† 125 mg PO⁷⁻⁹</td>
<td>• aprepitant‡ 80 mg PO daily on days 2 and 3, IF aprepitant used on day 1²⁻⁸,⁹</td>
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<tr>
<td></td>
<td>• PLUS one 5-HT₃ antagonist‖:</td>
<td>+/- ONE ANTIEMETIC “AS-NEEDED” (if not using olanzapine):</td>
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<tr>
<td></td>
<td>o ondansetron 8 mg PO³</td>
<td>• prochlorperazine 10 mg PO every 6 hours PRN x 3 to 4 days³,¹⁸ OR</td>
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<tr>
<td></td>
<td>o granisetron 1 mg PO¹⁷,¹⁹</td>
<td>• metoclopramide 10 to 20 mg PO every 4 to 6 hours PRN x 3 to 4 days³,⁴,¹⁸,¹⁹</td>
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<tr>
<td></td>
<td>o palonosetron 0.5 mg PO¹⁷,¹⁹</td>
<td>+/- olanzapine 5 to 10 mg PO daily on days 2, 3 and 4 (if olanzapine used on day 1¹⁻¹⁵,¹⁸; do not use with prochlorperazine or metoclopramide)</td>
</tr>
<tr>
<td></td>
<td>+/- olanzapine‖ 5 to 10 mg PO¹⁵,¹⁸</td>
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</tr>
<tr>
<td><strong>Moderate (MEC)</strong></td>
<td>dexamethasone§ 8 to 12 mg PO³,¹⁸ PLUS ONE 5-HT₃ ANTAGONIST:</td>
<td>+/- olanzapine 5 to 10 mg PO daily on days 2 and 3 (if olanzapine used on day 1¹¹⁵; do not use with prochlorperazine or metoclopramide)</td>
</tr>
<tr>
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<td>• ondansetron 8 mg PO³</td>
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<td></td>
<td>• palonosetron 0.5 mg PO¹⁷,¹⁹</td>
<td></td>
</tr>
<tr>
<td></td>
<td>+/- olanzapine‖ 5 to 10 mg PO¹⁵,¹⁶,¹⁸</td>
<td></td>
</tr>
<tr>
<td><strong>Low</strong></td>
<td>• dexamethasone§ 4 to 12 mg PO¹⁻² OR</td>
<td>• prochlorperazine 10 mg PO⁶⁻¹⁸ OR</td>
</tr>
<tr>
<td></td>
<td>• prochlorperazine 10 mg PO¹⁸ OR</td>
<td>• metoclopramide 10 to 20 mg PO³,⁴,¹⁸,¹⁹ OR</td>
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<td></td>
<td>• metoclopramide 10 to 20 mg PO³⁴,¹⁸,¹⁹ OR</td>
<td>• ondansetron 8 mg PO¹⁷⁻¹⁹ OR</td>
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<td>• ondansetron 8 mg PO¹⁷⁻¹⁹ OR</td>
<td>• granisetron 1 mg PO¹⁷⁻¹⁹ OR</td>
</tr>
<tr>
<td></td>
<td>• no prophylaxis¹⁹</td>
<td>• no prophylaxis³,¹⁸,¹⁹</td>
</tr>
<tr>
<td><strong>Minimal (Rare)</strong></td>
<td>Prophylactic treatment not normally required¹⁶,¹⁹</td>
<td>prochlorperazine 10 mg PO every 6 hours PRN x 3 to 4 days³,¹⁸ OR</td>
</tr>
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<td></td>
<td></td>
<td>metoclopramide 10 to 20 mg PO every 4 to 6 hours PRN x 3 to 4 days³,⁴,¹⁸,¹⁹ OR</td>
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<td></td>
<td></td>
<td>no prophylaxis³,¹⁸,¹⁹</td>
</tr>
</tbody>
</table>

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*Warning: The information contained in these documents are a statement of consensus of BC Cancer professionals regarding their views of currently accepted approaches to treatment. Any clinician seeking to apply or consult these documents is expected to use independent medical judgement in the context of individual clinical circumstances to determine any patient's care or treatment. Use of these documents is at your own risk and is subject to BC Cancer's terms of use available at www.bccancer.bc.ca/terms-of-use.*
Pre-chemotherapy is interpreted as 30 to 60 minutes prior to the start of chemotherapy.

