Current Oncology Reports (2020) 22: 1
https://doi.org/10.1007/s11912-020-0871-6

PALLIATIVE MEDICINE (A JATOI, SECTION EDITOR)

Nausea and Vomiting: a Palliative Care Imperative

Rita J. Wickham [1]

Published online: 20 January 2020

Abstract

Purpose of Review This review was undertaken to survey recent literature for research reports and comprehensive clinical reviews addressing the pharmacologic management of nausea and vomiting (N&V) in advanced cancer. The goal was to integrate findings in a comprehensive article that incorporates palliative care concepts into antiemetic treatment.

Recent Findings There are few published studies of N&V in advanced cancer; such research may be limited by the multicausal nature of N&V and participant burden to patients with life-limiting disease. Most articles are written by oncologists who also specialize in palliative care, and those addressing adverse effects of drugs used as antiemetics are found in other literature. Articles addressing more novel therapies, like cannabinoids and medical marijuana, are uncommon in the oncology literature.

Summary N&V in patients with progressive or advanced cancer is often multicausal. Nausea is more common and persistent, and even mild nausea is bothersome and may cause anxiety or depression. The mechanisms of nausea and vomiting overlap, but different neural pathways constitute the final pathway for each—the brainstem for vomiting and higher brain regions for nausea. Common causes of N&V in advanced cancer include constipation, opioids, and malignant bowel obstruction. About 40% have undetermined causes and may be exacerbated by impaired gastric emptying, chemical imbalances, or other factors. Several drugs that have antiemetic effects and act at different receptors are used to palliate N&V. There is a paucity of research that supports palliative antiemetic choices, and other research is needed to define potential therapeutic strategies that capitalize on differences between nausea and vomiting.

Keywords Nausea and vomiting · Palliative care · Extrapyramidal syndromes · Prolonged QT

Introduction

Nausea alone or nausea and vomiting (N&V) are common and often multicausal palliative care problems for persons with cancer. Estimated rates of N&V in advanced cancer vary highly, but incidence alone does not tell the entire story. Oncology professionals, particularly those in medical oncology, are well-versed in standard-of-care antiemetics for chemotherapy-induced N&V (CINV). However, there is scant research regarding palliative management of N&V. This article will address the mechanisms of nausea and of vomiting, the causes of N&V in advanced disease, the management principles, and the pharmacologic agents, incorporating palliative care principles of weighing benefits and burdens.

Box 1 Case—Mary F, 53 years old with recurrent ovarian carcinoma

Mary's gynecological oncologist recently started her on carboplatin (4.5 AUC) plus paclitaxel (175 mg/m^2) every 21 days for recurrent ovarian cancer. The hospital palliative care service (PCS) was consulted because of Mary's persistent moderate to severe nausea. The PCS APN notes Mary appears overweight but not obese, mildly chronically ill, and may have (by appearance) ascites. She reports feeling "queasy" almost all of the time, and this worsens after chemotherapy. She is also troubled by abdominal fullness and early satiety after eating, and a little worsening of nausea when she moves her head. Her mood is even; she does not seem depressed or anxious. She denies pain, constipation, and other symptoms. Ondansetron plus DEX have been ordered for day 1 and for 3 days after chemotherapy. Mary's treatment goal is palliative control, with a life expectancy of months to years.

Possible causes of nausea: acute and delayed CINV (suboptimal antiemetics), gastroparesis and early satiety (related to cancer and chemotherapy), mild abdominal compression (ascites), minor element of motion sickness, and anxiety related to inadequate control of CINV heightening risk.

This article is part of the Topical Collection on *Palliative Medicine*

✉ Rita J. Wickham
rita.j.wickham@gmail.com

[1] Adjunct Faculty, Rush University College of Nursing, Chicago, IL, USA

Goals of Care, Prognosis, and Survival

Palliative care, symptom control, and quality of life (QOL) are paramount for patients at all points across the cancer continuum—from diagnosis and treatment to recurrence, progression, and end-of-life or to survivorship care [1]. Many people have curable cancer at diagnosis but most with recurrent or advanced disease do not. It is thus important to estimate each patient's approximate survival: years, months to years, weeks to months, days to weeks, or hours to days—usually being a little optimistic. This aids in thinking about appropriate interventions and weigh benefits against acceptable burdens/harms. The steps in palliative care management of N&V are to 1) determine or confirm goals of care; 2) estimate a patient's prognosis and duration of survival; 3) identify possible causes; 4) consider whether causes are reversible or require palliative interventions; and 5) select treatment options, considering potential benefits and burdens. Hawley's [1] model of integrative palliative care (Fig. 1) can also be used for shared decision-making with the patient.

Nausea is a greater problem than vomiting in advanced cancer, and incidence increases with disease progression. A study that examined symptom severity and interference found patients rated nausea (after pain and fatigue) as most severe and most bothersome [2]. Even mild nausea (< 4/10) was bothersome, and patients with the most severe and most bothersome symptoms were highly depressed and anxious.

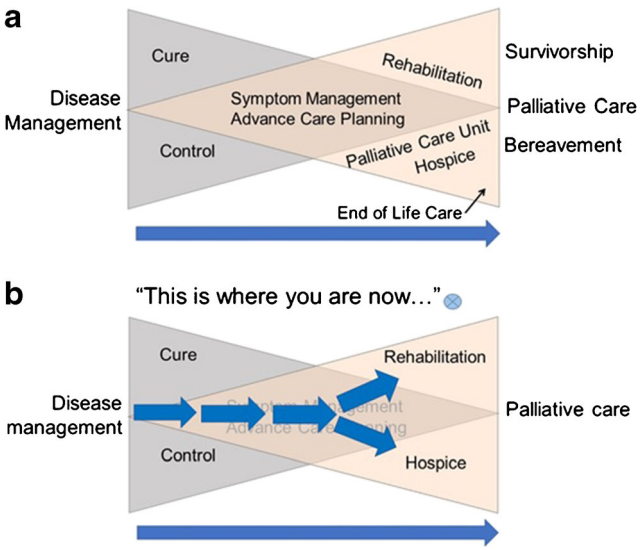

Fig. 1 Bow tie model of integrated palliative care. **a** The Bow Tie Model (BPC) illustrates that palliative care is integrated across and throughout the disease continuum, including diagnosis and treatment, survivorship or hospice and end-of-life care. **b** The BPC can be used as a patient teaching tool to aid in discussing treatment goals and focus of care. Adapted from Journal of Pain and Symptom Management, Volume 47, Issue 1, "The Bow Tie Model of 21st Century Palliative Care," pages e2–e5, ©2014, with permission from Elsevier.

Mechanisms of Nausea and Vomiting

Nausea and vomiting are different physiologic processes initiated by the same events, having distinctive and overlapping mechanisms [3•, 4, 5••]. Activation of the same neural pathways has been assumed to induce nausea and vomiting, but newer information questions this notion. Vomiting, the forceful expulsion of gastric contents through the mouth, is a complex reflex mediated in the medullary brainstem nucleus tractus solitarius (NTS) and dorsal motor nuclei of the vagus (DMV)—the so-called central pattern generator or vomiting center (VC). Emesis occurs by coordinated efferent gastrointestinal (GI), diaphragmatic and abdominal muscle actions.

