

# Nausea and Vomiting Not Related to Cancer Therapy: Intractable Problem or Clinical Challenge?

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## Abstract

**Purpose:** Unlike therapy-related nausea and vomiting (chemotherapy or radiotherapy induced), nausea and vomiting (N/V) in patients with advanced cancer is often multicausal and thus presents unique challenges. Few professional guidelines address the palliative management of N/V, and those that do are insufficiently detailed to bolster clinical decision-making. Nonetheless, oncology advanced practitioners (APs) are frequently challenged to manage these high-impact symptoms. This requires collaborating with other oncology care providers and cultivating a knowledge base to educate and mentor professional colleagues to optimize N/V unrelated to treatment. **Methods:** Literature reviewed included current and classic articles that address the physiologic bases of N/V related to disease and with malignant bowel obstruction, agents used to alleviate nausea or N/V, and nonpharmacologic adjunctive measures. This information was framed within palliative care and symptom management clinical experience. **Results:** This review article summarizes what is known about the neuropharmacology of N/V in advanced disease. Focused assessment, pharmacologic agents (antiemetics, central neuromodulators, and peripheral prokinetic agents), and nondrug adjunctive measures that may be useful for N/V are included. **Conclusions:** Managing N/V in advanced cancer is a quality-of-life imperative that requires persistence and interprofessional collaboration among oncology APs and other clinicians to personalize management. This work can change the perception that N/V related to progressive disease is frequently intractable to one that considers it as a manageable clinical challenge.

Over the past 40 years, major advances in knowledge and new drugs targeting chemotherapy-induced nausea and vomiting (CINV) have been incorporated into (largely) evidence-based antiemetic guidelines. Conversely, there is a thin evidence base underpinning guidelines for the palliative man-

agement of nausea and vomiting (N/V). Studies are difficult to implement because of the complex and multicausal nature of N/V, respondent burden, ethical issues of intervention studies in progressively ill patients, and lack of funding support (National Comprehensive Cancer Network [NCCN], 2019; Walsh et al., 2017). Nausea is more common than N/V in advanced disease. Both may be difficult to control, negatively affect quality of life (QOL), and often lead to significant morbidity (e.g., anorexia, electrolyte disturbances, dehydration, or aspiration pneumonia; Collis & Mather, 2015; Glare, Miller, Nikolova, & Tickoo, 2011).

Prescribing or administering an antiemetic ineffective for a particular patient might lead a clinician to conclude that the patient's N/V is "intractable." Oncology advanced practitioners (APs; physician assistants [PAs], nurse practitioners [NPs], clinical nurse specialists [CNS], and pharmacists) recognize the value and importance of incorporating and promoting primary palliative care across settings. Successful symptom management requires tenacity, persistence, and collaboration among oncology health-care providers (HCPs; physicians, APs, and clinic or hospital nurses). This article will briefly discuss the neuropharmacology of N/V and summarize thorough patient assessment. Commonly used pharmacologic agents and factors that might influence drug selection will be included, as well as nonpharmacologic measures that might add benefit.

## NEUROPATHWAYS FOR NAUSEA AND VOMITING

Nausea and vomiting can have one or more causes involving neurotransmitters and receptors in afferent peripheral and central nervous system (CNS) pathways. The gastrointestinal (GI) system and the vagus nerve are the major components of a bidirectional peripheral pathway: the gut-brain axis (Wickham, 2020). Central nervous system pathways include the brainstem area postrema (chemoreceptor trigger zone [CTZ]) and nucleus tractus solitarius (NTS) in the medulla, and the cortex and other higher regions. The same neurotransmitters and receptors occur in both pathways and include dopamine (and  $D_2$  receptors), gamma-Aminobutyric acid (GABA, GABA-A),

glucocorticoid, histamine ( $H_1$ ), endocannabinoid ( $CB_1$ ), muscarinic ( $M_3/M_2$ ), serotonin ( $5-HT_3$ ,  $5-HT_{1A}$ , and  $5-HT_4$ ), and tachykinin (neurokinin, NK1). The prevailing view that N/V occurs via activation of the NTS (the "vomiting center") with nausea reflecting lower level activation cannot be accurate because antiemetics that prevent vomiting often do not prevent nausea (Collis & Mather, 2015).

Regions involved with emotions, memory, and learning (the insular cortex, which is beneath the frontal, parietal, and temporal lobes) are particularly important to nausea (Craig, 2015). Neural impulses arrive at the posterior (visceral) insula and are transmitted to and reinterpreted in the mid-insula, and so on to the anterior, or interoceptive insular cortex (IIC). Nausea and all other emotional and physical interoceptive (internal) sensations (e.g., pain, maternal and erotic love, etc.) are experienced in the IIC; the anterior cingulate cortex (ACC) and amygdala add to learning, memory, and valence (distress and disgust). Animal studies illuminate how the endocannabinoid system mediates nausea in the insular cortex (Limebeer, Rock, Sharkey, & Parker, 2018). Administration of an agent that causes nausea leads to 5-HT elevation in the IIC and nausea; both are suppressed by pretreatment with cannabidiol (CBD) or a monoacylglycerol lipase (enzyme that hydrolyzes one endocannabinoid) inhibitor. Bidirectional communication between the IIC and the NTS influences prodromal autonomic nervous system manifestations of nausea (e.g., sweating, salivation, increased blood pressure, and tachycardia), anxiety, and the feeling of imminent vomiting (Cangemi & Kuo, 2019).

## DETERMINING LIKELY CAUSES OF NAUSEA AND VOMITING

A systematic assessment (Table 1) helps identify risk factors and determine if nausea or vomiting are more bothersome, and the onset, pattern, and severity of each (Collis & Mather, 2015; Glare et al., 2011; Harder, Groenvold, Herrstedt, & Johnsen, 2019a). No specific level of nausea is "not too bad." Cancer patients rated pain (66%), nausea (58%), and fatigue (40%) as most severe and most bothersome, and they considered even mild nausea bothersome (Li et al., 2019).

