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Treatment of Non Pain-Related Symptoms

Charles F. von Gunten, MD, PhD^{*} and Ellin Gafford, MD[†]

^{*}Hospice and Palliative Care, OhioHealth, Columbus, OH

[†]Division of Palliative Care, Department of Medicine, The Ohio State Medical Center, Columbus, OH

Abstract

Relieving the suffering associated with cancer and its treatment in the physical, emotional, practical and spiritual domains is impossible without impeccable symptom control. This review summarizes key features essential to the management of: anorexia/cachexia, bowel obstruction, diarrhea, fatigue, mucositis, and nausea/vomiting. Taken together, these are some of the most vexing symptoms for cancer patients. Well-managed symptoms enable the course of overall cancer care to be unimpeded.

Introduction

Palliative care, including the provision of targeted symptom management, has emerged as an important component of standard cancer care. The National Cancer Institute funded the Education in Palliative and End-of-Life Care Project for Oncology to facilitate the dissemination of this information. (1). The full product which is designed to enable the teaching of the subject, including slides, trigger tapes, and annotated references are available from the National Cancer Institute. The following represents a digest from that source for the purposes of this special issue, and provides a summary of the management of: anorexia/cachexia, bowel obstruction, diarrhea, fatigue, mucositis, and nausea/vomiting.

Anorexia / Cachexia

Anorexia is a lack or loss of appetite and frequently accompanies the wasting syndrome cachexia. The cachexia/anorexia syndrome is caused by an aberrant host response to cancer and occurs in patients with advanced, refractory malignancy. (2) The signs and symptoms of the anorexia/cachexia syndrome include preferential loss of lean tissue, a decline in performance status, fluctuations in resting energy expenditure, and loss of appetite.(3)

In addition to psychosocial distress, anorexia/cachexia limits therapeutic options. Weight loss correlates with treatment toxicity, poor tumor response, and lower chemotherapy response rates.(4,5) Loss of greater than 5% of pre-morbid weight prior to chemotherapy predicts death; independent of disease stage, tumor histology, and patient performance status.

Anorexia is also a powerful predictor of early death.(6,7) This observation persists even after adjusting for several other prognostic parameters. Thus, both weight loss and anorexia predict a poor prognosis for patients with advanced cancer.

Management of Anorexia and Cachexia

Secondary reasons for weight loss should be addressed or ruled out. Then consider the few treatments that have been shown to improve the Anorexia/Cachexia syndrome. More importantly, avoid those which don't help.

Feeding patients, either enterally or parenterally, does not reverse or slow the cancer anorexia/weight loss syndrome, improve appetite, or improve patient outcome. (8) In 1989, the American College of Physicians addressed the role of total parenteral nutrition in patients with advanced cancer receiving chemotherapy and radiation with the following statement (9) 'the routine use of parenteral nutritional for patients undergoing chemotherapy should be strongly discouraged.'

Similarly, dietary counseling does not improve patient outcome. (7)

Strong evidence suggests that corticosteroids and progestational agents are effective at improving appetite if appropriate doses are used. (9, 10)

Corticosteroids

Dexamethasone has been demonstrated to improve appetite on a short-term basis in patients with advanced disease. (11) Subsequent placebo-controlled clinical trials have replicated this finding. A common dosing regimen is:

- Dexamethasone 2–8 mg PO q AM

Appetite stimulation is usually transient, and ceases to be helpful after 3–4 weeks. Dexamethasone is often selected because of its absence of mineralocorticoid effects. However, fluorinated corticosteroids, eg, dexamethasone, are particularly prone to cause muscle breakdown. If long term use is deemed necessary in mobile patients, consider switching from dexamethasone to an alternate corticosteroid, eg, prednisolone. A common dose range is:

- Prednisolone 20–40mg PO q AM

Progestational agents increase appetite and weight in 35–60 % of patients. Megestrol acetate is the best studied progestational agent. (12) Megestrol acetate oral suspension has gained popularity because of its improved bioavailability. The medication is best absorbed when taken along with a high fat meal.

- Megestrol acetate 400 mg/day. (Titrate megestrol acetate 600 – 800 mg/day if no appetite improvement after 2 weeks.)