Nausea, an unpleasant and difficult to describe sensation in the stomach, is accompanied by a feeling of the need to vomit. Nausea has cognitive, emotional, and interoceptive domains, and forms in higher brain centers—the anterior insular cortex (AIC) and the anterior cingulate cortex (ACC), complementary regions activated together during subjective or emotional feelings. All internal sensations, including nausea, come together in the AIC. The ACC mediates cognitive and emotional influences, the amygdala adds negative value (stress, fear, and disgust), and other cortical regions also add input and influence [6, 7]. Nausea is more common, persistent, and difficult to control, more disabling and distressing than vomiting, and is associated with QOL symptoms (e.g., appetite loss) [8]. Physiologic stress response manifestations, including elevated plasma vasopressin, gastric dysrhythmia and decreased gastric emptying, and autonomic nervous system effects, often accompany nausea [5••, 9].

Causes of Nausea and Vomiting in Palliative Cancer Care

N&V in advanced cancer are often multifactorial and may have unclear etiologies. In a study of 821 adults with metastatic solid tumors, 375 (46%) had some degree of nausea; the most common identifiable causes were constipation (31.5%) and opioids (16.6%) [8]. "Other" causes (fungal infection or bacterial infections and reflux) accounted for 21.6%, but 42.3% had no identifiable cause. Opioid-induced N&V is not well understood, and antiemetics are often ineffective [10]. Other medications that may cause nausea include cardiovascular (e.g., digitalis [toxicity], antiarrhythmics, beta blockers and calcium channel antagonists), diuretics, hormones, GI (e.g., sulfasalazine, azathioprine), and central nervous system (CNS) (e.g., anticonvulsants) agents and theophylline [9].

Chronic nausea syndromes include impaired gastric emptying (35–45% of cases), characterized by intermittent nausea, early satiety and fullness or bloating after eating; nausea is relieved by small-volume emesis [11]. Chemically-caused

nausea (30–40% of cases) is aggravated by the sight and smell of food and not relieved by vomiting. Early morning N&V with headache suggests raised intracranial pressure (ICP), nausea aggravated by movement points to a vestibular component, and N&V with anxiety suggests a cortical component; these account for > 15% cases. Bowel obstruction accounts for 10–30% cases (discussed later).

Assessing Nausea or Vomiting

Palliative management approaches to N&V, driven by assessment, are etiological or empirical [12, 13]. Diagnostic measures (and antiemetic selection) are tailored to suspected causes and focus on putative mechanisms, neurotransmitters and receptors involved. If a specific cause cannot be identified, the empirical approach dictates selecting a broad-spectrum, multipurpose antiemetic [9]. Assessment, outlined in Table 1, focuses on identifying causes of N&V and correcting reversible causes (e.g., suppository or enema to alleviate rectal impaction and scheduled laxatives to prevent constipation, switching to a different opioid when a first causes nausea, or discontinuing other drugs that cause nausea). Imaging procedures and other tests should be limited to those that confirm or rule out suspected causes and would likely impact treatment [14].

Malignant Bowel Obstruction

Malignant bowel obstructions (MBO) secondary to diffuse peritoneal disease, or from direct or indirect obstruction from malignant adhesions, is most common in patients with end-stage (life expectancy of weeks to months) colorectal or ovarian cancer [14]. MBO typically occurs and remits over several weeks; multiple levels of subacute obstruction upregulate peptides that inhibit gut motility and intensify mucosal edema, thereby increasing retained intraluminal secretions. All patients with complete MBO have nausea and most vomit, have abdominal distension, colicky pain, and have had no stools or flatus for ≥ 72 h [12, 14, 15•].

Patients with intractable vomiting or distressing gastric distention require nasogastric tube (NGT) placement with low, intermittent suction to decrease symptoms, prevent aspiration and rest the bowel, allowing an intermittent MBO to resolve. NGTs for longer than a few days may cause painful nostril ulcers, pharyngitis, or esophageal erosion [12, 14]. If NGT drainage > 1 l/24 h continues despite treatment, a venting percutaneous gastrostomy will alleviate N&V and may allow eating small amounts of soft or liquid foods for pleasure. Initial medical management includes intravenous (IV) fluids and electrolytes, a short course (< 10 days) of dexamethasone (DEX) or methylprednisolone to lessen inflammation and edema and add antiemetic effect, along with metoclopramide,

Table 1 Focused assessment for nausea and vomiting

History
Assess nausea and vomiting separately
Onset, relationship to precipitating event (e.g., chemotherapy-induced nausea and vomiting) and duration
Intensity/severity (use same scale as used for pain, other symptoms (numerical rating [0 to 10] or verbal descriptor (none, mild, moderate, severe)
Frequency and character of vomiting episodes (e.g., large-volume suggests MBO; persistent or intermittent)
Temporal factors (relationship of vomiting to nausea, N&V to chemotherapy, drug dosing)
Aggravating factors ("Does anything make your nausea, vomiting worse?"—sight/smell of food, eating, movement)
Relieving factors ("Does anything make nausea, vomiting better?"—medications, over-the-counter remedies, nonpharmacologic measures)
Ability to keep fluids down (may influence antiemetic formulation options)
Associated symptoms (e.g., pain, altered bowel habit, headache, colic, polydipsia, polyuria, cognitive changes)
Assess for constipation, which can exacerbate nausea
Mood (anxious, depressed)
Review medications (including doses and schedules)
Basic blood tests (e.g., electrolytes, liver function tests, pancreatic enzymes, blood glucose), urinalysis aid in identifying possible correctable causes (e.g., electrolyte abnormalities, dehydration, hyperglycemia, infection)
Physical examination
Papilledema suggests brain metastasis
Abdominal assessment: inspect for distention; auscultate for hyperactive or borborygmi with obstruction, or absent bowel sounds with ileus; palpate for discreet tumor masses or diffuse, woody abdomen, stool, hepatomegaly, fluid wave, or tenderness; percuss for tympany that suggests obstruction or dullness with ascites
Rectal exam for stool; if present, start with rectal suppository
Orthostasis suggests autonomic insufficiency