**Table 1. Focused Assessment for Nausea and Vomiting**

**Baseline:** Determine if the patient has inherent risk factors for N&V (female, younger than age 55, CINV with previous chemotherapy, hyperemesis of pregnancy, anxiety, or poor sleep)

**History** (ask patient about nausea and vomiting separately):

- How severe/intense/bad and bothersome is your nausea or vomiting? (Use scale the patient best understands, such as 0 to 10, or none, mild, moderate, severe, for all symptoms)
- Is either nausea or vomiting worse for you?
- Describe the onset, pattern, and frequency of nausea and vomiting.
- Are you currently receiving new chemotherapy, radiation therapy, or targeted agents, and guideline-recommended antiemetics?
- Aggravating factors: Does anything make the nausea or vomiting worse (sight/smell of food, eating, movement)?
- Relieving factors: Does anything make the nausea or vomiting better (antiemetics, over-the-counter products, home remedies)?
- Ask about (and manage concurrently) associated symptoms/manifestations
  - » Constipation
  - » Malignant bowel obstruction or peritoneal carcinomatosis
  - » Pain, a dogged cough, confusion, excessive thirst and urination, etc.
- Mood: Does the patient appear or admit to feeling anxious or depressed, which may exacerbate nausea?
- Effects on usual activities and QOL: Does vomiting or nausea interfere with or change important parts of your life, such as activities that are enjoyable or important to you?

*Note.* N&V = nausea and vomiting; CINV = chemotherapy-induced nausea and vomiting; QOL = quality of life. Information from Collis & Mather, 2015; Ferguson et al., 2015; Franke et al., 2017; Glare et al., 2011; Harder et al., 2019a.

It is crucial to recognize and alleviate symptoms that cause or intensify N/V, particularly constipation (Rhondali et al., 2013). The comprehensive chemical panel is a cost effective screen for electrolyte abnormalities and organ dysfunction that might exacerbate N/V. Other diagnostic procedures should be tailored to clinical circumstances (e.g., patient performance status and life expectancy, and if a test result will change treatment) and selected according to the least costly and burdensome whenever feasible.

### Differentiating Constipation and Bowel Obstruction

Patients with pelvic or abdominal tumors, particularly advanced ovarian or GI cancer, are most likely to develop malignant bowel obstruction (MBO) accompanied by new continuous nausea, colicky abdominal pain, intermittent vomiting, bloating, and no flatus or bowel movements for 72 hours (Franke, Iqbal, Starr, Nair, & George, 2017). Subacute or intermittent MBO are common, and patients without crampy abdominal pain may have a functional ileus rather than a mechanical MBO. Severe constipation (obstipation) can imitate MBO, so the AP must do a digital rectal examination. A rectum full of hard, dry stool requires one or more suppositories or enemas to eliminate retained stool before MBO can be confirmed or ruled out (Ferguson, Ferguson, Speakman, & Ismail, 2015).

Other diagnostic clues may aid in distinguishing obstipation, obstruction, and peritoneal carcinomatosis. For example, a distended abdomen, hyperactive bowel sounds (BS), and tympany point to MBO, while absent BS and dullness to percussion reflect a paralytic problem. Palpation may reveal a discreet, noncompressible tumor mass, softer retained stool, or a “woody” abdomen with diffuse malignant infiltration.

A plain x-ray of the abdomen (kidney, ureters, and bladder [KUB]) may distinguish constipation with stool seen in the bowel from MBO, with distended bowel loops above an obstruction and nothing distally (Ferguson et al., 2015; Franke et al., 2017). Oral contrast can improve the ability to verify the level and extent of obstruction. Gastrografin is hyperosmolar, which increases water entering the bowel lumen to dilute it. Conversely, barium causes water loss and becomes more condensed and solid in an obstructed bowel. If surgery is a consideration, a CT scan can differentiate important tumor characteristics of obstruction, but is ineffective for diffuse peritoneal carcinomatosis in the small bowel or pelvis with small (< 1 cm) nodules. Malignant bowel obstruction and peritoneal carcinomatosis most often occur in end-stage disease, so the AP should assess patients’ functional status, review their understanding of their disease and goals of care, and address advance directives.

