Cancer Care Ontario's Symptom Management Guide-to-Practice: Nausea and Vomiting

Preamble

Ontario Cancer Symptom Management Collaborative

An initiative of Cancer Care Ontario, the Ontario Cancer Symptom Management Collaborative (OCSMC) was undertaken as a joint initiative of the Palliative Care, Psychosocial Oncology and Nursing Oncology Programs. The overall goal of the OCSMC is to promote a model of care enabling earlier identification, communication and documentation of symptoms, optimal symptom management and coordinated palliative care.

The OCSMC employs common assessment and care management tools, including the Edmonton Symptom Assessment System (ESAS) screening tool to allow patients to routinely report on any symptoms they are experiencing. Symptom Management Guides-to-Practice were developed to assist health care professionals in the assessment and appropriate management of a patient's cancer-related symptoms. In addition to the symptom specific Guides-to-Practice, quick-reference Pocket Guides and Algorithms were created. Additionally, for a comprehensive management plan for patients with advanced disease, please refer to the Palliative Care Collaborative Care Plans.

Objective

The objective of this initiative was to produce Guides-to-Practice for the management of patients with cancer-related symptoms. These documents are clinical tools designed to assist health care practitioners in providing appropriate patient care and are not intended to serve as standards of care.

Target Population

The target population consists of adult patients, who require symptom management related to cancer. It is outside the scope of these Guides-to-Practice to address in detail the management of patients experiencing acute adverse effects secondary to systemic or radiation therapy. Please visit the Program in Evidence-Based Care for guidelines related to these topics.

Target Users

The Guides-to-Practice will be of interest to health professionals who provide care to patients with cancer-related symptom management needs at various stages of the disease pathway.

Methodology

The Guides-to-Practice were developed by the interdisciplinary Symptom Management Group (SMG) which included regional representation from across the province (refer to Post-amble for details). As an alternative to de novo development, the Guides-to-Practice were developed using the ADAPTE guideline adaptation approach that includes identifying existing guidelines, appraising their quality, selecting recommendations for inclusion and obtaining expert feedback (refer to Appendix A and B for details).

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Considerations

The following guidelines were used as the basis for the development of this Guide: Fraser Health Hospice Palliative Care Program Symptom Guidelines (1), Cancer Care Nova Scotia Guidelines for the Management of Nausea and Vomiting in Cancer Patients (2), Association of Comprehensive Cancer Centres (ACCC) Nausea and Vomiting (3), and the National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology: Palliative Care (4).

The key recommendations are highlighted in shaded boxes. Additionally, the source documents for each recommendation are denoted according to the symbols shown in Table 1. For example, if a recommendation is based on the expert opinion of the nausea and vomiting working group, this is indicated by a check box, or if derived verbatim from the NCCN guideline, it is indicated by the symbol NCCN. Recommendations that are derived from the NCCN guideline but have been modified are designated as NCCN Modified.

Table 1. Sources of Evidence

Symbol	Definition
☑	Recommended best practice based on the clinical experience of the guide development group.
Fraser Health CCNS NCCN ACCC	Sections extracted verbatim from the guidelines.
Fraser Health Modified CCNS Modified NCCN Modified ACCC Modified	Sections extracted from the guidelines and modified to better reflect the Ontario context.

The Guide-to-Practice should be used in addition to the appropriate assessment and management of reversible, underlying causes of nausea and vomiting. While some references to specific articles are provided, this guide is not intended to be a comprehensive overview of nausea and vomiting management; for a more in depth review the reader is encouraged to seek out the original guidelines. For a quick reference tool on the management of nausea and vomiting, please refer to the Nausea and Vomiting Pocket Guide and Algorithm.

Definition of Terms

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Nausea is expressed as an unpleasant subjective sensation secondary to stimulation of the gastrointestinal lining, the chemoreceptor trigger zone (at the base of the fourth ventricle), the vestibular apparatus, or the cerebral cortex. **Vomiting** is an observable neuromuscular reflex that constitutes a final common pathway after stimulation of one or more of these regions. Vomiting can occur without nausea, and nausea does not always lead to vomiting. Both symptoms, whether together or alone, can be very disruptive and distressing for patients and families.

Assessment

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Ongoing comprehensive assessment is recommended, as it is the foundation of effective nausea and vomiting management.

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Comprehensive assessment includes: interview, physical assessment, nutrition assessment, medication review, medical and surgical review, psychosocial and physical environment review and appropriate diagnostics. The OPRSTUV Acronym (Table 2) suggests some assessment questions; however these may need to be tailored to each patient. Where a patient is not able to complete an assessment by self-reporting, then the health professional and/or the caregiver may act as a surrogate.

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Table 2: Nausea and Vomiting Assessment using Acronym O, P, Q, R, S, T, U and V (2)

Onset	When did it begin? How long does it last? How often does it occur? Is it there all the time?
Provoking/ Palliating	What brings it on? What makes it better? What makes it worse?
Quality	What does it feel like? Can you describe it?
Region / Radiation	Do you have nausea with or without vomiting?
Severity	What is the intensity of this symptom (On a scale of 0 to 10 with 0 being none and 10 being worst possible)? Right Now? At Best? At Worst? On Average? How bothered are you by this symptom? Are there any other symptom(s) that accompany this symptom?
Treatment	What medications or treatments are you currently using? How effective are these? Do you have any side effects from the medications/treatments? What medications/treatments have you used in the past?
Understanding / Impact on You	What do you believe is causing this symptom? How is this symptom affecting you and/or your family?
Values	What is your goal for this symptom? What is your comfort goal or acceptable level for this symptom (On a scale of 0 to 10 with 0 being none and 10 being worst possible)? Are there any other views or feelings about this symptom that are important to you or your family?
* **Physical Assessment**: vital signs; hydration status (e.g. decreased urine output, thirst, dry mouth, dizziness, muscle cramps); the abdomen (inspection, palpation, percussion and auscultation); the oropharynx / mucous membranes; the rectum to assess for obstruction /impaction/ constipation; other regions as appropriate, based on information from the interview (e.g. CNS exam or digital rectal examination (DRE) as appropriate). *** Pertinent History** risk factors, date of last bowel movement. ***If vomiting present:** Assess frequency, amount, colour.	