The length of response to megestrol is longer than with corticosteroids. The weight gained is primarily as fat (not a bad outcome in its own right). A geriatric study suggests that megestrol also has catabolic effects on muscle. (13) Patients on megestrol acetate may need

to receive corticosteroid repletion in the face of serious infections, trauma, or surgery because of the adrenal suppression. (14)

Megestrol acetate carries a slight increased risk of thromboembolic disease, which is increased by concomitant chemotherapy. History of thromboembolic disease is a relative contraindication to progestational agents. In contrast, dexamethasone puts patients at risk for myopathy, cushingoid body habitus, and peptic ulcer disease. These side effect profiles play some role in determining which agent might be better for a specific patient.

In general, patients with a life expectancy of a few months or more may do better with megestrol acetate. Those with a life expectancy of only a few weeks, or those with a history of thrombophlebitis, may be able to get by with dexamethasone, as they are less likely to suffer side effects from corticosteroids in the short term.

Cannabinoids

Studies support the use of a marijuana congener, dronabinol, in fostering weight gain. Most receptor activity is noted in 'hedonistic centres' such as the nucleus accumbens, with lesser hypothalamic activity. (15)

Increase gastric emptying

Early satiety may stem from abnormal hypothalamic signals and/or autonomic abnormalities with consequent delay in gastric emptying. Metoclopramide and domperidone may relieve early satiety through stimulation of gastric emptying. The fourteen ring macrolide antibiotics, eg, erythromycin and clarithromycin, also stimulate gastric emptying. Their use in cancer patients has only been studied in a few small Japanese trials. (16)

- Metoclopramide, 10–20 mg PO q 6 h (ac & HS)

Anabolic Steroids

Androgens build muscle. Fluoxymesterone can increase appetite, although not to the level achieved with megestrol. More recent reports show that oxandrolone, a steroid said to be more anabolic with less androgenic properties will boost appetite, lean body mass and function. (17) Combining exercise with androgen intake strongly enhances muscle size and function. Safer anabolic medications may include oxandrolone and testosterone undecenoate (less risk of hepatic toxicity). In hypogonadal patients, consider testosterone replacement.

Encourage muscular activity as long as it is safe. This is supported by a growing body of evidence that exercise may fundamentally affect cancer incidence and course, the adverse effects of therapy, and fatigue. (18–23) As a result, it is reasonable to advise weight losing patients to begin, or maintain, a rehabilitation program if dangerous bone metastases and cardiovascular capacity are taken into account.

Including physiotherapists on the comprehensive cancer care team will greatly enhance our ability to include exercise as part of an overall patient prescription for functional assessment and rehabilitation.

Bowel Obstruction

Malignant bowel obstruction is the mechanical or functional obstruction of the progress of food and fluids through the gastrointestinal tract. It causes misery from nausea, vomiting, and abdominal pain.

The prognosis of patients with both mechanical and functional obstruction due to advanced cancer who have received maximal surgical, chemotherapeutic, and radiological treatment is very poor, with survival ranging from a few weeks to few months., (24) Parenteral nutrition does not affect this prognosis.

Patients with far advanced disease and a short time to live should be spared extensive evaluation and treated medically.

Surgery

Palliative surgery can reverse malignant bowel obstruction. However, published data show that, in advanced cancer, the operative mortality is 30–40% and complication rates vary from 27–90%. The type of obstruction (partial vs. complete) and the method of surgical treatment (bypass vs. resection and reanastomosis) has no significant effect on the outcome. Improvements in surgical techniques and perioperative care appears not to influence the outcome. According to different authors, the rate of inoperable patients ranges from 6.2% to 50%.

Several authors have emphasized that prognostic criteria are needed to select patients who are likely to benefit from surgical intervention. The available data suggest that poor prognostic factors that preclude a surgical approach include the following: 1) intestinal motility problems due to diffuse intraperitoneal carcinomatosis; 2) patients over 65 (particularly if cachectic); 3) ascites requiring frequent paracentesis; 4) advanced cachexia; 5) previous radiotherapy of the abdomen or pelvis; 6) palpable intra-abdominal masses and liver involvement, or distant metastases, pleural effusion or pulmonary metastases; 7) multiple partial bowel obstruction with prolonged passage time on radiograph examination; and 8) poor general performance status.