Highly emetogenic chemotherapy (HEC), Moderately emetogenic chemotherapy (MEC); MEC replaces high-moderate and low-moderate in previous versions.

Dexamethasone doses may be individualized. When netupitant-palonosetron is used with anthracycline and cyclophosphamide (AC) based protocols, omission of day 2 to 4 dexamethasone doses is recommended. In general, lower dexamethasone doses and/or shorter durations may be considered for patients on non-CISplatin regimens. Steroids are not recommended as antiemetics for immunotherapies.

Netupitant-palonosetron 300 mg-0.5 mg capsules are a fixed dose, combination product given on day 1 only. Aprepitant is the NK1 antagonist of choice for docetaxel containing regimens; pharmacokinetic studies demonstrate a 35% increase in docetaxel AUC when co-administered with netupitant. Netupitant-palonosetron is likely safe to use in patients with soy/peanut allergies; however, a very low potential for allergic reaction does exist as trace amounts of soya lecithin may be present.

†For inpatients unable to swallow:
- Consider replacing pre-chemotherapy aprepitant with fosaprepitant IV 150 mg
- Post-chemotherapy fosaprepitant NOT needed, dose of 5-HT3 antagonist and dexamethasone remain the same (fosaprepitant 150 mg confers comparable serum level to aprepitant 125 mg which seems sufficient to cover days 2 and 3)

No additional 5-HT3 antagonist is required if netupitant-palonosetron combination used. Note palonosetron has a long duration of action (t1/2 ~44 h in adults).

Consider adding olanzapine if nausea / vomiting not controlled with 5-HT3 antagonist plus dexamethasone plus NK1 antagonist in previous cycle, especially if delayed nausea is a concern. Note: olanzapine adverse drug reactions including sedation and QTc prolongation, drug interactions and black box warning of increased mortality in elderly patients with dementia. Olanzapine should NOT be used with metoclopramide, prochlorperazine, or haloperidol due to increased risk of extrapyramidal symptoms.

For multiday chemotherapy regimens:
- Limited data exist for netupitant-palonosetron. Efficacy has been shown with standard dosing of 1 capsule on day one of a three-day HEC regimen.
- Aprepitant is the NK1 antagonist of choice for 3 and 5 day regimens. Limited data support dosing oral aprepitant over extended days.
- Suggested regimens based on 5-day cisplatin regimens:

<table>
<thead>
<tr>
<th>Aprepitant</th>
<th>5-HT3 antagonist</th>
<th>Dexamethasone</th>
</tr>
</thead>
<tbody>
<tr>
<td>125 mg PO day 1, then 80 mg PO days 2 to 7</td>
<td>days 1 to 5</td>
<td>days 1 to 8</td>
</tr>
<tr>
<td>125 mg PO day 3, then 80 mg PO days 4 to 7</td>
<td>days 1 to 5</td>
<td>days 1 and 2</td>
</tr>
</tbody>
</table>

Suggested regimens based on 3 day MEC and HEC regimens:

<table>
<thead>
<tr>
<th>Aprepitant</th>
<th>5-HT3 antagonist</th>
<th>Dexamethasone</th>
</tr>
</thead>
<tbody>
<tr>
<td>125 mg PO day 1, then 80 mg PO days 2 to 5 (i.e., dose 2 additional days post treatment)</td>
<td>On treatment days</td>
<td>days 1 to 5 (i.e., 2 additional days post)</td>
</tr>
</tbody>
</table>

PROPHYLACTIC ANTIEMETIC REGIMENS FOR ORAL CHEMOTHERAPY:

High or moderate emetogenic risk:
- choose one 5-HT3 antagonist pre-chemotherapy as listed for HEC/MEC in table above
- post chemotherapy breakthrough dosing as listed for HEC/MEC in table above

Low or minimal (rare) emetogenic risk:
- prn recommended
- if nausea/vomiting occurs:
  - metoclopramide 10 to 20 mg PO pre-chemotherapy then q6h prn OR
  - prochlorperazine 10 mg PO pre-chemotherapy then q6h prn (max 40 mg/day) OR
  - choose one 5-HT3 antagonist as listed in table above for low emetogenic risk, given daily prn
- post chemotherapy breakthrough dosing as listed in table above for low/minimal (rare) emetogenic risk
ADDITIONAL TREATMENT NOTES