Information from 9, 11, 13

Table 2 Managing nausea or vomiting in palliative care

Drug	Indications	Dosing	Comments
Metoclopramide	*GI* MBO (see comment) Gastroparesis	PO (tabs, ODT, liquid): 30-240 mg/d IV, IM, SC: 40-120 mg/d	Receptors: D2; 5HT3; 5HT4 Contraindicated for suspected, confirmed complete MBO AEs: EPS, depression, headache
Haloperidol	Squashed stomach (hepatomegaly, ascites) Chronic, unexplained Chemical (opioids, other drugs; infection; metabolic, (hypercalcemia)	PO: 1 mg PO q 12 h + q 4 h prn SC, IV: 0.5-2 mg q 4 h CIV: 5 mg /d	Receptors: D2 More frequent dosing may worsen AEs: dry mouth, sedation, EPS, risk for prolonged QTC
Olanzapine		PO (tabs, ODT): 2.5–20 mg at HS (average dose 5-15 mg/day) Elderly, frail: start at 2.5 mg /d	Receptors: D- 1, 2, & 4; 5HT2- A, & C, 5HT3; α1; H1; M - 1, 2, 3, & 4 AEs: sedation, reversible hyperglycemia; EPS unlikely
Mirtazapine		PO (tabs, ODT) 7.5-15 mg at HS (average dose 7.5-45 mg/d)	Receptors: D- 1, 2; 5HT1 -A, B, D; 5HT2 -A, B, C; 5HT3; α 1, 2; H1; M1 May improve appetite, weight, sleep, analgesia AEs: mild sedation, dry mouth, risk for prolonged QTC
Phenothiazines			All: Receptors: D2
Levomepromazine		PO: 6.25-25 mg 2 X/d IM, IV: 25-50 mg/d	Receptors: D2; H1; M1; α-1; 5HT2 Skin irritation with SC administration common AEs: drowsiness, dry mouth or constipation (tolerance may develop); EPS
Domperidone		PO: 5-10 mg Q 6-8 h PR: 25 mg Q 8-12 h IM: 5-10 mg Q 3-4 h (max 40 mg/d)	Receptors: peripheral D2 AEs: colic, risk for prolonged QTC, low risk for EPS
Chlorpromazine		PO (tabs, syrup): 10–25 mg Q 4-6 h IV: 12.5 mg Q 4 h PR: 25 or 100 mg Q 8-12 h Titrate to effect (max 100 mg Q 4 h)	Receptors: D-1,2,3,4; 5HT- 1A,2A; α 1,2; M 1,2 SC administration causes severe tissue necrosis AEs: EPS, risk for prolonged QTC suppositories may be inserted vaginally in women
Prochlorperazine		PO: 5-10 mg Q 6-8 h PR: 25 mg Q 8-12 h IM: 5-10 mg Q 3-4 h (max 40 mg/d)	Initial geriatric dose: decrease adult dose by 50%; titrate slowly (1-2 time/week); max daily dose 75 mg AEs: EPS
Cannabinoids			
Dronabinol Nabilone		PO: 5 mg 1-2 X /d; titrate to 10 mg 2X/ d or to AEs PO: 1–2 mg 2X /d	Receptors: CB1 dizziness, dry mouth, increased appetite, sleepiness or feeling high
Corticosteroid (e.g. methylprednisolone, dexamethasone)	CNS: tumor, RT MBO, hepatomegaly (squashed stomach)	Equivalent doses: DEX 0.75 mg; prednisone 5 mg, prednisolone 5 mg & methylprednisolone 4 mg	AEs: insomnia, increased appetite, muscle weakness, neuropsychiatric (depression, anxiety or irritability, or psychosis), and dyspepsia (increase with duration of use)
Other agent			
Octreotide	MBO	300- 600 mcg/24 h SC for 6 days; Effective - convert to lanreotide depot Q 4 weeks; ineffective – discontinue	AEs: flatulence, fatigue, flu-like syndrome, headache, dizziness, diarrhea
Anticholinergic antisecretory			
Glycopyrronium/ glycopyrrolate	MBO	0.1-0.2 mg SC or IV 3-4 times d 20 mg SC X 1, then Q 4 h	AEs: drowsiness, constipation, dry mouth Apply 1 or 2 scopolamine patches to upper chest or back, areas of high blood flow, rather than behind the ear

Table 2 (continued)

Drug	Indications	Dosing	Comments
Butylscopolamine / hyoscine Scopolamine		IV, SC, IM - 0.3-0.65 mg Q 6-8 h patch Q 72 h	

ODT oral dissolvable tablet, *PO* oral, *IM* intramuscular, *SC* subcutaneous, *PR* rectal, *CIV* continuous IV infusion, *CSC* continuous SC, *Q* every, *d* day, *HS* bed time
Information from 8, 11–13, 16, 19, 22, 28, 39, 43, 51, 54

haloperidol, olanzapine, or levomepromazine [12, 14, 15•]. Prokinetic-antiemetics (metoclopramide, mirtazapine or domperidone, and erythromycin) are contraindicated for suspected complete MBO because of increased risks for colicky pain and bowel perforation.

Octreotide, a synthetic somatostatin analog, is the first-line agent (with haloperidol or other antiemetic) for patients with complete MBO or peritoneal carcinomatosis, but high cost may dictate reserving it for when anticholinergic antisecretory drugs are ineffective for obstructive symptoms [12]. Octreotide blocks vasoactive intestinal polypeptide (VIP) release, reduces water, sodium, and chloride movement into the bowel, and increases water and electrolyte absorption from the bowel [16]. It more effectively and rapidly decreases vomiting episodes and nausea than anticholinergic antisecretory drugs [17, 18]. It is practical to start octreotide and escalate the dose as needed, and convert to lanreotide depo after 6 days if effective, or discontinue if not.

Anticholinergic antisecretory drugs (scopolamine, hyoscine-N-butyl bromide, or glycopyrrolate) have antispasmodic effects and reduce GI secretions [12, 14, 15•]. These agents—particularly glycopyrrolate—are generally well tolerated. Transdermal scopolamine is a convenient alternative to oral or parenteral administration.

Antiemetics Used in Palliative Care

In empirical management of N&V, a single antiemetic is started to assess its efficacy and adverse effects (AEs) [19]. If the drug decreases but does not totally alleviate N&V, the dose is increased as feasible. Antiemetics with no efficacy or that cause dose-limiting AEs should be discontinued and another started. Unlike antiemetics for CINV that target a single receptor, older drugs are "dirty" and bind to > 1 receptor (Table 2), allowing for a broader therapeutic effect but perhaps increasing AEs.

The most recent Multinational Association for Supportive Care in Cancer (MASCC) guidelines reiterate that few, small studies support metoclopramide and haloperidol as first- and second-line antiemetics in advanced cancer [12, 20]. Prescribing patterns may be changing; in a recent report, olanzapine (followed by corticosteroids) is most commonly prescribed for patients with nausea [8].

Metoclopramide

Metoclopramide (titrated to effect) is still an antiemetic of choice in advanced cancer, with widely varying suggested oral (PO) and parenteral (intravenous, IV or subcutaneous, SC) doses [12, 20, 21]. Its antiemetic properties are related to antagonist effects at dopamine (D2) and serotonin3 (5HT3) receptors (at doses > 120 mg/day) [16, 21, 22]. Metoclopramide

is also a 5HT4 agonist that accelerates gastric emptying and may alleviate gastroparesis [8]. Prokinetic actions explain its rationale for patients with partial MBO or ileus, and it is the same reason metoclopramide is contraindicated in patients with colic or complete MBO.

Extrapyramidal Syndromes

D2 antagonists are also responsible for acute extrapyramidal syndromes (EPS)—dystonias (~95% of metoclopramide-induced EPS's) and akathisia and later occurring reactions. EPS occurs in only ~0.2% (1 in 500) of patients taking metoclopramide [8, 21], but the European Medicines Agency (EMA) (https://www.ema.europa.eu/en/news/european-medicines-agency-recommends-changes-use-metoclopramide) and the US Food and Drug Administration (FDA) both recommend limiting its use because of acute EPS and tardive dyskinesia—unless therapeutic benefit outweighs potential risks for particular patients. This is usually true for palliative care patients, particularly as most are at low risk and can be carefully monitored [8].

Dystonias (e.g., torticollis opisthotonus), uncontrollable contractions in ≥1 body muscle groups with prolonged body part twisting, may cause patients to feel a frightening sense of being unable to breathe [22, 23]. Dystonias occur after a D2 antagonist is started or a dose increase, happening shortly after administration to within a few hours or days and resolving within 24–48 h after stopping the offending drug [24]. Dystonias are most likely in children (6 times greater risk than adults) and young adults (under age 30), and are less common after age 45 [24, 25].