Stents

The newest intervention for palliative care of malignant bowel obstruction is stent placement. (25–30) Radiologic or endoscopic enteral stent placement has been reported to be an effective alternative for palliation of high risk surgical candidates with malignant gastric outlet, small bowel, large bowel, and rectal obstruction. Significant complications include stent migration, perforation, biliary obstruction, and need for subsequent endoscopic, radiologic and surgical interventions. There are no comparisons of method of stent placement. In one randomized study, endoscopic stenting required less operative time, faster restoration of bowel function and oral intake and shorter median hospitalization than colostomy. However, ultimate symptom control, morbidity and mortality were the same.

Nasogastric suction and intravenous fluids

Nasogastric suction decompresses the stomach and/or intestine and intravenous fluids correct fluid and electrolyte imbalance before surgery, or while a decision is being made. The tube can clog, cause discomfort, create erosions, and contribute to infection. Only consider the long-term use of a nasogastric tube when pharmacological therapy for symptom control is ineffective or when gastrostomy cannot be carried out. It is no longer the principal therapy to manage malignant bowel obstruction.

Pharmacological management

The pharmacological management of malignant bowel obstruction due to advanced cancer focuses on the treatment of nausea, vomiting, pain, and other symptoms without the use of a nasogastric tube. Although a central venous access may be used if present, a continuous subcutaneous infusion of medications using a portable syringe driver allows the parenteral administration of different medication combinations, produces minimal discomfort for the patient, and is easy to use in a home setting.

Medications used for controlling pain and/or vomiting

Analgesics—Opioids are usually used to control continuous abdominal pain. The dose is titrated using standard opioid dosing guidelines until symptom control is achieved.

Antinauseants—Haloperidol is an effective antidopaminergic antiemetic. It can be combined with scopolamine and an opioid in the same solution for simpler administration parenterally. A standard dosing regimen is:

- Haloperidol, 1 mg IV/SC q 6–8 h

Metoclopramide is both an antidopaminergic antiemetic and a gastrointestinal prokinetic agent. A standard dosing range is:

- Metoclopramide, 10–20 mg IV/SC q 6 h or 2–4 mg/hour continuous infusion

Scopolamine butylbromide, also known as hyoscine butylbromide, decreases the tonus and peristalsis in smooth muscle, decreases the secretions in the gastrointestinal tract, and lessens the resulting pain. Scopolamine butylbromide is preferred over atropine and scopolamine hydrobromide as it is much less lipid soluble, does not penetrate the blood-brain barrier and produces less adverse effects, eg, somnolence and hallucinations, when administered in combination with opioids. (31–37) Standard dosing regimens include:

- Scopolamine, 0.1–0.4 mg SC q 6 h
- Scopolamine, 0.1 mg/hour SC/IV continuous infusion

Glycopyrrolate can be used with similar effects and properties. It is a quaternary ammonium anticholinergic agent that also has limited lipid solubility and less risk of both central nervous system and ocular effects. The onset of its action is 35–45 minutes when given subcutaneously and 1 minute when given intravenously. Glycopyrrolate cannot be mixed with diazepam, methylprednisolone, dexamethasone, dimenhydrinate, or Phenobarbital. A common dosing range is:

- Glycopyrrolate, 0.2–0.4 mg SC q 6 h or 0.02 mg/hour continuous infusion

Octreotide—Octreotide is a synthetic analogue of somatostatin. It has a more potent biological activity and a longer half-life than somatostatin, and has been used to successfully manage the symptoms of bowel obstruction.

The inhibitory effect of octreotide on both peristalsis and gastrointestinal secretions reduces bowel distension and the secretion of water and sodium by the intestinal epithelium, thereby reducing vomiting and pain. As a result, the medication may break the vicious circle represented by secretion, distension, and contractile hyperactivity.

Octreotide may be administered by subcutaneous bolus or continuous subcutaneous infusion. The recommended starting dose is 0.3 mg/day subcutaneously. The dose can be titrated upward until symptom control is achieved, usually at 0.6–0.9 mg/day. Octreotide is significantly more effective and faster than hyoscine butylbromide in reducing the amount of gastrointestinal secretions in patients with a nasogastric tube and in reducing the intensity of nausea and the number of vomiting episodes in patients without a nasogastric tube. Moreover octreotide may prevent the development of irreversible bowel obstruction in patients with recurrent episodes of obstruction.