To characterize the qualitative features of nausea and vomiting, questions should be asked regarding the following:

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- The onset, duration and frequency of nausea and vomiting
- Aggravating or alleviating factors
- A description of the emesis
- The severity on a scale of 0-10, with 10 being the worst
- Any other associated symptoms
- Treatments – current or previous medications; how effective are/were the medications? Do/did you have any side effects?
- What do you think is happening?
- What is the impact of this symptom on you and your family?
- What is an acceptable level of severity for this symptom on a scale of 0-10?
- Any triggers? What are the frequent triggers? Are there any patterns that alleviate the problem?

Physical Examination

On physical examination, it is important to assess:

- vital signs
- hydration status
- the abdomen (inspection, palpation, percussion and auscultation)

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- the oropharynx / mucous membranes
- the rectum, by digital rectal examination (DRE), to assess for obstruction /impaction/ constipation
- other regions as appropriate, based on information from the interview (e.g. CNS exam)

Investigations should be considered based on the information obtained from the history and physical examination, bearing in mind the patient's stage of disease, prognosis and goals of care. If specific causes are suspected, consider laboratory assessment (BUN, creatinine and electrolytes, serum calcium, magnesium, and albumin, liver function tests (LFT's), serum drug concentrations), abdominal x-ray, abdominal ultrasound or CT scan, gastroscopy, CT/MRI head.

Diagnosis

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Nausea and vomiting are common and have multiple etiologies, several of which may be present at the same time; hence identifying the underlying causes are essential.

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Management should include treating reversible causes where possible and desirable, according to the patients' goals of care. Interventions should be aimed at reducing nausea/vomiting taking into account the multi-factorial causes and the central emetogenic pathways and associated neurotransmitter receptors (See Table 3). All of these pathways stimulate the Integrative Vomiting Centre (IVC) which in turn initiates nausea and vomiting.

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Table 3. Diagnosis – Determining the Cause of Nausea and/or Vomiting (2)

Common Causes	Clinical Picture	Priniciple Site of Action
Chemical • **Drugs** (opioids, digoxin, steroids, antibiotics, anticonvulsants, cytotoxics) • **Biochemical** (hypercalcaemia, uremia, organ failure) • **Toxins** (tumour factors, infection, drug metabolites, radiation, ischemic bowel, food poisoning)	Symptoms of drug toxicity or underlying disease plus nausea as the prominent symptom. Nausea usually not relieved by vomiting.	Chemotrigger Zone (CTZ) Dopamine (D_2) Serotonin receptor antagonist ($5\text{-}HT_3$)
Gastrointestinal Tract-Vagal • **Gastric irritation** (ASA, NSAIDs, steroids, antibiotics, blood, ETOH, stress, radiotherapy) • **Obstruction** (partial or complete) • **Constipation** • **Gastric stasis** • **Mass effect** (GI, GU, hepatic distention, carcinomatosis) • **Anatomic/Structural**	Epigastric pain, fullness, acid reflux, early satiety, flatulence, hiccup, intermittent nausea relieved with vimiting. Altered bowel habit, pain may occur with oral intake. Vomitus may be large volume and fecal smelling.	Vagal & sympathetic afferent nerve pathways. Dopamine (D_2) Serotonin receptor antagonist ($5\text{-}HT_3$) $5HT_4$ receptors H_2 receptors Acetylcholine
Cerebral • **Increased Intracranial Pressure** (brain metastases, infectious meningitis, cerebral edema, bleeding) • **Psychological** (fear, anxiety, pain)	Headache +/- cranial nerve signs, (diurnal). Vomiting often without nausea. Anticipatory nausea / vomiting to sights, smells, etc.	Histamine (H_1) receptors
Vestibular • **Motion sickness** • **Cerebellar tumour**	Nausea +/- vomiting with movement	Histamine (H_1) receptors Acetylcholine

Note: ASA = Acetylsalicylic Acid; CNS= Central Nervous System; ETOH = Alcohol; GI= Gastrointestinal; GU=Genitourinary; NSAIDs= Non-steroidal anti-inflammatory drugs

Non-Pharmacological Treatment

Nausea and/or vomiting can be distressing to experience and/or witness.

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Providing information and education is recommended as it is fundamental to enhance the patient and family's ability to cope (5-9).

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- Consult with the interprofessional team members (e.g., social worker, spiritual practitioner, physiotherapist, occupational therapist, counselor for psychosocial care and anxiety reduction) (9-11).
- Explain to the patient/family what is understood about the multiple triggers of nausea and/or vomiting and that it may take a number of strategies to make a difference (12).

Consult with a Clinical Dietitian and have them provide dietary/nutritional advice after an assessment of current intake.

- Limit spicy, fatty and excessively salty or sweet foods, foods with strong odours and foods not well tolerated (6,7,11-13,15,18).
- Use small, frequent, bland meals and snacks throughout the day (6-8,11,14,16-19). Suggest small amounts of food every few hours (hunger can make feelings of nausea stronger).

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- Hard candies, such as peppermints or lemon drops may be helpful.
- Sip water and other fluids (fruit juice, flat pop, sports drinks, broth and herbal teas such as ginger tea) and suck on ice chips, popsicles or frozen fruit (15,18). It is important to try and drink fluids throughout the day even when not feeling thirsty.
- Limit the use of caffeine, including colas and other caffeinated soft drinks, such as coffee drinks, and tea (both hot and cold).
- Reduce meal size when gastric distension is a factor.
- Ingest liquids and solids separately (11,14,15). It is often helpful to drink fluids after and/or in between meals.
- Consume food/liquids cold or at room temperature to decrease odours (15).
- Sit upright or recline with head elevated for 30-60 minutes after meals (11).
- If vomiting, limit all food and drink until vomiting stops; wait for 30-60 minutes after vomiting, then initiate sips of clear fluid.
- When clear fluids are tolerated, add dry starchy foods (crackers, dry toast, dry cereal, pretzels).
- When starchy foods are tolerated, increase diet to include protein rich foods (eggs, chicken, fish) and lastly incorporate dairy products into the diet.

Environmental modification (where possible)

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- Eliminate strong smells and sights (5-8,10,11,13-17).
- Optimize oral hygiene, especially after episodes of vomiting (6-8,10,15,20). Rinse with ½ tsp baking soda, ½ tsp salt in 2 cups water.
- Rinse mouth before eating to remove thick oral mucus and help clean and moisten mouth.

ACCC

- Wear loose clothing.
- If possible try to create a peaceful eating place with a relaxed, calm atmosphere. A well ventilated room may also be helpful.