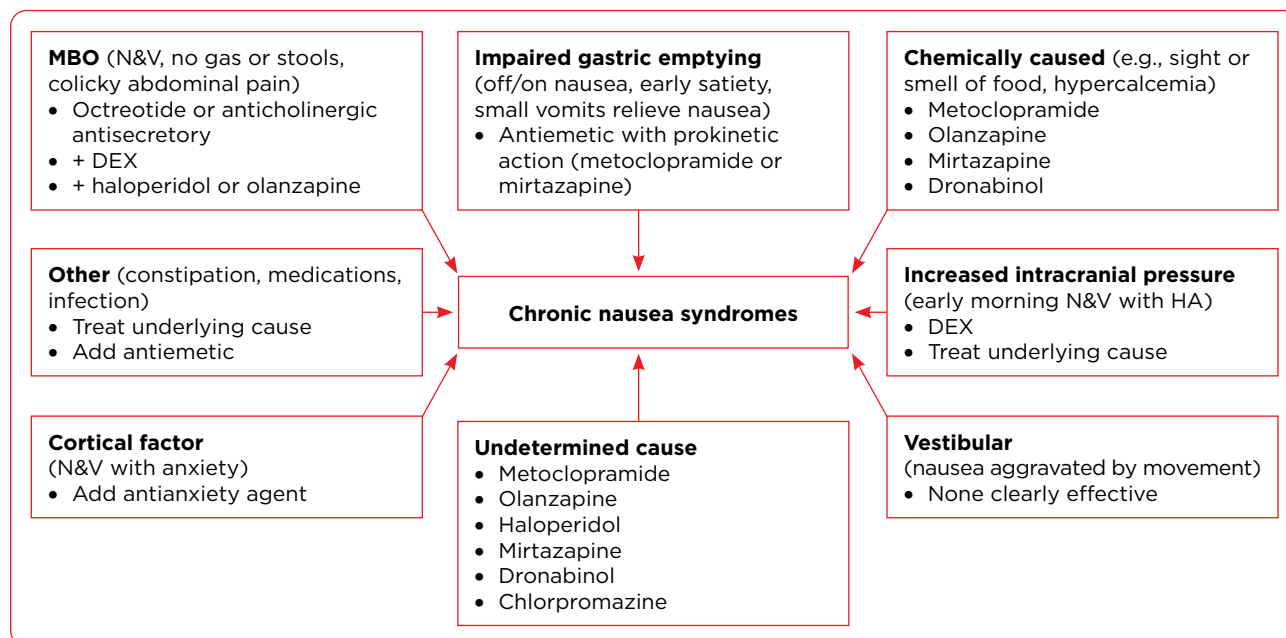
## SELECT ANTIEMETICS AND ADJUVANT AGENTS BASED ON PROBABLE BENEFITS AND HARMS

Nausea/vomiting assessment often leads to no clear etiology or several possible causes. As depicted in Figure 1, antiemetic selection considers pharmacology and receptor actions, emetic pathway redundancy, and using agents that bind at more than one receptor (Cangemi & Kuo, 2019; Collis & Mather, 2015; Glare et al., 2011). For example, antiemetics (metoclopramide and chlorpromazine) and central neuromodulators (haloperidol, olanzapine, and mirtazapine) usually act in the CNS, whereas prokinetic agents (metoclopramide, erythromycin, and mirtazapine) typically act in the stomach and upper GI tract. Antihistamines block prokinetic actions and should be avoided when increased GI motility is a goal. Conversely, prokinetic agents are contraindicated in patients with complete MBO, which usually signifies terminal disease. Furthermore, initial treatment of MBO focuses on decreasing associated symptoms (crampy or colicky pain, nausea, and vomiting) with bowel rest, antisecretory and antiemetic drugs (hyoscine, glycopyrrolate, scopolamine, or octreotide, plus chlorpromazine or olanzapine, plus dexamethasone), and a nasogas-

tric tube for 2 or 3 days (Franke et al., 2017). These measures allow for resolution of partial MBO (which may recur), decisions about further treatment measures, and percutaneous gastrostomy if necessary (Figure 1).

Palliative antiemetic selection is often empirical, based on previous clinical experience and palliative medication principles. A first antiemetic should be scheduled and titrated to efficacy, maximum recommended dose, or dose-limiting side effects (Collis & Mather, 2015). If a first drug does not adequately control N/V, a second (and perhaps) subsequent agents with different receptor binding can be added in a stepwise manner. The severity of N/V dictates how often a patient should be reassessed (for efficacy and side effects). For example, severe symptoms are ideally reevaluated within 8 hours of a new intervention. The AP can ask the patient how their nausea (or vomiting) compares to the last assessment: the same, better, or worse. It is also helpful to ask if control is “good enough” or if they would “like it to be better,” as well to inquire about any new and bothersome symptoms.

Oral antiemetics are recommended unless the patient is vomiting or has symptomatic gastric stasis. Drugs that block several receptors



**Figure 1.** Chronic nausea syndromes and interventions. N&V = nausea and vomiting; HA = headache; DEX = dexamethasone; MBO = malignant bowel obstruction. Information from Cangemi & Kuo, 2019; Collis & Mather, 2015; Franke et al., 2017; Glare et al., 2011; Moorthy & Letizia, 2018.

(e.g., mirtazapine or olanzapine) may be advantageous if N/V seems refractory (Allen et al., 2016; MacKintosh, 2016). Persistence is crucial: In one large study, a variety of antiemetics (olanzapine, a corticosteroid, metoclopramide, haloperidol, a 5-HT<sub>3</sub> receptor antagonist, or others) were initially prescribed (Harder et al., 2019b). None were effective for all patients, olanzapine was overall most effective, and the combined benefit of all antiemetics was almost 80%. Table 2 summarizes antiemetics used in advanced disease. Metoclopramide, haloperidol, and olanzapine have been used frequently, and mirtazapine could be used more often (NCCN, 2019; Walsh et al., 2017). Serotonin 3 (5-HT<sub>3</sub>) and neurokinin-1 (NK1) receptor antagonists, indicated for CINV, are cost-prohibitive (except for ondansetron) and rarely used for palliation of N/V (Table 2).

### Metoclopramide

Metoclopramide is a D<sub>2</sub> receptor antagonist antiemetic in the CTZ and a 5-HT<sub>4</sub> receptor agonist in the gut to mediate prokinetic effects. Doses ≥ 120 mg/day have 5-HT<sub>3</sub> antagonist effects (Cangdem & Kuo, 2019; Hendren, Aponte-Feliciano, & Kovac, 2015). It may be useful for N/V of undetermined or chemical causes, or neoplastic gastroparesis (Collis & Mather, 2015; Wiebe, 2012). Extrapyramidal syndromes (EPS), particularly dystonias and akathisia, are uncommon but clinically relevant adverse effects of metoclopramide and other D<sub>2</sub> receptor antagonists (which are discussed later in the article).

### Haloperidol

Haloperidol, a first-generation antipsychotic, is used to palliate N/V and delirium. It has strong affinity for D<sub>2</sub> receptors, but EPS is rare with palliative doses. Weak binding at other receptors (5-HT, alpha adrenergic [α<sub>1</sub>], muscarinic cholinergic [M<sub>1</sub>], and histamine [H<sub>1</sub>]) have little clinical relevance (Prommer, 2012). Typical doses are 0.5 mg every 4 to 6 hours (po, IV, or subcutaneous); more frequent dosing may increase side effects (Prommer, 2012). A recent pharmacovigilance study examined haloperidol (average 1.7 mg per day, range: 0.5–5 mg) prescribed for N/V to 150 consecutive palliative care patients (Digges et al., 2018). N/V resolved in 79% by 48 hours, and after 7 days, 26%

had mild to moderate side effects (e.g., constipation, dry mouth, and sleepiness). Haloperidol has a risk to prolong corrected QT (QTc) with subsequent torsades de pointes (TdP).