As octreotide is an expensive medication, consider its cost-benefit ratio, as it may reduce the need for admission or the length of stay in the inpatient unit and improve the patient's quality of life. Common dosing regimens include:

- Octreotide, 50–100 micrograms SC q 8 h
- Octreotide, 10 micrograms/hour IV/SC continuous infusion

Corticosteroids

To date no controlled clinical trials of corticosteroids have been carried out and the various administration routes and dosing of these medications have not been standardized.

Percutaneous gastrostomy

Percutaneous gastrostomy is believed to be a more effective and acceptable alternative to the prolonged use of a nasogastric tube when obstructive symptoms cannot be controlled by medications.

Hydration and total parenteral nutrition

Carefully assess the amount of fluid you will administer. High levels of oral or parenteral fluids may result in more bowel secretions. However, the intensity of nausea is significantly lower in patients treated with more than 1 liter/day of fluids. Balance the efficacy of the treatment and the risk of adverse effects such as increased vomiting, abdominal distension, and pain.

The intensity of dry mouth and thirst are independent of the quantity of both oral and parenteral hydration. (38) Hypodermoclysis is a simple technique for rehydration that offers many advantages over the intravenous route. Patients with a distal bowel obstruction may

tolerate and find some oral fluid intake to be pleasurable. Limit daily oral intake to a volume equal to the volume of urine output in 24 hours plus 500 ml for insensible losses.

The role of total parenteral nutrition in the management of patients with inoperable bowel obstruction has been controversial. (39) It is effective for patients with short gut syndrome, but not for patients with advanced progressive cancer.

Diarrhea

Diarrhea is defined as stools that are looser than normal and may be increased in frequency. It may be acute (< 14 days), persistent (>14 days), or chronic (> 30 days). Diarrhea can lead to dehydration, malabsorption, fatigue, hemorrhoids, and perianal skin breakdown. Secondly, it can lead to electrolyte abnormalities. In the setting of chemotherapy, unrecognized and/or untreated diarrhea can be fatal.

Most cases of acute diarrhea are viral and self-limited. Those that are serious (watery diarrhea with signs of hypovolemia, stools containing blood and mucus, fever, >6 unformed stools in 24 hours, severe abdominal pain, recent antibiotic use or hospitalization) are likely bacterial.

Management

General approaches

- Establish normal bowel habits (there is wide variation).
- Assure adequate hydration. Oral rehydration solutions that contain sodium chloride, eg, soups, red juices with salt and sport drinks may be adequate. Subcutaneous hypodermoclysis or intravenous rehydration is sometimes needed.
- Avoid gas-forming foods, particularly lactose. Acute diarrhea is frequently associated with transient lactose intolerance.
- Increase bulk, eg, psyllium, bran, pectin.

Specific approaches

For the transient or mild diarrhea consider:

- Attapulgite, 30 ml or 2 tablets PO PRN. This forms a gel in the bowel without affecting the overall volume of diarrhea. However, for some patients, passing formed stools will help skin integrity and decrease the frequency of bowel movements.
- Bismuth subsalicylate, 30 ml or 2 tablets PO every 30 minutes PRN up to a maximum of eight doses. This has both anti-inflammatory and antibacterial actions.

For persistent and bothersome diarrhea, to slow peristalsis, consider:

- Codeine, 15 – 30 mg PO q 4 h PRN

- Diphenoxylate/atropine, 5.0 mg (2 tablets) PO q 6 h. Maximum 20 mg/24h. Diphenoxylate is a central opiate. Atropine is an anticholinergic agent which dries the bowel and decreases peristalsis.
- Loperamide, 4 mg (2 tablets) initially, then 2–4 mg PO q 6 h to a maximum of 16 mg/24h. This is a peripheral acting opioid. It may be used with acute diarrhea even if there is a low grade fever, as long as there is not blood in the stool.
- Paregoric, 5 ml PO q 4 h. This camphorated tincture of opium is less concentrated than tincture of opium at 0.4 mg/ml.
- Tincture of opium, 0.7 ml PO q 4 h and titrate to effect. This is alcoholized morphine at approximately 10 mg/ml; very bitter tasting; and more potent than loperamide and diphenoxylate.

For persistent, severe secretory diarrhea provide parenteral fluid support, as needed and appropriate to treat or prevent dehydration and consider octreotide, a synthetic congener of somatostatin. For a more detailed explanation of octreotide action (see EPEC-O Module 3e: Symptoms - Bowel Obstruction).