Complementary Therapies

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- Acupuncture or acupressure points (8,9,14,21)
- Visualization or hypnosis (5,9,14,18)
- Distraction (5,8,10,13,15)

Pharmacological Treatment

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Selection of antiemetics should be based on the most likely etiology of nausea and vomiting and site of action of medication.

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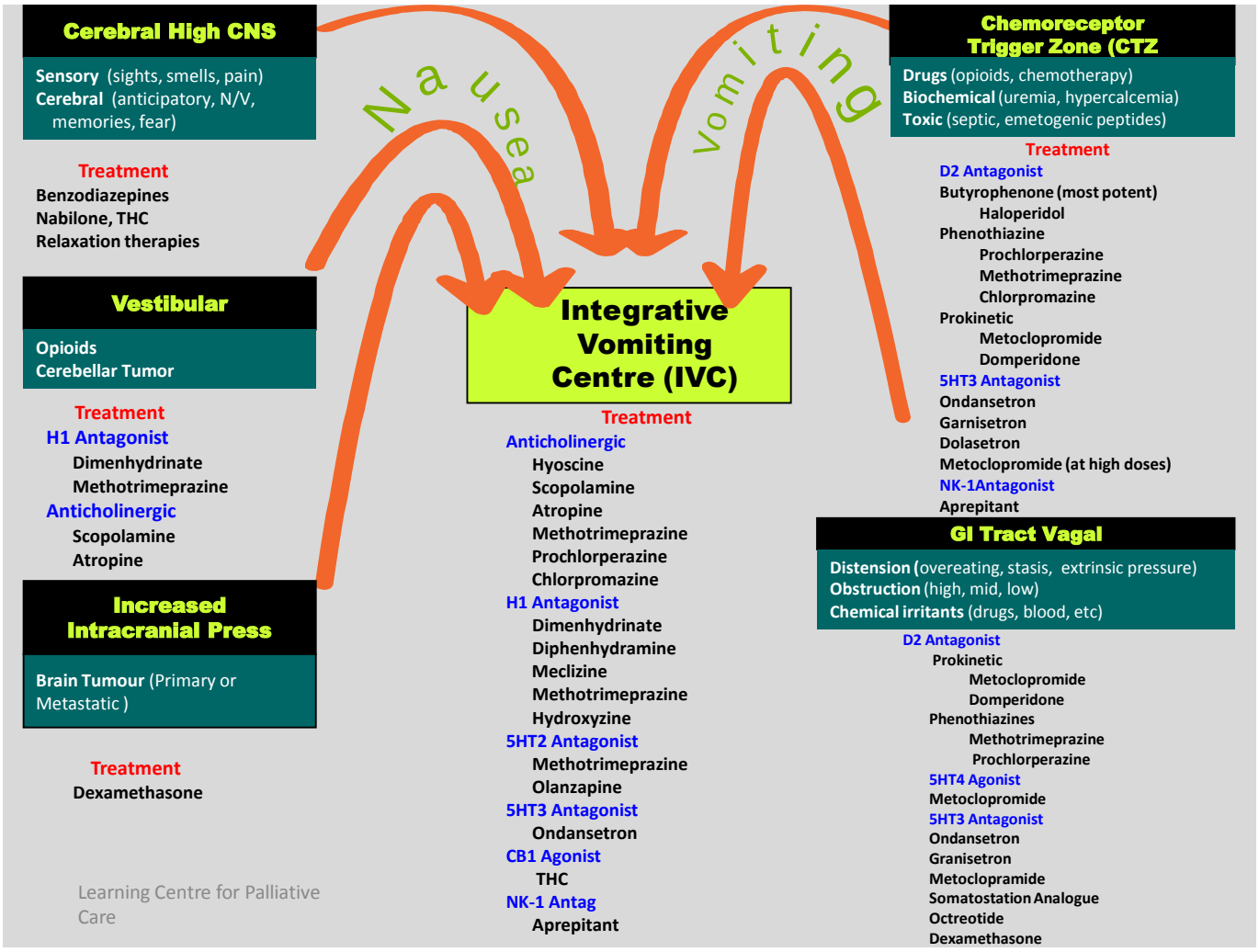
The four main neurotransmitters in the mediation of nausea are serotonin ($5HT_3$), dopamine (D_2), acetylcholine (Ach_m) and histamine (H_1) (See figure 1).

Figure 1: Mechanism-Based Etiology and Treatment Considerations (22)



N.B. Metoclopramide is a weak 5HT3 antagonist.
(Source: Medical Care of the Dying 4th Edition, pg. 319. Used with permission from Dr. Michael Downing)

Identify the pathway and neurotransmitters involved. Choose the most potent antagonist to the identified receptor.

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Any unnecessary medications that may be contributing to nausea and vomiting should be discontinued.

☑ **Constipation may be a factor contributing to nausea and vomiting and requires treatment.**

☑ **It is necessary to rule out bowel obstruction and if present, appropriate treatment should be undertaken.**

Choosing an Antiemetic

ACCC *Modified*

- Metoclopramide is recommended as the drug of first choice to control chronic nausea/vomiting in patients with advanced cancer (3,4).

NCCN

- Titrate metoclopramide to maximum benefit and tolerance. If not effective add/switch to another dopamine antagonist (e.g. haloperidol) (4).

CCNS

- Domperidone may be substituted for patients who can swallow medications and who have difficulties with extrapyramidal reactions (2).

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- Titrate antiemetics to their full dose, unless patient develops undesirable effects, before adding another drug (18).

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- If nausea is not controlled with a specific antiemetic within 48h, add another antiemetic from another group, but do not stop the initial agent (7,9,15,24).

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- Consider combinations but monitor overlapping toxicities (12,15).

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- Use regular dosing of antiemetics if experiencing constant nausea and/or vomiting (9,13).

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For persistent nausea and/or vomiting, antiemetics should be prescribed on a regular dosing schedule with a breakthrough dose available.

All medications need to be individually titrated to the smallest effective dose or until undesirable side effects occur.

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- A variety of routes and combinations of medications may be used to alleviate nausea (7,10,18).

Fraser Health

- Give antiemetics prophylactically to prevent nausea with high dose opioids and chemotherapeutic agents (9,12,15).

Fraser Health

- Ondansetron, although useful for chemotherapy induced nausea, is considered as a fourth line therapy for chronic nausea in Palliative Care (19). For this latter situation, this drug is not covered by the Ontario Drug Benefit Program.

☑

- Ondansetron is useful for radiation therapy induced nausea.

Fraser Health

- Dexamethasone is recommended for nausea and vomiting in the advanced cancer population (4).