### Olanzapine

Olanzapine is a second-generation antipsychotic, and valuable for CINV and palliative N/V because of moderate or strong binding at several D, 5-HT, α, and H receptors (Harder et al., 2019b; Langley-DeGroot, Ma, Hirst, & Roeland, 2015). Olanzapine has greater binding affinity for 5-HT<sub>2</sub> than D<sub>2</sub> receptors, and is less likely to cause EPS but is more sedating than haloperidol. It may improve appetite (with increased weight), has few drug interactions, and is safe for patients with renal or liver dysfunction. Oral dissolvable tablets (ODT) may be useful for patients with dysphagia or MBO, allowing avoidance of parenteral dosing.

In one multisite, retrospective study with 106 patients with advanced cancer, olanzapine at 2.5 mg or 5 mg once-daily controlled N/V for months (Kaneishi et al., 2016). Similarly, a prospectively accrued case series of 16 cancer patients had N/V uncontrolled by metoclopramide, haloperidol, promethazine, ondansetron, and/or prochlorperazine (MacKintosh, 2016). Olanzapine at 5 mg po at bedtime relieved N/V in 14 patients (87.5%) for up to 5 months, but was discontinued in two patients (one with inadequate antiemetic control and another with excessive sedation). A third prospective study included 40 cancer patients with N/V uncontrolled by other antiemetics who were given olanzapine at 10 mg once daily for 5 days (Harder et al., 2019). Within 24 hours after the first dose, 35 reported improved nausea ( $p < .001$ ) and vomiting ( $p = .003$ ). Olanzapine was reduced to 5 mg in three patients because of fatigue, dizziness, or sedation.

### Mirtazapine

Mirtazapine is a tetracyclic antidepressant that is an antagonist at D, 5-HT, α, H, and M receptors. A psychiatrist consultant recommended mirtazapine for specific physical symptoms in 475 medically ill, hospitalized patients (Allen et al., 2016). Medical records were reviewed, and there was documented improvement in nausea, sleep, pain, and appetite (37.0%, 37.7%, 36.4%, and 23.5%, respectively) in

**Table 2. Antiemetics and Other Medications Used to Palliate Nausea and Vomiting**

Drug	Indications	Routes and doses	Comments
Olanzapine (5-mg tabs, #30: \$9-\$97)	MBO and other GI, metabolic, chronic unexplained, opioids, other drugs, infection	<ul style="list-style-type: none"> <li>• po, ODT</li> <li>• Start at 2.5–5 mg at hs; titrate to 20 mg</li> <li>• Add second dose prn</li> </ul>	<ul style="list-style-type: none"> <li>• Receptors: D (1, 2, 4), 5-HT<sub>2</sub> (A, C), 5-HT<sub>3</sub>, <math>\alpha</math>, H, M (1–4)</li> <li>• Metabolism: liver, no dose modification</li> <li>• SEs: sedation, reversible hyperglycemia</li> <li>• Risks: EPS (rare)</li> </ul>
Mirtazapine (7.5-mg tabs #30: \$13-\$34)	MBO, other GI, unexplained, metabolic, opioids and other drugs, infection	<ul style="list-style-type: none"> <li>• po, ODT</li> <li>• Start at 7.5 mg at hs; titrate to 15 mg</li> <li>• Add second dose prn</li> </ul>	<ul style="list-style-type: none"> <li>• Receptors: D (1, 2), 5-HT<sub>1</sub> (A, B, D), 5-HT (2A, B, C), 5-HT<sub>3</sub>, <math>\alpha</math> (1–2), H<sub>1</sub>, M<sub>1</sub></li> <li>• Metabolism: liver</li> <li>• SE: mild sedation, dry mouth</li> <li>• Possible dose reduction for liver or renal dysfunction</li> <li>• Risks: prolonged QT (rare)</li> </ul>
Metoclopramide (10-mg tabs, #30: \$4-\$9)	GI, unexplained, metabolic, opioids, other drugs, infection AVOID: suspected, confirmed MBO	<ul style="list-style-type: none"> <li>• po: start at 10 mg 3–4 times/day, titrate prn (dose ranges: 30–240 mg/d)</li> <li>• IV, IM, SC: 40–120 mg/d</li> </ul>	<ul style="list-style-type: none"> <li>• Receptors: D<sub>2</sub>, 5-HT<sub>4</sub> (agonist), 5-HT<sub>3</sub> (&gt; 120 mg/d)</li> <li>• Metabolism: liver, reduce doses renal dysfunction</li> <li>• SEs: depression, headache, colic</li> <li>• Risks: EPS (low)</li> </ul>
Haloperidol (1-mg tabs, #30: \$9-\$12)	First- or second-line: MBO, other GI, chronic unexplained, metabolic, opioids and other drugs, infection	<ul style="list-style-type: none"> <li>• po: start at 1 mg q12h with prn doses 0.5 mg q4–6h</li> <li>• SC, IV: 0.5–2 mg q4h</li> </ul>	<ul style="list-style-type: none"> <li>• Receptors: D (2, 3, 4, 5), 5-HT<sub>1A</sub>, <math>\alpha_2</math>-agonist</li> <li>• Metabolism: liver, reduce doses in liver disease</li> <li>• SEs: dry mouth, sleepiness</li> <li>• Risks: EPS (low), prolonged QT (rare)</li> </ul>
Dexamethasone (4-mg tabs, #30: \$8-\$16)	GI: MBO, hepatomegaly, ascites, gastroparesis CNS: brain tumor	<ul style="list-style-type: none"> <li>• po, IV (see article)</li> </ul>	<ul style="list-style-type: none"> <li>• Receptors: unknown</li> <li>• Metabolism: liver, inactive metabolites</li> <li>• SEs: insomnia, appetite increase, muscle weakness, dyspepsia, depression, anxiety, or psychosis</li> </ul>
Dronabinol (5-mg caps, #60: \$158-\$264)	Unexplained, drug-induced, infection, MBO, ascites, hepatomegaly, gastroparesis, metabolic (e.g., hypercalcemia), brain tumor	<ul style="list-style-type: none"> <li>• po: start at 5 mg 1–2 times per day; titrate doses to 10 mg (this is a small dose)</li> </ul>	<ul style="list-style-type: none"> <li>• Receptors: CB<sub>1</sub></li> <li>• SEs: feeling “high,” sleepiness, dizziness, dry mouth, increased appetite</li> </ul>
Chlorpromazine (25-mg tabs, #30: \$54-\$85)	-	<ul style="list-style-type: none"> <li>• po: 5–25 mg q4–6h</li> <li>• IM: 5 mg/mL q3–4h</li> <li>• IV: 20–40 mg q4–6h</li> <li>• pr: 25–100 mg q6–8h</li> <li>• Titrate more slowly in elderly</li> </ul>	<ul style="list-style-type: none"> <li>• Avoid SC dosing</li> <li>• Receptors: D (1–4), 5-HT (1A, 2A), <math>\alpha</math> (1–2), M (1–2)</li> <li>• Metabolism: liver</li> <li>• Suppositories: Insert into rectum or vagina</li> <li>• SEs: sedation, dry mouth, constipation, hypotension</li> <li>• Risks: EPS (low); prolonged QT (rare)</li> </ul>