Akathisia secondary to metoclopramide or other D2 antagonists is often not recognized because it is infrequent and mimics other conditions (e.g., agitation, anxiety, restless leg syndrome, or movement disorder). Akathisia occurs in the lower extremities and is more common in older adult. Patients feel distressing tenseness or anxiety, restless, have the urge to move—like they cannot sit or stand still or have drawing sensations in their legs [24, 25]. They may persistently fidget, repetitively tap or shuffle their feet, shift their weight, rock, or pace. Akathisia may start within days after treatment and usually resolves after the drug is stopped. High doses and long treatment periods (months to years) increase the risk factors for later effects—tardive dyskinesia (involuntary repetitive, jerking movements in the face, neck, and tongue) and Parkinsonism, 1% and 4% of reactions respectively, are potentially irreversible.

The cornerstones of using medications that can cause EPS—especially acute reactions—are knowledge, patient/family teaching, consistent patient monitoring, and intervention/management. Physicians, nurses, and pharmacists must know that D2 antagonists (metoclopramide, haloperidol, and phenothiazines) can cause EPS, articulate the clinical manifestations of dystonias and akathisias, and identify first line

Table 3 Acute extrapyramidal syndromes

Acute dystonic reactions	Management
Torticollis—abnormal flexion, extension, or twisting of neck muscles	Administer IV agents over 2–3 min; usual response within 10–20 min
Oculogyris—spasm of the extraocular muscles, involuntary upward deviation of the eyes	Antihistamine: diphenhydramine 50 mg IV, then 25–50 mg PO every 6 h for 1–2 days to prevent recurrence
Opisthotonis—back muscle spasms with extreme arching and thrown back head	Benzodiazepine: diazepam 0.1 mg/kg IV or lorazepam 0.05 to 0.10 mg/kg
Laryngeal dystonia—dysphonia, stridor	Centrally acting anticholinergic agent: benztropine 1–4 mg IV, then 1–2 mg PO BID for up to 7 days to prevent recurrence
Buccolingual—trismus, rictus grin (sustained facial muscle spasm appears like grinning), dysarthria, dysphagia, grimacing, tongue protrusion	
Tortipelvic crisis—abnormal contractions of the abdominal wall, hip, and pelvic musculature	
Pseudomacroglossia—patient describes sensation of tongue swelling and protrusion	
Akathisia	
Acute akathisia—occurs as soon after D2 antagonist started or dose increased; with intense dysphoria and restlessness	Lower offending medication dose or switch to alternative drug
	Low-dose mirtazapine (≤15 mg po daily) (first-line treatment)
Chronic—persists >6 months after last dose of offending medication; mild dysphoria and restlessness, limb and orofacial dyskinesia	Benzodiazepine (e.g., lorazepam or diazepam) may be useful for anxiety, other symptoms
Tardive akathisia—delayed onset, usually >3 months since offending medication; often associated with tardive dyskinesia	Anticholinergic (e.g., benztropine 2 mg po bid) when other patient has other EPS manifestations; mainly for patients with concurrent Parkinsonism

Information from 21, 24, 25, 26

Table 4 Medications used in oncology that may increase QTc and the risk for torsades de pointes

Known risk of TdP	Possible risk of TdP	Conditional risk of TdP
Drugs prolong QT; clearly associated with risk for TdP, even when taken as directed	Drugs can prolong QT but lack evidence for risk of TdP when taken as directed	Drugs associated with TdP; only under certain conditions of use or facilitating conditions that create or induce TdP
Antiemetics		
Chlorpromazine	Dolasetron*	Metoclopramide*
Domperidone*	Granisetron	Olanzapine*
Erythromycin*	Mirtazapine*	
Haloperidol*	Palonosetron	
Ondansetron*	Promethazine*	
Droperidol*	Tropisetron*	
Anti-cancer agents		
Aclarubicin*	Abarelix*	Inotuzumab ozogamicin* Amsacrine*
Arsenic trioxide*	Apalutamide*	
Oxaliplatin*	Bendamustine*	Ivosidenib*
Vandetanib*	Bortezomib*	Lapatinib*
	Bosutinib*	Lenvatinib*
	Cabozantinib*	Leuprolide*
	Capecitabine*	Midostaurin*
	Ceritinib*	Necitumumab*
	Cobimetinib*	Nilotinib*
	Crizotinib*	Osimertinib*
	Dabrafenib*	Panobinostat*
	Dasatinib*	Pazopanib*
	Degarelix*	Ribociclib*
	Encorafenib*	Romidepsin*
	Epirubicin*	Sorafenib*
	Eribulin mesylate*	Sunitinib*
	Fluorouracil*	Tamoxifen*
	Gilteritinib*	Tipiracil*
	Glasdegib*	Toremifene*
		Vemurafenib*
		Vorinostat*

Information available at https://crediblemeds.org/healthcare-providers/

management agents used for each (Table 3). A simple instruction sheet (1 or 2 syllable words that avoid medical jargon, short sentences, large font, brief content) can reinforce verbal teaching about EPS and include actions to take and who to call. Continued monitoring and communication between care providers and patient are essential to timely recognition and interventions [8, 23].

Dystonic reactions are reversible with an IV antihistamine, benzodiazepine, or centrally acting anticholinergic agent administered over 2–3 min [21, 23]. Anticholinergic agents are less effective for akathisia than for acute dystonia or Parkinsonism. Low-dose (15 mg po) mirtazapine, a 5HT2A receptor antagonist, is the recommended first-line agent to alleviate akathisia, and a benzodiazepine may be added for anxiety [24–26]. Mirtazapine is as effective and better tolerated than propranolol (a beta-adrenergic blocker), limited by potential hypotension and bradycardia.

Haloperidol

Haloperidol is a butyrophenone and first generation (typical) antipsychotic agent used as an antiemetic in palliative care and is the first-line drug for delirium [16]. It has a long half-life (12–35 h) and can be given in a single dose at bedtime, which may enhance adherence [27, 28]. Antiemetic doses are PO 1.5–3 mg (or parenteral equivalent—half of PO doses) over 24 h; higher doses may not add further benefit. Haloperidol may control nausea in 65% of patients, and administering it with ondansetron may alleviate intractable N&V in advanced cancer [28, 29]. A recent prospective pharmacovigilance

study of haloperidol for N&V was implemented in 22 multinational centers. One hundred fifty consecutive palliative care patients (86% with cancer) were started on haloperidol (median PO or IV dose 1.5 mg (0.5–5 mg)/24 h) [30]. At baseline, nausea was moderate (89%) or severe (11%) and 96.6% of patients had vomiting. Benefits were assessed at 48 h; N&V were completely controlled in 114 (79%). Harms were documented in 62 (26%) of patients on day 7, most commonly constipation, dry mouth, and sleepiness.