Pharmacological Treatment of Symptoms: Stepwise Approach

The section below presents a stepwise approach to the pharmacological treatment of nausea and vomiting symptoms. For information on the corresponding levels of evidence for the recommendations below please refer to the ACCC guideline (3).

Treatment and Management

1. Treat the cause, if possible.
2. Symptomatic management:

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- Fluid and electrolyte replacement as appropriate
- Nutritional advice – consider making patient NPO (Nothing Per Os = Nothing by mouth) if obstructed or until emesis has resolved for several hours; if not obstructed, gradually change diet as appropriate, depending on the cause of nausea.
- Treat gastrointestinal obstruction (may need to consider interventions such as nasogastric tube (NGT), venting gastrostomy tube (PEG), stents, ostomies, possible surgical resection).
- Pharmacological treatment of symptoms

Pharmacological Treatment of Symptoms: Step 1

The choice of antiemetic depends on the cause (see Table 4 or Figure 1) and the receptors and neurotransmitters involved:

- For delayed gastric emptying or abdominal causes (excluding bowel obstruction, see above):
  - Metoclopramide 5-20 mg po/subcut/IV q6h (or tid AC meals plus qhs); may be used q4h if needed; 40-100 mg/24 h subcut/IV continuous infusion

ACCC *Modified*

  - Alternative (if metoclopramide is not well tolerated): domperidone 10mg tid to qid; causes less extrapyramidal side effects than metoclopramide. However, risk of serious abnormal heart rhythms or sudden death (cardiac arrest) may be higher in patients taking domperidone at doses greater than 30mg a day or in patients who are more than 60 years old.
- For patients treated with palliative radiotherapy:
  - For symptoms that occur within 24 hours of administration of radiotherapy: ondansetron 8 mg po/subcut/IV q8 – 24h; granisetron 1 mg po q12h or 1 mg IV once daily
  - For anticipatory nausea or vomiting: lorazepam 1-2 mg po/sl/IV/subcut
  - The above agents are also best given prior to radiation for optimal effect.
- For opioid-induced nausea:
  - Metoclopramide 10-20 mg po/subcut/IV q6h
  - Alternative: haloperidol 0.5-2.5 mg po/subcut q12h
- For other chemical/metabolic causes:
  - Haloperidol 0.5-2.5 mg po/subcut q12h
  - Alternative: metoclopramide 10-20 mg po/subcut/IV q6h
- For brain metastases: dexamethasone 4-8 mg po/subcut/IV bid (0800 and 1300 h); for brain metastases that do not respond to dexamethasone or for leptomeningeal carcinomatosis:
  - Haloperidol 1-2 mg po/subcut q12h

- For vestibular causes:
  - Scopolamine (transdermal patch) one or two 1.5 mg patches q72h
  - Alternate: dimenhydrinate 25-50 mg po/subcut/IV q4h
- If psychogenic factors play a role:
  - Oxazepam 10 mg po tid or lorazepam 1-2 mg po/sl/subcut/IV tid
  - Psychological techniques (particularly for chemotherapy-induced nausea and vomiting)

Pharmacological Treatment of Symptoms: Step 2

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A combination of different antiemetics is required in approximately 30% of cases. Combination therapy is only beneficial if different neurotransmitters are targeted. If the response to monotherapy is inadequate, the following combinations may be considered:

- Metoclopramide po/subcut/IV + dexamethasone po/subcut/IV
- Haloperidol po/subcut + dexamethasone po/subcut/IV

Pharmacological Treatment of Symptoms: Step 3

ACCC *Modified*

If dexamethasone combined with either metoclopramide or haloperidol yields insufficient results, the following approaches may be considered:

- Serotonin (5HT3) antagonists (ondansetron 4 - 8 mg po/subcut/IV q8-12h; granisetron 1 mg po q12h/1mg IV once daily; or dolasetron 100 mg po/IV once daily); in principle, combine with dexamethasone 4 mg po/subcut/IV once daily. Disadvantages of the serotonin antagonists: high costs; side effects include constipation, headaches
- Methotrimeprazine monotherapy using a starting dose of 5 – 10 mg po q8h PRN or 6.25-12.5 mg subcut q8h PRN. Increase as needed to maximum of 25 mg per dose.
- Olanzapine monotherapy 2.5 – 5 mg po/sl/subcut once daily or bid

☑ Diphenhydramine may be used for the treatment of akathesias secondary to increased doses of metoclopramide.

Table 4. Drug Therapy for Nausea and Vomiting in Advanced Cancer

a. May require additional PRN dosing
b. Anticholinergic effects (ie. dry mouth, sedation, urinary retention, blurred vision, constipation, etc)

Drug Class	Drug Name	Mechanism of Action		Route	Dose Range	Freq-uency	Side Effects	Drug interactions
		Receptor(s) Involved (If applicable)	Relative Potency					
Prokinetic Agents (3,23)	Metoclopramide	Antagonist - dopamine (D_2) Agonist - $5HT_4$ Antagonist - $5HT_3$ (25-27)	++ ++ Mild	Subcut PO IV	10 - 20 mg 10 - 20 mg 10 - 20 mg	q6h[a]	Sedation, fatigue, dizziness, dose-related diarrhea, abdominal cramps and distention, headache, hyperprolac-tinemia, extrapyramidal symptoms (EPS) (28,29)	• Anticholinergic agents and narcotics may antagonize GI motility effects (28) • Additive sedation with alcohol and CNS depressants (28) • Decreases stomach absorption of Digoxin (30) • Increase drug absorption in small bowel (i.e. acetaminophen, cyclosporine, levodopa, tetracycline) (30)

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		Receptor(s) Involved (If applicable)	Relative Potency					
	Domperidone	Antagonist - D_1, D_2 dopamine (Does not cross the blood-brain barrier) (25,27)	++	PO	10 - 30 mg	q6h	Diarrhea, abdominal cramps and distention, headache, hyperprolac-tinemia (28,30) Risk of serious abnormal heart rhythms or sudden death (cardiac arrest) may be higher in patients taking domperidone at doses greater than 30mg a day or in patients who are more than 60 years old.	• Major substrate of CYP3A4 (29) • CYP3A4 inhibitors (i.e. clarithromycin, ritonavir, itraconazole, verapamil, grapefruit juice) may increase domperidone plasma levels • Contraindicated with ketoconazole (29,30) • Anticholinergic agents and narcotics may antagonize GI motility effects (29,30) • Drugs that may prolong QT interval (i.e. amiodarone, amitriptyline, methadone, ciprofloxacin) (30) • Accelerates drug absorption from small bowel; slows drug absorption from stomach (30)