Note. D = dopamine; 5-HT = serotonin;  $\alpha$  = alpha adrenergic; M = muscarinic cholinergic; H = histamine; ODT = oral dissolvable tablet; SC = subcutaneous; IV = intravenous; po = orally; pr = rectally; SE = side effect; EPS = extrapyramidal symptoms; LAR = long-acting depot; MBO = malignant bowel obstruction; SL = sublingual; TD = transdermal. Prices from goodrx.com.

Information from Allen et al., 2016; Collis & Mather, 2015; Digges et al., 2018; Harder et al., 2019b; Hendren et al., 2015; Hernandez et al., 2015; Jaward et al., 2019; Kaneishi et al., 2016; Khanna et al., 2019; Khoo & Quinlan, 2016; Langley-DeGroot et al., 2015; Lovell et al., 2018; MacKintosh, 2016; Prohotsky et al., 2014; Prommer, 2012; Riordan et al., 2019; van der Meer et al., 2014; Wiebe, 2012.

mirtazapine-treated patients. These may have been underestimates of symptom improvement, because 229 patients had no follow-up documentation and were counted as “no improvement.” Antidepressant

effects are not seen for weeks, but gastric stasis, anorexia, chronic pruritus, dyspnea, and anxiety with advanced lung disease may improve with the first dose (Cangemi & Kuo, 2019; Khanna, Boo-

**Table 2. Antiemetics and Other Medications Used to Palliate Nausea and Vomiting (cont.)**

Drug	Indications	Routes and doses	Comments
<i>Anticholinergic antisecretory agents</i>			
Glycopyrrolate	MBO (partial or complete)	• SC, IV: 0.1–0.2 mg q4–8h prn	• Receptors: M (1–4) • SEs: dry mouth, sleepiness, constipation
Hyoscyamine (0.375 mg tabs, #120: \$54–\$68)	MBO (partial or complete)	• SL, SC, IV: 0.125–0.5 mg q4–6h prn	• Receptors: M (1–4) • SEs: dry mouth, sleepiness, constipation
Scopolamine (4 patches [12 days] \$30–\$66)	MBO (partial or complete)	• TD: 1–2 patches	• Receptors: M (1–4) • SEs: dry mouth, sleepiness, constipation
Octreotide (somatostatin analog; 2–5-mL vials, 200 µg/mL: \$56–\$89 for 6 days)	Complete MBO	• SC: 300–600 µg for 6 days • Depot injection (LAR) q4wk	• Receptors: somatostatin • Give daily SC for 3–6 days to determine efficacy; if effective, convert to octreotide long-acting depot; discontinue if not • SEs: fatigue, headache, flu-like syndrome, dizziness, gas, and diarrhea
<p><i>Note.</i> D = dopamine; 5-HT = serotonin; <math>\alpha</math> = alpha adrenergic; M = muscarinic cholinergic; H = histamine; ODT = oral dissolvable tablet; SC = subcutaneous; IV = intravenous; po = orally; pr = rectally; SE = side effect; EPS = extrapyramidal symptoms; LAR = long-acting depot; MBO = malignant bowel obstruction; SL = sublingual; TD = transdermal. Prices from goodrx.com.</p> <p>Information from Allen et al., 2016; Collis &amp; Mather, 2015; Digges et al., 2018; Harder et al., 2019b; Hendren et al., 2015; Hernandez et al., 2015; Jaward et al., 2019; Kaneishi et al., 2016; Khanna et al., 2019; Khoo &amp; Quinlan, 2016; Langley-DeGroot et al., 2015; Lovell et al., 2018; MacKintosh, 2016; Prohotsky et al., 2014; Prommer, 2012; Riordan et al., 2019; van der Meer et al., 2014; Wiebe, 2012.</p>			

zalis, Belzberg, Zampella, & Kwatra, 2019; Khoo & Quinlan, 2016; Lovell, Bajwah, Maddocks, Wilcock, & Higginson, 2018). Mirtazapine has a long half-life (20–40 hours), so antiemetic doses (7.5 to 15 mg) are given at bedtime (Khoo & Quinlan, 2016). High affinity for H<sub>1</sub> receptors may improve sleep quality or cause daytime sedation, which may decrease with 6:00 pm dosing. Other possible side effects are dry mouth and constipation.