Haloperidol is a selective D2 receptor antagonist and can induce akathisia and tardive dyskinesia. Akathisia might incorrectly be assessed as terminal agitated delirium, and the dose mistakenly escalated instead of correctly stopping haloperidol and administering a 5HT2 antagonist [31]. Haloperidol has a black box warning for QTc interval prolongation and a risk for torsades de pointe (TdP). Table 4 lists other antiemetics (and many anticancer agents) that also have a confirmed or potential risk for prolonged QT and TdP [32, 33•]. However, most of these are only contraindicated in patients with congenital long QT syndrome, which is rare (1 in 2500 births) and characterized by an inherited germline potassium or sodium channel LQT gene mutation, prolonged basal QT interval, T wave abnormalities, syncopal episodes, and sudden cardiac death in otherwise healthy children and teenagers [34]. Routine electrocardiograms (EKGs) are not indicated in terminally ill patients and most non-cardiologist clinicians would not be able to appreciate millisecond (msec) QT changes [22].

Olanzapine

Olanzapine is useful for refractory nausea and for other symptoms (e.g., sleep, anxiety, and delirium); it has a long half-life (33 h, range 21–54 h) and can be given once daily (plus a second prn dose) [35]. An oral (PO) dissolvable form may obviate the need for parenteral administration. Olanzapine often increases appetite and causes weight gain, increases leptin, insulin, and blood lipids, and may cause asymptomatic transaminase elevations. It is a second-generation (atypical) antipsychotic with moderate to high affinity for multiple D, 5HT, alpha adrenergic (α), histamine (H), and muscarinic cholinergic (M) receptors [22, 35, 36]. EPS is much less common than with haloperidol [31].

In a personal conversation, Dr. Rudy Navari stated psychiatrists' observations that olanzapine decreased nausea led to numerous successful prospective trials of olanzapine for CINV (R Navari 2019, personal communication, 22 June). Olanzapine is the recommended second-line agent for palliative patients with N&V uncontrolled by standard antiemetics. A prospective pilot study suggested a dose-response: cancer patients' nausea decreased significantly as placebo was changed to olanzapine 2.5 mg and escalated to 5 mg and then 10 mg [37]. Five and 10 mg doses were significantly superior to 2.5 mg, but patients rated QOL as highest with 5 mg, perhaps because of AEs. After other antiemetics (haloperidol, ondansetron, metoclopramide, and promethazine) were ineffective, MacKintosh [31] successfully managed a patient's N&V with olanzapine; he subsequently accrued a prospective case series of 14 cancer patients whose N&V were similarly controlled with olanzapine 5 mg at bedtime (HS). In another retrospective study, olanzapine (2.5 to 20 mg/day) significantly reduced nausea in 90% and vomiting frequency in 80% of cancer patients with MBO [38]. Olanzapine oral dissolvable tablets (ODT) are suitable for patients with dysphagia or MBO and may obviate the need for SC or IV administration [16].

Mirtazapine

Mirtazapine, a tetracyclic antidepressant, may increase appetite, lead to significant weight gain, and lessen several other symptoms [39, 40]. Allen and others [40] completed a retrospective chart review of medically ill inpatients (most without psychiatric diagnoses) for whom psychiatric liaison practitioners had recommended mirtazapine for specific physical symptoms. Over 4.5 years, 475 were started mirtazapine for sleep, nausea, pain, or appetite; improvement was noted for about 38%, 37%, 36%, and 24% of patients, respectively. Mirtazapine was generally well tolerated; the most common AEs were daytime sedation (5.3%), worsening mental status (2.3%), and nightmares (1%).

Mirtazapine has complex pharmacology and high affinity for numerous D, 5HT, α adrenergic, H, and M receptors [41]. It also has prokinetic properties. Healthy adults with symptomatic gastroparesis started on 15 mg PO at HS reported significantly improved nausea, vomiting, retching, and appetite loss [42]. The effects mirtazapine on gastric emptying was also studied in 28 cancer patients with anorexia [43]. At baseline, 7 (25%) had normal gastric emptying, whereas after 15 days of mirtazapine (7.5 mg once daily), this was significantly improved in 64% and 52% had normalized gastric emptying. It is well tolerated that side effects are generally mild and may diminish, even with dose increases. Mirtazapine has a long half-life (21 h, range 20–40 h) and usually require once daily dosing [35].

Corticosteroids

Corticosteroids, thought to act via several unidentified mechanisms and pathways, may be effective for N&V from multiple or undetermined causes, particularly when administered with other antiemetics. They have broad-spectrum antiemetic activity for N&V from central nervous system (CNS) or GI causes, including primary or metastatic brain tumors, raised intracranial pressure (ICP) from other causes, MBO, or chronic nausea of advanced cancer [11, 12, 19]. Pharmacokinetic differences contribute to variable efficacy and AEs. DEX, most commonly prescribed, has a long half-life (≤ 36 h) and

can be administered once daily, while duration of action for prednisone, prednisolone, and methylprednisolone are 12 to 36 h [19]. Large daily doses and longer treatment courses lead to a greater likelihood of AEs. Thus, the lowest possible corticosteroid dose should be used for the shortest time, the dose titrated down once maximal effect is reached, after an adequate trial (7–10 days) without desired effect or if dose-limiting AEs occur [11, 44].

In a recent systematic review of corticosteroids for N&V in advanced cancer, only 3 studies met inclusion criteria; these compared PO DEX with placebo, chlorpromazine, metoclopramide, or tropisetron [45]. The authors concluded evidence is insufficient to support or refute corticosteroid antiemetic efficacy in palliative care. Another such review included 27 randomized controlled trials (RCTs) and 12 observational cohort studies that examined AEs of corticosteroid prescribed for any reason to patients with advanced cancer; N&V was the primary outcome in 8 RCTs [46]. Almost 60% of studies did not report a method for assessing AEs, which could underestimate actual corticosteroid harms, and only 3 cohort studies used a validated AE assessment tool.

Phenothiazines

Phenothiazines are infrequently used to manage N&V in palliative care, but may be appropriate for patients unresponsive to first or second line antiemetics [11, 12, 47]. They act at several receptors and have broad actions, and may be useful for patients with MBO. They are D2 receptor antagonists and can cause EPS.

Levomepromazine (methotrimeprazine in the US), an antagonist several D, H, M, α-adrenergic, and 5HT receptors, is used to treat N&V and severe end-of-life delirium or agitation in non-ambulatory patients. It also has analgesic properties (for moderate to severe pain) and may be more cost-effective than other antiemetics [11, 47]. Levomepromazine's half-life is 15–30 h, which may allow once daily dosing. It is more sedating and more likely to cause postural hypotension than chlorpromazine, while dystonia, Parkinsonism, and neuroleptic malignant syndrome are uncommon. It should be used cautiously (or avoided) in ambulatory patients, particularly those with renal or hepatic impairment.

Domperidone is an unusual phenothiazine; it is a potent peripheral D2 antagonist, but does not penetrate into brain structures in rats [48]. Others posit it antagonizes D binding in the chemoreceptor trigger zone (CTZ), which is not enclosed in the blood–brain barrier (BBB), and further blocks transmission of neural impulses to the vomiting center [49, 50]. Domperidone also binds with GI cholinergic D2 receptors to mediate smooth muscle effects, thereby significantly improving gastric dysmotility and delayed emptying. There are few case reports of domperidone-induced EPS in adults (and children) administered parenteral or high PO doses, and the risk is minimal with doses ≤ 30 mg/day.