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Dopamine Antagonists (3,23)	Phenothiazines: Prochlorperazine	Antagonist - D_2 dopamine Antagonist - H_1 histamine (25,27)	++ +	PO PR IV Avoid subcut administration due to risk of irritation.	5 - 10 mg 10 mg 10 - 20 mg	q4 - 6h q4 - 6h q4 - 6h (usually given as PRN)	Sedation, anticholinergic effects[b], dizziness, headache, orthostatic hypotension (IM/IV use), EPS, pancytopenia (rare), QT prolongation (rare) (28,29)	• Additive sedation with alcohol and CNS depressants (i.e. benzodiazepines) (28,29) • Drugs that may prolong QT interval (29) • Anticholinergic agents – additive anticholinergic effects (29)
	Phenothiazines: Methotrimeprazine	Antagonist - D_2 dopamine Antagonist - H_1 histamine Antagonist - muscarinic cholinergic Antagonist - $5HT_2$ serotonin (25,27)	++ +++ ++ +++	PO Subcut	5 - 25 mg 6.25 – 25 mg	q8h[a] q8h[a]	Drowsiness, EPS (high doses), dry mouth, orthostatic hypotension (parenteral/ high doses), urinary retention and constipation (occasional in elderly), QT prolongation (rare) (29)	• Additive sedation with alcohol and CNS depressants (29) • Inhibits CYP2D6; • May decrease effects of CYP2D6 prodrug substrates (codeine, oxycodone, tramadol); may increase plasma concentration of CYP2D6 substrates (i.e. Metoprolol, Fluoxetine, Tamoxifen, amitriptyline) (29) • Drugs that may prolong QT interval (29)

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		Receptor(s) Involved (If applicable)	Relative Potency					
	Butyrophenones: haloperidol	Antagonist - D_2 dopamine (25)	+++	Subcut PO IV	0.5 - 2.5 mg 0.5 - 2.5 mg 0.5 - 2.5 mg	q8 - 12h [a]	Sedation, EPS, akathesia, QT prolongation (rare), hyperprolac-tinemia, anticholinergic effects[b] (mild) (28,29)	• Substrate for CYP2D6 and CYP3A4 (29) • Additive sedation with alcohol and CNS depressants (28,29) • Drugs that may prolong QT interval (29) • CYP3A4 inducers (i.e. rifampin, phenytoin, carbamazepine, phenobarbital, st. John's wort) may increase haloperidol clearance; CYP3A4 and CYP2D6 inhibitors (i.e. bupropion, paroxetine) may decrease clearance (29) • Inhibits CYP2D6 (29) • Lithium – potential neurotoxicity, EPS (25,29)

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		Receptor(s) Involved (If applicable)	Relative Potency					
	Olanzapine	Antagonist - D_1, D_2, D_4 Dopamine Antagonist - $5HT_2$, $5HT_3$, $5HT_6$ serotonin Alpha 1 adrenergic Antagonist - H_1 histamine Antagonist - M_1 muscarinic (25,26)	Inhibition potency: 5HT > D_4 > D_2 (25)	PO (regular or disintegrating tablet) Subcut	2.5 to 5 mg 2.5 to 5 mg	Daily - bid Daily - bid	Sedation, anticholinergic effects[b], hypotension, EPS, dizziness, hyperglycemia	• Substrate for CYP1A2 and CYP2D6 (29) • carbamazepine • CYP1A2 inducers (i.e. omeprazole) increase olanzapine clearance (29) • CYP1A2 inhibitors (i.e. fluvoxamine, ciprofloxacin) increase olanzapine exposure (29) • May potentiate hypotensive effects of antihypertensives (29)
Corticosteroids (3)	Dexamethasone	No specific mechanism of action Reduced intracranial pressure if brain metastases	Not applicable	PO Subcut IV	Usual dose is 2 to 16 mg per day. In specific circumstances such as brain metastases and, cerebral disease dose can go up to 24 mg per day. Note: For all doses, re-assess and wean appropriately	Daily - bid (08:00 and 13/ 14:00 hours)	Mood changes, increased appetite, GI irritation/ ulceration, fluid retention, weight gain, hyperglycemia, mask infections (28)	• Induces metabolism of other CYP3A4 drugs (i.e. cyclosporine, tacrolimus, diltiazem, atorvastatin) • Other CYP3A4 inducers/ inhibitors may increase/ decrease dexamethasone metabolism (29) • warfarin – may increase or decrease INR (25,29)

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		Receptor(s) Involved (If applicable)	Relative Potency					
Antihistamines (23)	Dimenhydrinate	Antagonist - H_1 histamine Antagonist - muscarinic Antagonist - $5HT_2$ (27)		PO IV PR Minimize Subcut administration due to risk of irritation.	25 - 50 mg 25 - 50 mg 25 - 50 mg	q4 - 6h (usually given as PRN)	Sedation, dizziness, anticholinergic effects[b], confusion (especially in the elderly) (28)	• Additive sedation with alcohol and CNS depressants (28) • Potential to inhibit metabolism of CYP2D6 drugs (also see diphenhydramine) (28)
	Diphenhydramine	Antagonist – H_1 histamine Antagonist - muscarinic Antagonist - $5HT_2$ (25,27)		PO/IV	25 - 50 mg	q4 - 6h (usually given as PRN)	Sedation, dizziness, anticholinergic effects[b], confusion (rare, especially in the elderly) (28)	• Inhibit metabolism of CYP2D6 substrates (25,28) • Additive sedation with alcohol and CNS depressants (28)
	Scopolamine Patch	Anticholinergic		Transdermal	1 - 2 patches (1.5mg/patch)	q72h	Sedation, anticholinergic effects[b], skin irritation, hypotension, blurred vision, confusion (rare, especially in the elderly) (29)	• Additive sedation with alcohol and CNS depressants (28,29)
	Methotrimeprazine			See Dopamine Antagonists – Methotrimeprazine				

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b. Anticholinergic effects (ie. dry mouth, sedation, urinary retention, blurred vision, constipation, etc)