### Corticosteroids

Corticosteroids are inexpensive and useful for N/V related to primary or metastatic brain tumors, MBO, or with unexplained N/V (Collis & Mather, 2015; Glare et al., 2011; Hendren et al., 2015). The duration of action of dexamethasone is 36 to 72 hours; prednisone and methylprednisolone act for 12 to 36 hours (Jaward, O’Neil, Marks, & Smith, 2019). Dexamethasone is the most potent anti-inflammatory: dexamethasone at 0.75 mg  $\approx$  prednisone at 5 mg  $\approx$  methylprednisolone at 4 mg. Typical dexamethasone “antiemetic” doses are 4 to 8 mg once daily, and  $\leq$  16 mg daily for MBO or increased intracranial pressure (Glare et al., 2011). The lowest effective steroid dose should be used

for the shortest time, such as 7 to 10 days for patients with MBO (Collis & Mather, 2015; Jaward et al., 2019). Higher doses for longer periods increase risks for adverse events in many body systems.

### Chlorpromazine

Chlorpromazine (and other phenothiazines) have D<sub>2</sub> antagonist antiemetics in the CTZ. Binding at other receptors (D, 5-HT,  $\alpha$ , H, and M) may lead to EPS, sedation, anticholinergic effects (e.g., dry mouth, constipation), hypotension, and prolonged QTc (Glare et al., 2011; Hendren et al., 2015). Chlorpromazine may be useful for nausea with MBO or in dying patients when sedation is beneficial. Antiemetic doses can be titrated to 100 mg every 4 hours. Suppositories, inserted in the rectum or vagina, are not routine but might be useful for patients who cannot swallow or keep pills down but wish to remain at home. A compounding pharmacist could admix a concentrated chlorpromazine at 100 mg/mL for sublingual or buccal dosing, an alternative to tablets or injectables in dysphagic patients with advanced disease (Prohotsky, Juba, & Zhao, 2014). Subcutaneous administration can cause severe tissue necrosis and must be avoided.

## Cannabinoids

The endocannabinoid system (ECS) includes endogenous cannabinoids (endocannabinoids) synthesized on demand to bind at ECS receptors (CB<sub>1</sub> or CB<sub>2</sub>) and act largely as neuromodulators, and are then rapidly metabolized to constituent molecules (Lu & Anderson, 2017; Sharkey, Darmani, & Parker, 2014). The ECS has essential roles in virtually every homeostatic physiologic process in all organ systems (Hendren et al., 2015; Wickham, 2020). In the 1970s, a few small studies found delta-9-tetrahydrocannabinol (THC) synthesized in dronabinol or nabilone was as or more effective for CINV than chlorpromazine, metoclopramide, and other antiemetics (Cangemi & Kuo, 2019). Research into these agents largely ended with the discovery of how 5-HT mediates CINV and the development of selective 5-HT<sub>3</sub> receptor antagonists (Andrews & Sanger, 2014). THC can induce psychoactive effects—a “high,” drowsiness, and (rarely) hallucinations, which are usually not bothersome to patients (Hendren et al., 2015).

There are few case reports of dronabinol or nabilone for palliation of N/V due to high costs, lack of palliative indication, and little clinical experience in adjusting doses. One patient with advanced ovarian cancer and peritoneal carcinomatosis had rapid onset of severe (10 of 10) nausea and up to 20 painful vomiting episodes per day (Hernandez, Sheyner, Stover, & Stewart, 2015). IV ondansetron plus dexamethasone followed by IV metoclopramide and then subcutaneous haloperidol were ineffective for N/V. Oral dronabinol was started and titrated to 15 mg/day; the patient's vomiting stopped, she rated nausea as 0 or 1 (on no other antiemetics), and resumed enjoyable activities with her family.

## EXTRAPYRAMIDAL SYNDROMES AND QTc PROLONGATION

Recognizing rare adverse effects, such as EPS and QTc prolongation, is important to enhance patient QOL and safety. D<sub>2</sub> antagonists (metoclopramide, haloperidol, chlorpromazine, and [rarely] olanzapine) seldom cause acute EPS. The absolute risk for acute EPS (dystonias or akathisia) with D<sub>2</sub> antagonist antiemetics is low; over 15 years, 479 EPS reactions were reported out of approximately 16 million metoclopramide prescriptions, rep-

resenting an incidence of 0.003% (van der Meer, Venhuizen, Heyland, & van Zanten, 2014). The risk is greatest in elderly and very young patients, and with larger doses (metoclopramide > 30 mg/day) taken for months to years. Genetic inheritance may increase risk, as there are case reports of persons with two inactive CYP2D6 alleles having greater risk for EPS than those with wild-type alleles (Chua, Harger, & Kennedy, 2019; van der Padt, van Schaik, & Sonneveld, 2006).

Dystonias are focal, possibly painful contractions in muscle groups in the neck, jaw, eyes, or mouth (e.g., torticollis, retrocollis, or trismus) that start soon after a first D<sub>2</sub> antagonist dose, hours to days later, with a dose increase, or with high doses (Caroff & Campbell, 2016; Mehta et al., 2015). The patient feels very anxious and has spasmodic twisting postures or muscle tightness. Young adult and adolescent males, and boys have a 2:1 greater risk than older females, and Black people have a greater risk than others. An IV antihistamine (diphenhydramine at 50 mg), anticholinergic (benztropine at 1–4 mg), or benzodiazepine (diazepam at 0.1 mg/kg or lorazepam at 0.05 to 0.10 mg/kg) usually reverses dystonias within 10 to 20 minutes.