- If IV administration of a 5-HT₃ antagonist is clinically indicated, use the same IV dose as the oral dose for ondansetron and granisetron. In contrast, palonosetron 0.5 mg PO is equivalent to palonosetron 0.25 mg IV.
- Single doses of 5-HT₃ antagonists are as effective as multiple doses.
- First generation 5-HT₃ antagonists (ondansetron, granisetron) are equally effective. Choose based on availability and cost.
- Palonosetron, a second generation 5-HT₃ antagonist, has a longer duration of action compared to first generation 5-HT₃ antagonists.
- First generation 5-HT₃ antagonists may increase the risk of arrhythmia and Torsade de Pointes in patients:
  - with congenital long QT syndrome, congestive heart failure, or bradyarrhythmias
  - with pre-existing hypokalemia or hypomagnesemia,
  - using medications that prolong QT interval or cardiotoxic chemotherapy.
  ECG monitoring is recommended in the above patients.
- Except for highly emetogenic chemotherapy, a corticosteroid alone is the cornerstone of therapy for prevention of delayed nausea and vomiting. There is no role for the routine use of 5-HT₃ antagonists more than 24 hours after chemotherapy.
- Currently available NK₁ antagonists are equally effective.
- Olanzapine may be included on days 1 to 4 of HEC or on days 1 to 3 of MEC for additional control of delayed nausea. A lower dose of 5 mg should be considered for elderly and over-sedated patients. Other cautions include:
  - Increased risk of death in elderly patients with dementia related psychosis
  - Concomitant administration of parenteral olanzapine and parenteral benzodiazepine is not recommended (toxicity may occur regardless of route)
  - QTc prolongation (see above monitoring recommendations for 5-HT₃ antagonists)
  - Sedation, most notable on day 2
  - Fall risk
  - Extrapyramidal symptoms
- Olanzapine and single-agent palonosetron are not covered by PharmaCare.

DETERMINING EMETOGENICITY OF CHEMOTHERAPY

- Emetogenicity: percentage of patients who will experience acute emesis if not treated.
  - high = greater than 90%
  - moderate = 30% to 90%
  - low = 10% to less than 30%
  - minimal (rare) = less than 10%
- Combination chemotherapy:
  - Consult chemotherapy protocol.
  - If emetogenicity is not specified, consult Cancer Drug Manual.
  - Treat for the most emetogenic agent OR use Hesketh Algorithm.

HESKETH ALGORITHM

- Identify the most highly emetogenic agent in the combination, then add the contribution of other agents using the following rules:
  - high/moderate: increase emetogenicity of the combination by one level per agent.
  - low: increase emetogenicity of the combination by one level, regardless of how many such agents are added.
  - rare: do not contribute.
TREATMENT FAILURES

If a patient experiences nausea or vomiting despite optimal prophylactic therapy, complete steps 1, 2, and 3 as follows:

1. Rule out or treat other causes of nausea and vomiting:
   - intestinal obstruction, gastroparesis, gastritis
   - medications (pain meds, bronchodilators)
   - brain metastases
   - vestibular dysfunction
   - electrolyte imbalance, uremia
   - infection

2. Control this episode of nausea and vomiting.
   - Approach to treatment of vomiting:
     - give additional antiemetic agent from a different class if vomiting/retching occurs while on antiemetics
     - give 5-HT\textsubscript{3} antagonist +/- dexamethasone if vomiting/retching occurs after antiemetics are finished
     - use rectal, parenteral or sublingual route of administration
     - use around-the-clock dosing rather than prn until vomiting stops
     - monitor and correct hydration and electrolytes as required
     - consider admission to hospital

Possible additional ongoing antiemetics to use if patient is:

<table>
<thead>
<tr>
<th>vomiting</th>
<th>nauseated*</th>
</tr>
</thead>
<tbody>
<tr>
<td>haloperidol 0.5 to 2 mg PO/IV every 4 to 6 hours\textsuperscript{18}</td>
<td>olanzapine 5 to 10 mg PO daily (if not previously given and if not using metoclopramide, prochlorperazine or haloperidol)\textsuperscript{17,18}</td>
</tr>
<tr>
<td>scopelamine 1.5 mg transdermal patch q72 hours\textsuperscript{18}</td>
<td>dimenhydrinate 100 mg PO every 12 hours alternating with prochlorperazine 10 mg PO every 12 hours (for a q6h regimen)\textsuperscript{3}</td>
</tr>
<tr>
<td>nabilone 1 to 2 mg PO bid\textsuperscript{18}</td>
<td>prochlorperazine 25 mg PR every 12 hours or 10 mg PO/IV every 6 hours\textsuperscript{18}</td>
</tr>
<tr>
<td></td>
<td>metoclopramide 10 to 20 mg PO every 4 to 6 hours\textsuperscript{18}</td>
</tr>
<tr>
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<td>nabilone 1 to 2 mg PO bid\textsuperscript{18}</td>
</tr>
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</table>

*5-HT\textsubscript{3} antagonist plus dexamethasone if above choices are ineffective\textsuperscript{3}

3. Plan prophylactic regimen for next cycle using Figure 1.
Figure 1. SUBSEQUENT ANTIEMETIC REGIMENS AFTER TREATMENT FAILURE

Did patient have ANY nausea or vomiting last cycle?

- yes
  - Anxiety or signs of anticipatory nausea and vomiting?
    - yes
      - Continue optimal prophylactic regimen and add one or more of:
        - lorazepam 0.5-2 mg PO/SL q12h, start the night before chemo\(^{3,18}\)
        - behavioural therapy [e.g., relaxation, cognitive distraction, hypnosis, music therapy, yoga (if approved by physician)]\(^{18}\)
        - avoid strong smells that may precipitate symptoms\(^{18}\)
    - no
  - no

- no
  - Vomited within 24 h of start of chemo?
    - yes
      - Acute nausea and vomiting:
        - Is patient on highest pre-chemo antiemetic regimen?
          - yes
            - Increase to a higher risk regimen pre-chemo\(^{1,3}\)
          - no
            - controlled
              - Continue current management
            - not controlled

    - no
      - Vomited > 24 h after chemo?
        - yes
          - Delayed nausea and vomiting: treat for duration of emesis + 1 day\(^{3}\)
          - Is patient on highest post-chemo antiemetic regimen?
            - yes
              - Increase to a higher risk regimen post-chemo\(^{1,3}\)
            - no
              - not controlled

        - no
          - May increase or change 5-HT\(_3\) antagonist (anecdotal evidence)\(^{2}\)
  - not controlled

May add one or more of:
- olanzapine 5 to 10 mg PO daily\(^{16-18}\) (see cautions under treatment notes / treatment failures)\(^{16}\)
- metoclopramide 10 to 20 mg PO q4 to 6h\(^{18}\)
- LORazepam 0.5 to 2 mg PO/SL bid to qid\(^{3,18}\)
- haloperidol 0.5 to 2 mg PO q4 to 6h\(^{18}\)
- prochlorperazine 25 mg PR q12h or 10 mg PO q6h\(^{18}\)
- dimenhyDRINATE 100 mg PO q12h, alternate with prochlorperazine 10 mg PO q12h (i.e., q6h regimen)\(^3\)
- H2 blocker or proton pump inhibitor (if patient has dyspepsia)\(^{18}\)
- scoPOlamine 1.5 mg transdermal patch q72h\(^{18}\)

- May change chemo regimen\(^2,3\)

Consider one or more of
- nabilone 1 to 2 mg PO q12h\(^{18}\)
- behavioural modification\(^3\)
- inpatient chemo (monitoring, hydration and electrolyte replacement prn)\(^9\)

- not controlled

Did patient have ANY nausea or vomiting last cycle?

- yes
  - Continue current management
- no
  - Controlled
    - Continue current management
  - not controlled
    - May change chemo regimen\(^2,3\)
REFERENCES (see appendix for separate document “Antiemetic Guidelines”)

27. BC PharmaCare Limited Coverage Drugs. Accessed 16 Dec 2019 at: https://www2.gov.bc.ca/gov/content/health/practitioner-professional-resources/pharmaceuticprescribers/limited-coverage-drug-program/limited-coverage-drugs-olanzapine