Drug Class	Drug Name	Mechanism of Action		Route	Dose Range	Freq-uency	Side Effects	Drug interactions
		Receptor(s) Involved (If applicable)	Relative Potency					
Serotonin receptor antagonists (3,23)	Ondansetron	Antagonist – $5HT_3$ serotonin (26,27)	+++	PO IV Subcut	4 to 8 mg 4 to 8 mg 4 to 8 mg	q8-24h	Headache, constipation, dizziness, increased LFTs, bradycardia or ECG interval changes (rare) (28,29)	• Substrate for CYP1A2, CYP2D6, CYP2E1, CYP3A4 (29) • Drugs that prolong QT (28) • CYP3A4 inducers increase ondansetron clearance (28, 30)
	Granisetron			PO or PO IV	1mg 2mg 1mg	q12h q24h q24h		• Substrate for CYP3A4 (29)
	Dolasetron			PO IV	100 mg (1.8 mg/kg) 100 mg (1.8 mg/kg)	q24h q24h		• Substrate for CYP2D6 and 3A4 (29) • CYP3A4 inducers and inhibitors increase/ decrease dolasetron clearance (29) • Drugs that prolong QT (29) • Atenolol decreases dolasetron clearance (29)

Table 4. Drug Therapy for Nausea and Vomiting in Advanced Cancer

a. May require additional PRN dosing
b. Anticholinergic effects (ie. dry mouth, sedation, urinary retention, blurred vision, constipation, etc)

Drug Class	Drug Name	Mechanism of Action		Route	Dose Range	Freq-uency	Side Effects	Drug interactions
		Receptor(s) Involved (If applicable)	Relative Potency					
Benzodiazepines	Oxazepam lorazepam	GABA (inhibitory neurotransmitter); mainly CNS		PO IV Subcut PO / SL	10 - 15 mg 1-2 mg 1-2 mg 1-2 mg	q8h q8h	Drowsiness, confusion, respiratory depression, amnesia	• Additive sedation with alcohol and CNS depressants (28, 29)
Somatostatin Analogue (3,23)	Octreotide	Reduction of secretions in gastrointestinal tract Reduction of nausea may be associated with improved hydration Useful for patients with inoperable bowel obstruction		Subcut	50-500 ug	q8h	Abdominal discomfort, fatigue, flatulence, headache, dizziness, cholelithiasis, hypothyroidism, hyperglycemia (29)	• May decrease blood levels of cyclosporine; delay the intestinal absorption of cyclosporine or cimetidine (29) • Increases bioavailability of bromocriptine (29) • May decrease metabolism of CYP3A4 substrates; caution for CYP3A4 drugs with narrow therapeutic range (29)

Table 4. Drug Therapy for Nausea and Vomiting in Advanced Cancer

a. May require additional PRN dosing
b. Anticholinergic effects (ie. dry mouth, sedation, urinary retention, blurred vision, constipation, etc)

Drug Class	Drug Name	Mechanism of Action		Route	Dose Range	Freq-uency	Side Effects	Drug interactions
		Receptor(s) Involved (If applicable)	Relative Potency					
Cannabinoids	Dronabinol	Agonist - CB_1, CB_2 (26,29)		PO	2.5 mg (Start at lowest possible dose and titrate to effect)	q6-12h	Drowsiness, dizziness, euphoria, mood or cognitive changes, visual disturbances, confusion, dry mouth, tachycardia, facial flushing/ vasodilation (28,29) (Side effects limit use in advanced cancer patients)	• Substrate for CYP2C9 and CYP3A4 (29) • Additive sedation with alcohol and CNS depressants (28, 29) • TCAs (i.e. amitriptyline), sympathomi-metics (i.e. Amphetamines)– additive tachycardia, drowsiness, hypertension (29) • ritonavir increases dronabinol levels (25,26) • May inhibit metabolism of CYP3A4 substrates. • Additive drowsiness, tachycardia with antihistamines, anticholinergic agents, or sympathomi-metics (29)

Table 4. Drug Therapy for Nausea and Vomiting in Advanced Cancer

a. May require additional PRN dosing
b. Anticholinergic effects (ie. dry mouth, sedation, urinary retention, blurred vision, constipation, etc)

Drug Class	Drug Name	Mechanism of Action		Route	Dose Range	Freq-uency	Side Effects	Drug interactions
		Receptor(s) Involved (If applicable)	Relative Potency					
	Nabilone			PO	0.5-2 mg (Start at lowest possible dose and titrate to effect)	q12h	Sedation, dizziness, poor concentration, ataxia, psychotropic (i.e. euphoria), mood or sensation changes, hallucinations, headache, anorexia, tachycardia, orthostatic hypotension, dry mouth (29) (Side effects limit use in advanced cancer patients)	• Additive sedation with alcohol and CNS depressants (29) • TCAs (i.e. amitriptyline), sympathomi-metics (i.e. amphetamines)– additive tachycardia, drowsiness, hypertension (26) • Additive drowsiness, tachycardia with antihistamines, anticholinergic agents, or sympathomi-metic (26)

Note: ACCC= Association of Comprehensive Cancer Centres; bid= twice daily; CNS= Central Nervous System; h= hour; IV= Intravenous; mg = milligrams; NCCN= National Comprehensive Cancer Network; PO= per os, by mouth; q=every; PRN = as required; Subcut= subcutaneous; tid= thrice daily

Appendices

Appendix A: Methodology

The Standards, Guidelines and Indicators Sub-group of the Re-Balance Focus Action Group, established under the Canadian Cancer Control Strategy, performed a literature review and environmental scan.[i] This review was used by the SMG as a source from which to identify existing guidelines relative to the four symptoms of interest. Additionally, SMG members reached programs in Ontario, searched the Cancer Care Ontario Program in Evidence-based website and their own personal sources for any relevant guidelines.

The Re-Balanced Focus Action Group used the following search criteria:

Inclusion Criteria

1. Standards focused on care delivered by cancer organizations; and/or processes of care; and/or professional practice standards specific to cancer.
2. Guidelines focused on clinical practice of practitioners relevant to psychosocial, supportive or palliative care provision to cancer patient populations.
3. Guidelines that were more generic in focus but relevant to supportive care aspects of cancer populations in areas such as prevention and screening were also included.

Exclusion Criteria

1.Guidelines that did not base the development of substantive statements/recommendations 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.
2. Guidelines that were focused on providing direction to patients and families 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.

Databases Searched

Health Sciences literature databases used in this scan include HealthStar, Medline, CINHAL, Embase and PsycINFO. The internet search engine Google Scholar was utilized for the grey literature search for scientific and non-scientific sources. Databases for the following organizations were also reviewed: a) All oncology professional associations and organizations for Psychosocial Oncology and Palliative Care inclusive of Oncology Social Workers, Clinical Oncology; b) All Canadian Provincial Cancer Care Organizations within provinces; c) International organizations or agencies or associations whose mandate is focused on systematic reviews or guideline development. The literature search and environmental scan was updated in December 2008 and again in January 2009.