Domperidone data are conflicting, but case reports and case-control studies have raised concerns about prolonged QT and ventricular arrhythmias [51]. A meta-analysis of 9 retrospective studies with 101,155 patients examined cardiac (CV) risks of domperidone and metoclopramide; risk was lower with domperidone than metoclopramide, but a greater than no treatment [50]. Subgroup analysis of doses found no CV event risk with domperidone ≤ 30 mg/day, but risk increased with larger doses. Another retrospective chart review of patients with N&V who received domperidone 80 to 120 mg doses concluded these doses were efficacious and had minimal risk for CV AEs [52]. One prospective study examined the cardiac safety of domperidone (30 and 80 mg per day) in 246 patients followed for > 1–4 years (mean 1.67 years) [51]. QTc interval was evaluated on EKGs at baseline ($N = 246$), at 2 to 6 months ($N = 170$), 6 to 12 months ($N = 135$), and ≥ 12 months ($N = 152$) after starting domperidone. The primary and secondary study endpoints were clinically significant prolonged QTc (> 500 msec) and clinically non-significant QTc prolongation. No patients experienced a QTc of > 500 msec, but 15 (6.1%) had non-clinically significant prolonged QTc. The authors concluded doses of 30–80 mg/day are safe and intensive EKG monitoring of all patients is unnecessary.

Chlorpromazine, effective in 20–30% of patients, and prochlorperazine are not commonly used antiemetics for patients with advanced cancer [11, 21]. Both are available as rectal suppositories, a potentially useful short-term option for patients at home with worsening N&V. Chlorpromazine is more sedating than prochlorperazine, but this might be beneficial in actively dying patients. Chlorpromazine can cause severe tissue necrosis and SC is contraindicated, and prochlorperazine should not be given to patients with an absolute neutrophil count of 1000 cells/μl because of increased risk for neutropenia. Confusion, EPS, and anticholinergic effects may be minimized by gradual dose titration.

Cannabinoids

In the 1970's, anecdotal reports of decreased post-chemotherapy nausea in patients who smoked marijuana led to studies investigating dronabinol and nabilone for CINV (and appetite in AIDS patients). A relatively small number of controlled trials led to approval of both for CINV not controlled with standard antiemetics. However, interest in cannabinoids languished with development of 5HT3 antagonists. The research base for synthetic cannabinoids (dronabinol and nabilone) and of phytocannabinoids (tetrahydrocannabinol [THC] and cannabidiol [CBD] for palliative management of N&V is limited to few case reports or case series [53–55]. Patients typically had visceral metastases or abdominal carcinomatous with ascites and had received several other antiemetics (e.g., prochlorperazine, DEX, metoclopramide,

haloperidol, ondansetron) without effect before starting dronabinol. Resolution of both N&V were reported as rapid and dramatic and sometimes accompanied by improved appetite and oral intake, decreased pain, and improved social interactions.

Two events are changing the landscape of general disinterest in cannabinoids: the discovery of the endocannabinoid system around 1990 and its roles in virtually every body system and changing sociocultural attitudes about therapeutic cannabis (medical marijuana) with loosening legal restriction in many countries [56, 57, 58••]. Israel's government-mandated medical cannabis program began in 2007, and investigators collected routine treatment data for 2970 cancer patients prescribed medical cannabis and followed for >2 years [59•]. Data were analyzed to identify symptoms, efficacy and safety of cannabis. At baseline, patients had an average of 11.1 ± 7.5 symptoms (e.g., sleep problems, severe pain, weakness, and lack of appetite) related to advanced solid tumors; 65% reported nausea. After six months, ~96% reported improvement, which was greatest for nausea (91%), followed by sleep, restlessness, anxiety and depression, pruritus, and headaches (> 80% improvement). Less than 20% reported "good" QOL at baseline, while ~70% did so after 6 months on medical cannabis. Fewer than a third reported ≥1 minor (and easy to cope with) side effects.

Similarly, Abrams [60], an oncologist in California where medical marijuana has long been available, recognizing the weakness of cannabis clinical trial data wrote "…I need a clinical trial to demonstrate that cannabis is an effective antiemetic about as much as I need a placebo-controlled trial to demonstrate that penicillin is an antibiotic!" (PS10). He quoted one (of many) patients who finally used cannabis near the end of his chemotherapy, *"…did not use it until my last 5 sessions of chemo (me getting over the stigma of its use), it did what no other drug could do, completely solved the severe nausea I had...allowed me to play with my children…function very normally in day to day activities. I cannot thank you enough for giving me that option!"*.

Conclusions

Nausea or N&V in patients with advanced cancer are complex problems that may present a greater treatment challenge than cancer pain. A patient's primary oncology team can usually manage N&V in almost all instances. For patients who have the most complex, difficult to manage symptoms, palliative care specialists may add expertise. Such collaborative efforts among physicians, nurses, and pharmacists are most likely to maximized patient symptom control and QOL.

Box 2 Case continued—Mary F

Aprepitant was added to Mary's palliative chemotherapy antiemetic regimen (per guideline recommendation). Her nausea improved, but was not totally relieved. PO mirtazapine (7.5 mg at HS) was added. Within 3 days, her nausea was 0–1 (0 to 10 scale), although she still had "a little nausea" with movement, and her appetite was improved. Mary, with her oncology and palliative care team, decides not to add further medications (that might add side effects) at this time.

Mary's N&V was well controlled over many months during which she continued carboplatin/paclitaxel, and when she was started on a salvage regimen after disease progression. Soon after, she experienced worsening N&V, increased anorexia, post-prandial fullness, and ascites. Mirtazapine was increased to 15 mg at HS, which increased sleepiness. She wanted to try this for a few days to see if her nausea and sleepiness improved (they did). The PCS again saw Mary when she experienced rapid disease progression with declining performance status, massive ascites, and symptoms of MBO. Her oncologist explained further chemotherapy would add only toxicity without any benefit; she and Mary decided to focus solely on aggressive palliative care. Mary had a venting gastrostomy and a tunneled peritoneal catheter (for as needed drainage of ascites) placed so she could be cared for at home. Mirtazapine was switched to olanzapine ODT (5 mg at HS and 5 mg Q 4–6 h PRN). Mary was able to stay at home with PCS support. She died peacefully, surrounded by family, weeks later.

Compliance with Ethical Standards

Conflict of Interest Rita J. Wickham has received compensation from Helsinn Healthcare SA and Insys Therapeutics for service as a consultant.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

References

Papers of particular interest, published recently, have been highlighted as:
- • Of importance
- •• Of major importance

1. Hawley PH. The bow tie model of 21st century palliative care. J Pain Symptom Manag. 2014;47(1):e2–5. https://doi.org/10.1016/j.jpainsymman.2013.10.009.
2. Li B, Mah K, Swami N, et al. Symptom assessment in patients with advanced cancer: are the most severe symptoms the most bothersome? J Palliat Med. 2019. https://doi.org/10.1089/jpm.2018.0622.
3.• Napadow V, Sheehan JD, Kim J, et al. The brain circuitry underlying the temporal evolution of nausea in humans. Cereb Cortex. 2013;23:806–13. https://doi.org/10.1093/cercor/bhs073. **Functional MRI study investigated brain regions involved in temporal evolution of nausea; greater nausea intensity was associated sustained activation in a broader network of interoceptive, limbic, somatosensory, and cognitive processing areas in the human brain.**
4. Balaban CD, Yates BJ. What is nausea? A historical analysis of changing views. Auton Neurosci. 2017;202:5–17. https://doi.org/10.1016/j.autneu.2016.07.003.