Clinicians often miss akathisia, which is an EPS that is not as outwardly dramatic. The patient feels restless: they may be unable to sit still, or may shift their weight, tap or shuffle their feet, or pace (Caroff & Campbell, 2016; Mehta et al., 2015). These behaviors may be misinterpreted as agitation, anxiety, or restless legs syndrome. Adults, particularly women, over age 40 are at greatest risk. Akathisia begins hours to weeks after a D<sub>2</sub> is started or a dose increase, and may intensify with continued use. Rapid administration may increase the incidence of akathisia, which was 24.7% after metoclopramide as a 2-minute IV bolus, but 5.8% when administered as a 15-minute infusion (van der Meer et al., 2014). Mirtazapine ≤ 15 mg po, the treatment of choice for akathisia, is as effective as propranolol or benztropine and associated with fewer side effects.

Chlorpromazine, erythromycin, 5-HT<sub>3</sub> antagonists, haloperidol, mirtazapine and promethazine, and many anticancer agents have been identified as possible causative agents for prolonging QTc, and with extremely rare progression to potentially fatal TdP. CredibleMeds (<https://www.>



crediblemeds.org) maintains an up-to-date list that categorizes agents by risk (known, possible, or conditional) for prolonged QTc and TdP. All listed agents are absolutely contraindicated only in persons with congenital long QT syndrome. Of course, clinicians always weigh each drug's benefits against potential harms and implement measures that decrease risks. For example, hypocalcemia, hypokalemia, or hypomagnesemia would be corrected in patients whose QTc is > 500 milliseconds (Riordan, Briscoe, Uritsky, Jones, & Webb, 2019).

## SUPPLEMENTARY NONDRUG MEASURES

Advanced practitioners can explore nondrug measures for nausea that might be useful antiemetic adjuncts for patients with nausea. Any added benefit is gained at little to no cost, minimal risks for adverse effects, and perhaps an improved sense of patient control.

### Acupuncture and Acupressure

Actual (vs. sham) acupuncture is more likely to decrease nausea and reduce antiemetic requirements in patients receiving chemoradiation (Cangemi & Kuo, 2019). One integrative medicine service followed 172 hospitalized cancer patients who had multiple symptoms. Patients who received at least one acupuncture treatment reported significantly improved pain, nausea, fatigue, drowsiness, or anxiety (Garcia et al., 2018). Digital acupuncture, using an inexpensive OTC digital acupressure band, may be similarly effective. Lee, Dibble, Dodd, Abrams, and Burns' 2010 study found P6 digital acupressure (Figure 2) was significantly more effective than placebo acupressure for delayed CINV in women with breast cancer. Patients snugly position the band's bead at P6 for approximately three minutes or until nausea decreases, and reapply whenever nausea reoccurs.

### Ginger

Oral ginger has confirmed benefit for post-surgical N/V, motion sickness-related N/V, pregnancy-related N/V, and acute CINV (Crichton, Marshall, Marx, McCarthy, & Isenring, 2019; Marx et al., 2017). Bioactive compounds may act at 5-HT<sub>3</sub> and other receptors to enhance gastric emptying and

GI motility, enhance anti-inflammatory properties, or alter vasopressin release. One small study found ginger at 1,650 mg per day for 14 days improved gastric myoelectric activity, nausea, dysmotility, and reflux-like symptoms in 60% of those who took it (Bhargava, Chasen, Elten, & MacDonald, 2019).

Ginger can also be formulated as an essential oil for aromatherapy or topical administration. Nurse members of an integrative health service offered essential oils to almost 6,000 patients in almost 8,000 aromatherapy sessions (Johnson et al., 2016). Lavender, ginger, sweet marjoram, and mandarin oils reduced pain and anxiety; ginger oil decreased nausea (mandarin oil to a lesser degree).

### Medical Cannabis

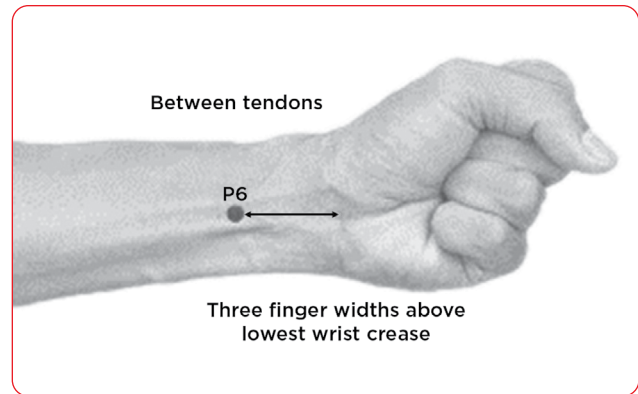
Cannabis has two major phytocannabinoids: THC (induces a high) and cannabidiol (CBD, nonintoxicating). Medical cannabis (MC) products may be THC rich, CBC rich, or balanced. Medical cannabis has been legal in Canada and Israel for many years. THC is illegal in the US, but CBC derived from industrial hemp (< 0.3% THC) is legal, and MC is legal in many states. Research interest into CBD is increasing because of documented antiemetic, analgesic, alerting, antianxiety, anticonvulsant, antipsychotic, anti-inflammatory, and antioxidant properties (Russo, 2017). Many people are using widely available nonstandardized, over-the-counter CBD products to self-manage symptoms (Hight, Lesser, Johnson, & Kaur, 2020; VanDolah, Bauer, & Mauck, 2019). CBD most likely has entourage effects with THC, other cannabinoids, and terpenes in cannabis that counter sedating and other effects, and THC "hangover."

In an Israeli MC study, 2,970 symptomatic cancer patients were prospectively followed by an interprofessional oncology team over a 2-year period (Schleider et al., 2018). Before starting MC, patients had 11.1 ± 7.5 symptoms (e.g., N/V, pain, and fatigue). One or more of 16 cannabis varieties (with varying THC/CBD concentrations) in different formulations (flowers, capsules, cigarettes, and oils) and doses were individualized for each patient. Ninety-six percent of patients who continued MC for 6 months reported improvement or disappearance of several symptoms, with 91% for N/V (two thirds discontinued other antiemetics).