Results

Based on the literature review and environmental scan described above, the Nausea and Vomiting SMG identified twelve guidelines for inclusion in this Guide-to-Practice. Seven guidelines (10,31-36) were rejected at the onset by the group because they fell outside of the

[i] Re-Balance Focus Action Group. Literature Review and Environmental Scan: Psychosocial, Supportive and Palliative Care Standards and Guidelines. Updated 2009.

scope of the Guides-to-Practice or were not methodologically sound. The remaining five guidelines (1-5) were screened and assessed for quality, currency, content, consistency, and acceptability/applicability, using the Appraisal of Guidelines Research and Evaluation (AGREE) instrument (www.agreetrust.com). Taking into consideration the AGREE scores and expert consensus, the working group chose the most applicable and relevant guidelines (1-4) to be included in the Guide-to-Practice (refer to Table 5).

Table 5. AGREE Scores

AGREE Scores	Fraser Health (1)	CCNS (2)	ACCC (3)	NCCN (4)	ICSI (5)
Scope & Purpose	77.78	73.33	55.56	85.19	70.4
Stakeholder Involvement	43.06	50.00	40.00	41.67	53
Rigour of Development	68.25	73.33	23.81	38.10	65
Clarity & Presentation	75.00	88.33	65.00	77.78	75
Acceptability	27.78	33.33	8.89	22.22	33
Editorial Independence	25.00	46.67	10.00	77.78	61
Overall Quality Assessment	Recommend with provisos; Clearly presented, good flowcharts, algorithms, etc.; interventions speak to acute patients not palliative patients; when you look at references most of them are chemo induced; very cancer oriented; end-of-life perspective could be added e.g. touched on hypercalcemia and bowel obstruction	Clearly presented, liked the flowcharts, algorithms, etc.; wanted to hear a bit more palliative voice; interventions speak to acute patients not palliative patient; when you look at references most of them are chemo induced; very cancer oriented; could look at palliative perspective more; end-of-life perspective could be added e.g. touched on hypercalcemia and bowel obstruction; significant work would need to be done	Recommend with provisos; Rigor of development and clarity/ presentation were much better; new information; patients were not involved, no mention of a pilot, cost, funding or conflict of interest information; acceptability and editorial independence sections were weak	Recommend with provisos; Meds used are not used in Ontario; happy to see antipsychotics were used as they are often more effective; did not specify when meds should be used	Rejected; Well developed but lacked depth and detail

Note: ACCA = Association of Comprehensive Cancer Centres; CCNS=Cancer Care Nova Scotia; ICSI= Institute for Clinical Systems Improvement; NCCN= National Comprehensive Cancer Network

The ADAPTE process (http://www.adapte.org/) was then used to systematically endorse or modify applicable components of the four guidelines. The guideline development process, utilizing ADAPTE, proceeds under the assumption that the original recommendations are reasonable and supported by the evidence. Confidence in this assumption is fostered from satisfactory AGREE scores. In situations were evidence was not available or not applicable to specific clinical situations, systems and contexts recommendations were modified based on the expert consensus of the working group. It is beyond the scope of the guideline development process and this document to make the connection between the recommendations and the original key evidence. For those who wish to do so, please refer to the Fraser Health (1), Cancer Care Nova Scotia (CCNS) (2), Association of Comprehensive

Cancer Centres (ACCC) (3), and the National Comprehensive Cancer Network (NCCN) (4) documents.

Appendix B: Peer Review Summary

Expert feedback was obtained through an internal and external review.

Internal Review

The internal review consisted of an anonymous appraisal of the guides by members from each of the working groups. The intent of this review was to ensure that the guide development process was methodologically rigourous; the recommendations are supported by the evidence in a transparent way; and that the guide was clinically relevant and applicable to practice.

A total of 39 online surveys were collected during the internal review (refer to Table 6 for details). Ten participants completed the nausea and vomiting Guide-to-Practice survey; however one respondent only provided written commentary. The survey feedback was thoroughly reviewed by each of the corresponding working groups and, where appropriate, changes were made.

Table 6. Responses to the Nausea and Vomiting internal review survey (8 respondents)

Question	**Strongly Agree** % (Response count)	**Agree** % (Response count)	**Disagree** % (Response count)	**Strongly Disagree** % (Response count)
The methods for formulating the recommendations are clearly described.	12.5 % (1)	62.5% (5)	25% (2)	0%
There is an explicit link between the supporting evidence and the recommendations.	12.5 % (1)	87.5% (7)	0%	0%
The recommendations are in agreement with my understanding of the evidence.	12.5 % (1)	87.5% (7)	0%	0%
The recommendations are specific and unambiguous.	12.5 % (1)	87.5% (7)	0%	0%
The recommendations are easily identifiable.	12.5 % (1)	75% (6)	12.5 % (1)	0%
The recommendations are achievable.	12.5 % (1)	87.5% (7)	0%	0%
Health benefits, side effects, and risks have been considered in formulating the recommendations.	12.5 % (1)	87.5% (7)	0%	0%
When applied, the Guide-to-Practice will produce more benefits for patients than harm.	12.5 % (1)	87.5% (7)	0%	0%
The different options for management of the condition are clearly presented.	12.5 % (1)	87.5% (7)	0%	0%
The Guide-to-Practice is supported with tools for application.	12.5 % (1)	62.5% (5)	25% (2)	0%
The Guide-to-Practice is user friendly.	12.5 % (1)	62.5% (5)	25% (2)	0%
The Guide-to-Practice presents a series of options that can be implemented.	12.5 % (1)	87.5% (7)	0%	0%

Question	**Yes, Strongly Agree** Percent (Response count)	**No, Strongly Disagree** Percent (Response count)
Do you perceive any barriers or challenges in using this Guide-to-Practice?	12.5 % (1)	87.5% (7)
Would you be able to apply these recommendations to the clinical care decisions for which you are professionally responsible?	87.5% (7)	12.5 % (1)

Appendix C: External Review Summary

External Review

The external review process consisted of I) a Targeted Peer Review intended to obtain direct feedback on the draft guides from a small number of specified content experts and II) a Professional Consultation that intended to disseminate the draft guide as widely as possible to its intended readership, provide a forum for recipients to explain any disagreement with the recommendations, and to further ensure the quality and relevance of the document.