5.•• Wickham RJ. Revisiting the physiology of nausea and vomiting—challenging the paradigm. Support Care Cancer. Online first: 06 August 2019. https://doi.org/10.1007/s00520. **Current, in-depth review of differing physiological mechanisms, neural pathways, transmitters and receptors for vomiting and for nausea; new proposed paradigm for nausea and for vomiting.**
6. Gogolla N. The insular cortex. Curr Biol. 2017;27:R573–91. https://doi.org/10.1016/j.cub.2017.05.010.
7. Craig AD. How do you feel — now? The anterior insula and human awareness. Nat Rev Neurosci. 2009;10:59–70. https://doi.org/10.1038/nrn2555.
8. Harder S, Herrstedt J, Isaksen J, et al. The nature of nausea: prevalence, etiology, and treatment in patients with advanced cancer not receiving antineoplastic treatment. Support Care Cancer. 2019. https://doi.org/10.1007/s00520-018-4623-1.
9. Singh P, Yoon SS, Kuo B. Nausea: a review of pathophysiology and therapeutics. Ther Adv Gastroenterol. 2016;9(1):98–112. https://doi.org/10.1177/1756283X15618131.
10. Sande TA, Laird BJ, Fallon MT. The management of opioid-induced nausea and vomiting in patients with cancer: a systematic review. J Palliat Med. 2019;22(1):90–7. https://doi.org/10.1089/jpm.2018.0260.
11. Glare P, Miller J, Nikolova T, Tickoo R. Treating nausea and vomiting in palliative care: a review. Clin Interv Aging. 2011;6:243–59. https://doi.org/10.2147/CIA.S13109.
12. Walsh D, Davis M, Ripamonti C, Bruera E, Davies A, Molassiotis A. 2016 updated MASCC/ESMO consensus recommendations: management of nausea and vomiting in advanced cancer. Support Care Cancer. 2017;25:333–40. https://doi.org/10.1007/s00520-016-3371-3.
13. Collis E, Mather H. Nausea and vomiting in palliative care. BMJ. 2015;351:h6249. https://doi.org/10.1136/bmj.h6249.
14. Ferguson HJM, Ferguson CI, Speakman J, Ismail T. Management of intestinal obstruction in advanced malignancy. Ann Med Surg (Lond). 2015;4(3):264–70. https://doi.org/10.1016/j.amsu.2015.07.018.
15.• Laval G, Marcelin-Benazech B, Guirimand F, et al. Recommendations for bowel obstruction with peritoneal carcinomatosis. J Pain Symptom Manag. 2014;8(1):75–91. https://doi.org/10.1016/j.jpainsymman.2013.08.022. **French Health Authority (HAS) evidence-based clinical guidelines for the diagnosis and management of bowel obstruction.**
16. Soriano A, Davis MP. Malignant bowel obstruction: individualized treatment near the end of life. Cleve Clin J Med. 2011;78(3):197–206. https://doi.org/10.3949/ccjm.78a.10052.
17. Obita GP, Boland EG, Currow DC, Johnson MJ, Boland JW. Somatostatin analogues compared with placebo and other pharmacologic agents in the management of symptoms of inoperable malignant bowel obstruction: a systematic review. J Pain Symptom Manag. 2016;52(6):901–19. https://doi.org/10.1016/j.jpainsymman.2016.05.032.
18. Peng X, Wang P, Li S, Zhang G, Hu S. Randomized clinical trial comparing octreotide and scopolamine butylbromide in symptom control of patients with inoperable bowel obstruction due to advanced ovarian cancer. World J Surg Oncol. 2015;13:50. https://doi.org/10.1186/s12957-015-0455-3.
19. Harris DG. Nausea and vomiting in advanced cancer. Br Med Bull. 2010;96(1):175–85. https://doi.org/10.1093/bmb/ldq031.
20. To THM, Agar M, Yates P, Currow DC. Prescribing for nausea in palliative care: a cross-sectional national survey of Australian palliative medicine doctors. J Palliat Med. 2014;17(9):1032–6. https://doi.org/10.1089/jpm.2013.0610.
21. Valkova M, Stamenov B, Peychinska D, et al. Metoclopramide-induced extrapyramidal signs and symptoms – brief review of literature and case report. J IMAB. 2014;20(6):539–41. https://doi.org/10.5272/jimab.2014206.539.
22. Gordon P, LeGrand SB, Walsh D. Nausea and vomiting in advanced cancer. Eur J Pharmacol. 2014;722:187–91. https://doi.org/10.1016/j.ejphar.2013.10.010.
23. Gupta N, Puri S, Kumar V, Garg R, Bharati SJ, Mishra S, et al. Olanzapine in the treatment of refractory nausea and vomiting in palliative care settings. Indian J Palliat Care. 2018;24(3):372–4. https://doi.org/10.4103/IJPC.IJPC_30_18.
24. Lewis K, O'Day CS. Dystonic reactions. In: StatPearls (nternet). Updated3/23/ 2019. Treasure Island: StatPearls Publishing. Available at: https://www.ncbi.nlm.nih.gov/books/NBK531466/?report=classic. Accessed 11 Sept 2019.
25. Caroff SN, Campbell EC. Drug-induced extrapyramidal syndromes: implications for contemporary practice. Psychiatr Clin North Am. 2016;39(3):391–411. https://doi.org/10.1016/j.psc.2016.04.003.
26. Tachere RO, Modirrousta M. Beyond anxiety and agitation: a clinical approach to akathisia. Aust Fam Physician. 2017;46(5):296–8.
27. Poyurovsky M, Weizman A. Treatment of antipsychotic-related akathisia revisited. The role of serotonin 2A receptor antagonists. J Clin Psychopharmacol. 2015;35(6):711–4. https://doi.org/10.1097/JCP.0000000000000412.
28. Vella-Brincat J, Macleod AD. Haloperidol in palliative care. Palliat Med. 2004;18:195–201. https://doi.org/10.1191/0269216304pm881oa.
29. Prommer E. Role of haloperidol in palliative medicine: an update. Am J Hosp Palliat Care. 2012;29(4):295–301. https://doi.org/10.1177/1049909111423094.
30. Murray-Brown F, Dorman S. Haloperidol for the treatment of nausea and vomiting in palliative care patients (review). Cochrane Database Syst Rev. 2015;(11). https://doi.org/10.1002/14651858.CD006271.pub3.
31. Digges M, Hussein A, Wilcock A, et al. Pharmacovigilance in hospice/palliative care: net effect of haloperidol for nausea or vomiting. J Palliat Med. 2018;21(1):37–43. https://doi.org/10.1089/jpm.2017.0159.
32. MacKintosh D. Olanzapine in the management of difficult to control nausea and vomiting in a palliative care population: a case series. J Palliat Med. 2016;19(1):87–90. https://doi.org/10.1089/jpm.2015.0224.
33.• Credible Meds. 2019. Available at https://crediblemeds.org/healthcare-providers/. **This site, which is frequently updated, lists evidence-based prescription and recreational (cocaine) drugs having the potential to increase the QT interval and induce Torsades de pointes.**
34. Crotti L, Celano G, Dagradi F, Schwartz PJ. Congenital long QT syndrome. Orphanet J Rare Dis. 2008;3:18. https://doi.org/10.1186/1750-1172-3-18.
35. Kast RE, Foley KF. Cancer chemotherapy and cachexia: mirtazapine and olanzapine are 5-HT3 antagonists with good anti-nausea effects. Eur J Cancer Care. 2007l;16(4):351–4. https://doi.org/10.1111/j.1365-2354.2006.00760.x.
36. Bymaster FP, Calligaro DO, Falcone JF, et al. Radioreceptor binding profile of the atypical antipsychotic olanzapine. Neuropsychopharmacology. 1996;14(2):87–96. https://doi.org/10.1016/0893-133X(94)00129-N.
37. Passik SD, Lundberg J, Kirsh KL. A pilot exploration of the anti-emetic activity of olanzapine for the relief of nausea in patients with advanced cancer and pain. J Pain Symptom Manag. 2002;23(6):526–32. https://doi.org/10.1016/S0885-3924(02)00391.
38. Kaneishi K, Kawabata M, Morita T. Olanzapine for the relief of nausea in patients with advanced cancer and incomplete bowel obstruction. J Pain Symptom Manag. 2012;44(4):604–7. https://doi.org/10.1016/j.jpainsymman.2011.10.023.
39. Raji MA. Management of chemotherapy-induced side-effects. Lancet Oncol. 2005;6(6):357. https://doi.org/10.1016/S1470-2045(05)70182-0.