Responses of more than 80% improvement were documented for pain (36% stopped all opioids), fatigue, digestive problems, anorexia, depression or anxiety, and other symptoms. Patients rating their QOL as good increased from 18.7% at baseline to 69.5% at 6 months.

Three recent US studies surveyed patients about MC/marijuana use; 222 of 926 (24%), 32 of 175 (18.3%), and 83 of 299 (27%) used cannabis to control one or more symptoms, most commonly nausea or N/V, pain, appetite, insomnia, anxiety, dealing with stress, and depression (Pergam et al., 2017; Saadeh & Rustem, 2018; Wilson, Masterson, & Broglio, 2019). When asked explicitly, patients wanted information about cannabis from their oncology providers (usually not provided). Patients were left to their own devices to try cannabis to self-manage symptoms. Although these states had MC programs, not all patients had MC cards, perhaps due to difficulty finding an approved physician to certify a qualifying diagnosis, or associated costs of obtaining a MC card or buying products from an approved dispensary.

Unlike other “nonpharmacologic” measures, MC is increasingly becoming part of mainstream medicine. For instance, in states where MC is legal, physicians (and APs in a few instances) must certify patients with allowable diagnoses to purchase cannabis from approved dispensaries. Even if MC remains illegal at the national level, APs need to help patients make decisions about how to use it (e.g., smoking, vaping, edibles), possible side effects (especially impaired motor function, increasing the risk for vehicle accidents), associated costs for MC cards and cannabis products, potential drug interactions with MC, and so forth. A recent survey of Canadian NPs (who had recently been legislated MC prescriptive authority) is instructive (Balneaves, Alraja, Ziemianski, McCuaig, & Ware, 2018). Almost 80% agreed NPs should be authorized to approve MC, but responded that knowledge gaps, lack of clinical guidelines, and inadequate information about appropriate use were major barriers to use. NPs recognized they had great educational needs about clinical aspects of MC (e.g., dosing protocols, formulating effective treatment plans, similarities and differences among varieties, using different formulations, and potential benefits and risks), basic information



**Figure 2.** P6 acupressure point. Patients can be taught to apply an acupressure band to P6 of the dominant arm (sometimes applying it to the other arm is more effective). P6 is located by placing three fingers at the radial pulse with distal finger on the lowest wrist crease and sliding the fingers medially to between the tendons; P6 is three finger widths above the wrist crease.

about the ECS and cannabinoid mechanisms of action, and current laws and regulations impacting NP practice.

### IMPLICATIONS FOR ADVANCED PRACTITIONERS

Oncology pharmacists, PAs, NPs, and CNSs recognize their value-adding roles of providing and promoting primary palliative care for all patients across the illness continuum, as well as collaborating with oncology and other care professionals to deliver care that enhances patients' quality as well as quantity of life. This often centers on maximizing control of challenging symptoms, such as N/V unrelated to cancer therapies. Clinical trials buttress our current standard of care antiemetics for CINV, but these drugs are expensive (except for olanzapine), and there is no research to directly support their use in palliative care. Advanced practitioners therefore use palliative management principles for N/V (Table 3), as well as clinical knowledge gained from caring for other patients. Oncology APs should incorporate such clinical evidence and keep abreast of new information in symptom management literature. It will also be important to be aware of evolving knowledge that may lead to better therapies for N/V, particularly a basic understanding of the endocannabinoid system and its possible role in the interoception of nausea and potential targeted therapies for nausea. ●

**Table 3. Pharmacologic Principles for Palliation of Nausea and Vomiting**

- Antiemetic selection: weigh possible benefits and harms, consider patient life expectancy (e.g., weeks to months vs. hours to days), site of care (home, hospital, hospice), family involvement, ease of administration, costs
- Use po antiemetics when possible (unless patient is vomiting or has severe gastric stasis)
- Start with a single antiemetic, unless there is a clear rationale for a combination regimen (e.g., haloperidol plus dexamethasone for MBO or IICP).
- Start at a relatively low dose (e.g., po metoclopramide at 10 mg every 6 hours)
- Titrate doses up as indicated; monitor efficacy (nausea control, vomiting control, side effects)
- If first antiemetic inadequately controls nausea or vomiting or causes dose-limiting side effects, add second antiemetic with different receptor actions
- Consider "broad spectrum" antiemetic (olanzapine or mirtazapine) in patients with > 1 probable cause for N/V
- If nausea or N/V uncontrolled despite (maximized) doses of first- and second-line antiemetics:
  - » Consider other causes and interventions (e.g., hydroxyzine or scopolamine TD may decrease motion-related nausea or N/V with intermittent MBO)
  - » 1 or 2 scopolamine patches to the upper chest; may require parenteral doses for 12–16 hours to overcome skin depot effect
  - » Prescribe less commonly used agents (mirtazapine or olanzapine, if not previously used, dronabinol, chlorpromazine)
- One dose daily of long half-life agents (olanzapine, mirtazapine, dexamethasone). Bedtime administration if sedating (olanzapine/mirtazapine) or paradoxical sedation (dexamethasone)
- Suspected or confirmed MBO: Avoid antiemetic drugs with prokinetic effects, particularly metoclopramide and erythromycin, and perhaps mirtazapine
- Explore and teach nondrug, adjunctive measures with interested patients when feasible and practical
  - » Acupressure bands: where to buy, how to use
  - » Ginger: capsules available at health food stores, cookies, or tea (make with ginger root)
  - » State law status of medical cannabis, current or previous recreational cannabis use, known benefits and harms, how to select CBD products

Note. MBO = malignant bowel obstruction; ICP = increased intracranial pressure; TD = transdermal.

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