I) Targeted Peer Review

Thirteen reviewers were invited to participate in the external target review and 11 provided responses (refer to Table 7 and 8 for details).

Table 7. Overview of the Nausea and Vomiting targeted peer reviewers

Guide	Sample	Results
N/V	**13 Reviewers:** 1 Palliative care physician 1 Medical Oncologist 1 Nurse practitioner 3 Pharmacists 5 Dietitians 2 Methodology experts	**11 Responses:** 1 Palliative care physician 1 Nurse practitioner 1 Pharmacist 6 Dietitians 2 Methodology experts

Table 8. Responses to key questions on the Nausea and Vomiting targeted peer review survey (11 respondents)

Question*	1 Lowest Quality % (Response count)	2 % (Response count)	3 % (Response count)	4 % (Response count)	5 Highest Quality % (Response count)
Rate the Guide-to-Practice development methods.	0%	0%	18% (2)	73% (8)	9%(1)
Rate the Guide-to-Practice presentation.	0%	9% (1)	18% (2)	55% (6)	18% (2)
Rate the Guide-to-Practice recommendations.	0%	0%	10% (1)	70% (7)	0%
Rate the completeness of the reporting.	0%	9% (1)	18% (2)	46% (5)	27% (3)
Does this document provide sufficient information to inform your decisions?	0%	0%	18%(2)	9% (1)	70% (7)
Rate the overall quality of the Guide-to-Practice.	0%	0%	18% (2)	27% (3)	27% (3)
Question	**1 Lowest Quality** % (Response count)	**2** % (Response count)	**3** % (Response count)	**4** % (Response count)	**5 Highest Quality** % (Response count)
I would make use of this Guide-to-Practice in my professional decisions.	0%	0%	0%	27% (3)	36% (4)
I would recommend this Guide-to-Practice for use in practice.	0%	0%	0%	18% (2)	55% (6)

*Some participants skipped questions; hence numbers may not add up to 100%

II) Professional Consultation

The Professional Consultation consisted of a sample of approximately 290 health care practitioners. Participants were contacted by email and asked to read the guides and complete a brief corresponding electronic survey. Forty-nine responses were received (refer to Table 9 and 10). Fifteen respondents completed the Nausea and Vomiting survey.

Table 9. Overview of the Professional Consultation sample

Profession	Sample	Results
Palliative Care Physicians	49	18
Nurses	32	15
Pharmacists	20	1
Family Physicians	6	4
Medical Oncologists	14	4
Radiation Oncologists	17	1
Surgical Oncologists	11	0
Provincial Palliative Care Committee	9	0
PEBC Supporting Care Group/ Administrative/Researchers	9	3
Dietitians	75	2
Psychiatrists	6	1
Neurologists	16	0
Respirologists	26	0
TOTAL:	290*	49 (Response rate 17%)

* Participant were encouraged to forward the electronic survey to interested colleagues, hence the total sample size is only an estimate.

Table 10. Responses to key questions on the Professional Consultation survey (40 respondents)

Question	1 **Strongly Disagree** Percent (Response count)	2 Percent (Response count)	3 Percent (Response count)	4 Percent (Response count)	5 **Strongly Agree** Percent (Response count)
I would make use of this Guide-to-Practice in my professional decisions.	2.1% (1)	2.1% (1)	14.65% (7)	31.2% (15)	50% (24)
I would recommend this Guide-to-Practice for use in practice.	2.1% (1)	2.1% (1)	10.3% (5)	29.2% (14)	56.3% (27)
Question	**1 Lowest Quality** Percent (Response count)	**2** Percent (Response count)	**3** Percent (Response count)	**4** Percent (Response count)	**5 Highest Quality** Percent (Response count)
Rate the overall quality of the Guide-to-Practice.	0	2.1% (1)	14.6% (7)	35.4% (17)	47.9% (23)

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Post-amble

Working Group

A wide variety of health professionals were invited to participate in the development of this Guide-to-Practice, as well as in the external review. Every effort was made to ensure as broad a professional and regional representation as possible.

Ingrid Harle MD, FRCS(C), CCFP, FCFP, ABHPM(cert)
SMG Co-Chair, Delirium Group Lead
Assistant Professor, Palliative Care Medicine Program, Queen's University
34 Barrie Street, Kingston, Ontario, K7L 3J7

Kate Bak
Policy Research Analyst
Oncology Nursing, Psychosocial and Palliative Care
Cancer Care Ontario
620 University Avenue
Toronto, Ontario M5G 2L7

Annie Cheung
Formulary Pharmacist
Cancer Care Ontario
620 University Avenue
Toronto, Ontario, M5G 2L7

Ebru Kaya
Palliative Care Physician
University Health Network
Toronto General Hospital
200 Elizabeth Street, 9N-926
Toronto, Ontario M5G 2C4

Jane Keown
Nurse Manager
Sudbury Regional Cancer Centre
Hopital Regional de Sudbury Regional Hospital
41 Ramsey Lake Road
Sudbury, Ontario P3E 5J1

Andrew Knight
General Practitioner in Oncology & Clinical Leader,
Palliative Care (LHIN 13)
Regional Cancer Program
Hôpital Regional de Sudbury Regional Hospital
41 Ramsey Lake Road
Sudbury, ON P3E 5J1

Megan Miller
Palliative Medicine Physician
London Health Sciences Centre
800 Commissioners Road East
PO Box 5010
London, Ontario N6A 5W9

Prabhjot Minhas
Project Coordinator
Oncology Nursing, Psychosocial and Palliative Care
Cancer Care Ontario
620 University Avenue
Toronto, Ontario M5G 2L7

Trish Murphy-Kane
Advanced Practice Nurse - Clinical Nurse Specialist in Palliative Care
Princess Margaret Hospital
610 University Avenue
Toronto, Ontario M5G 2M9

Catherine Root
Chief Executive Officer
North Simcoe Muskoka Palliative Care Network
190 Memorial Ave. Unit P
Orillia, Ontario L3V 5X6

Sally Tierney
Clinical Pharmacist – Palliative Care
Elisabeth Bruyère Hospital SCOHS,
43 Bruyere Street
Ottawa, ON K1N 5C8

Ron Woit
Clinical Pharmacist
Woit's Pharmacy Ontario
100-1265 Arthur Street East
Thunder Bay, Ontario P7E 6E7

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Conflict of Interest

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