40. Allen ND, Leung JG, Betcher HK, Borreggine KL, Hosker DK, Minton BA, et al. Mirtazapine for symptomatic relief on a psychiatric consultation service: a case series. Psychosomatics. 2016;57(4):409–13. https://doi.org/10.1016/j.psym.2016.02.012.
41. Anttila SAK, Leinonen EVJ. A review of the pharmacological and clinical profile of mirtazapine. CNS Drug Rev. 2001;7(3):249–64. https://doi.org/10.1111/j.1527-3458.2001.tb00198.x.
42. Malamood M, Roberts A, Kataria R, Parkman HP, Schey R. Mirtazapine for symptom control in refractory gastroparesis. Drug Des Devel Ther. 2017;11:1035–41. https://doi.org/10.2147/DDDT.S125743.
43. Kumar N, Barai S, Gambhir S, Rastogi N. Effect of mirtazapine on gastric emptying in patients with cancer-associated anorexia. Indian J Palliat Care. 2017;23(3):335–7. https://doi.org/10.4103/IJPC.IJPC_17_17.
44. Jaward LR, O'Neil TA, Marks A, Smith MA. Differences adverse effect profiles of corticosteroids in palliative care patients. Am J Hosp Palliat Med. 2019;36(2):158–68. https://doi.org/10.1177/1049909118797283.
45. Vayne-Bossert P, Haywood A, Good P, et al. Corticosteroids for adult patients with advanced cancer who have nausea and vomiting (not related to chemotherapy, radiotherapy, or surgery). Cochrane Database Syst Rev. 2017;(7). https://doi.org/10.1002/14651858.CD012002.pub2.
46. Hatano Y, Matsuoka H, Lam L, Currow DC. Side effects of corticosteroids in patients with advanced cancer: a systematic review. Support Care Cancer. 2018;26:3979–83. https://doi.org/10.1007/s00520-018-4339-2.
47. Dietz I, Schmitz A, Lampey I, Schulz C. Evidence for the use of levomepromazine for symptom control in the palliative care setting: a systematic review. BMC Palliat Care. 2013;12:2. https://doi.org/10.1186/1472-684X-12-2.
48. Laduron PM, Leysen JE. Domperidone, a specific in vitro dopamine antagonist, devoid of in vivo central dopaminergic activity. Biochem Pharmacol. 1979;28:2161–5. https://doi.org/10.1016/0006-2952(79)90198-9.
49. Barone JA. Domperidone: a peripherally acting dopamine2-receptor antagonist. Ann Pharmacother. 1999;33(4):429–40.
50. Bor S, Demir M, Ozdemi O, Yuksel K. A meta-analysis on the cardiac safety profile of domperidone compared to metoclopramide. United European Gastroenterol J. 2018v;6(9):1331–46. https://doi.org/10.1177/2050640618799153.
51. Field J, Wasilewski M, Bhuta R, et al. Effect of chronic domperidone use on QT interval: a large single center study. J Clin Gastroenterol. 2019. https://doi.org/10.1097/MCG.0000000000001183.
52. Ortiz A, Cooper CJ, Alvarez A, Gomez Y, Sarosiek I, McCallum R. Cardiovascular safety profile and clinical experience with high-dose domperidone therapy for nausea and vomiting. Am J Med Sci. 2015;349:421–4. https://doi.org/10.1097/MAJ.0000000000000439.
53. Gonzalez-Rosales F, Walsh D. Intractable nausea and vomiting due to gastrointestinal mucosal metastases relieved by tetrahydrocannabinol (dronabinol). J Pain Symptom Manag. 1997;14(5):311–4. https://doi.org/10.1016/S0885-3924(97)00229-7.
54. Zutt M, Hänßle H, Emmert S, et al. Dronabinol zur supportiven Therapie metastasierter maligner Melanome mit Lebermetastasen (Dronabinol for supportive therapy in patients with malignant melanoma and liver metastases). Hautarzt. 2006;57(5):423–7. https://doi.org/10.1007/s00105-005-1063.
55. Hernandez SL, Sheyner I, Stover KT, Stewart JT. Dronabinol treatment of refractory nausea and vomiting related to peritoneal carcinomatosis. Am J Hosp Palliat Care. 2015;32(1):5–7. https://doi.org/10.1177/1049909113504240.
56. Di Marzo V. A brief history of cannabinoid and endocannabinoid pharmacology as inspired by the work of British scientists. Trends Pharmacol Sci. 2006;27(3):134–40. https://doi.org/10.1016/j.tips.2006.01.010.
57. Lu Y, Anderson HD. Cannabinoid signaling in health and disease. Can J Physiol Pharmacol. 2017;95:311–27. https://doi.org/10.1139/cjpp-2016-0346.
58.•• National Academies of Sciences, Engineering, and Medicine. The health effects of cannabis and cannabinoids: the current state of evidence and recommendations for research. Washington, DC: The National Academies Press; 2017. https://doi.org/10.17226/24625. **A comprehensive, in-depth review of existing evidence and summary recommendations regarding health effects of cannabis and cannabis-derived products, as well as potential therapeutic uses. This work was implemented to help advance research and inform public health decisions.**
59.• Schleider LB-L, Mechoulam R, Lederman V, et al. Prospective analysis of safety and efficacy of medical cannabis in large unselected population of patients with cancer. Eur J Intern Med. 2018;49:37–43. https://doi.org/10.1016/j.ejim.2018.01.023. **Analysis of routinely collected data regarding the benefits and burdens of medical marijuana, prescribed to almost 3000 cancer patients with symptomatic disease who were followed over 2 years. This article also describes the processes of physician prescription and nurse selection (with patient) of particular cannabis strains, dose escalation, and patient and family teaching.**
60. Abrams DI. Integrating cannabis into clinical cancer care. Curr Oncol. 2016;23(2):S8–S14. https://doi.org/10.3747/co.23.3099.