- Octreotide, 50 µg SC q 8–12 h, then titrate up to 500 µg q 8 h SC, or higher, or 10–80 µg q 1 h by continuous SC, IV infusion.

Two long-acting preparations of octreotide are available:

- Octreotide long-acting, 20 mg IM once a month
Lanreotide SR, 20 – 30 mg IM every 10 days

If there is severe diarrhea, nausea, vomiting, fever, sepsis, neutropenia, or bleeding, admit to hospital for close observation and management.

Management of chemotherapy-associated diarrhea

Assess patients treated with combination irinotecan, fluorouracil, and leucovorin weekly, at least during the first cycle. Consider abdominal cramping to be equivalent to diarrhea. Mucosal injury leads to a temporary lactase deficiency, so limit milk-containing foods.

Aggressively orally rehydrate patients with fluids that contain water, salt, and sugar such as broth/soups, red vegetable juices with added salt, or sports drinks.

- Loperamide, 4 mg PO followed by 2 mg PO q 2–4 h or after every formed stool to start. Titrate until diarrhea-free for 12 hours.

Administer intravenous or subcutaneous fluids if there is evidence of dehydration. Octreotide can be used as a second-line therapy if the diarrhea is refractory to loperamide.¹ If there is severe diarrhea, nausea, vomiting, fever, sepsis, neutropenia, or bleeding, admit to hospital for close observation and management.

Management of carcinoid-associated diarrhea

Patients with carcinoid syndrome frequently develop an associated secretory diarrhea. Mild diarrhea may respond to an opiate. Cholestyramine may ameliorate the diarrhea if the patient has had a distal ileal resection to remove the primary tumor causing a bile acid diarrhea.

Octreotide, a synthetic somatostatin, is usually well tolerated. It has some adverse effects including nausea, abdominal discomfort, bloating, loose stools, and fat malabsorption. These adverse effects usually subside after the first several weeks of therapy. Long-term octreotide therapy reduces postprandial gallbladder contractility and delays gallbladder emptying that predisposes the patient to gallstones or sludge. (40)

Pancreatic insufficiency-associated diarrhea

Patients treated with total pancreatectomy, ie, Whipple Procedure, frequently experience diarrhea due to maldigestion and steatorrhea due to exocrine pancreatic insufficiency. This is treated with a low fat diet and administration of exogenous pancreatic enzymes. Several commercial preparations are microencapsulated so that they are stomach acid-resistant to avoid enzyme inactivation. As a general rule, 30,000 IU of pancreatic lipase, swallowed during each meal, should suffice in reducing steatorrhea and preventing weight loss. Nonencapsulated formulations may be more successful in patients who are achlorhydric or who have dyssynchronous gastric emptying, eg, Billroth II anatomy, since there is no need to protect the enzymes from acid. (41)

Summary

After managing underlying pathophysiology, symptomatic management of diarrhea involves measures that either thickens the stool, slow peristalsis to permit more time for water absorption, or agents to decrease secretion of fluid into the gut.

Mucositis

Oral mucositis is a common complication of both chemotherapy and radiation therapy. It is the dose limiting toxicity of concurrent chemotherapy and radiotherapy and of accelerated and hyperfractionated radiotherapy. From the patient's perspective, mucositis is a debilitating toxicity of therapy.

Mucositis is generally self-limiting. The prognosis is generally good if the comorbidities such as pain, decreased oral intake, fluid deficits, and dental caries are also managed. In patients receiving hematopoietic stem cell transplantation, mucositis is associated with an increased risk of infection and additional hospital days, days of parenteral nutrition, intravenous opioid use, and greater 100-day mortality. (42)

Management

Prevention—The prevention of oral mucositis has been an important goal. Four theoretical approaches have been articulated. (43)

1. **Reduce mucous membrane exposure to the cytotoxic agent.** Oral cryotherapy is recommended for patients receiving bolus 5-FU. (44) Theoretically, placing ice in

the mouth 5 minutes before bolus treatment with 5-FU and for 30 minutes after chemotherapy, cools the oral cavity leading to vasoconstriction and decreased oral cavity medication exposure. Randomized trials have demonstrated a 50% reduction in 5-FU induced oral mucositis with cryotherapy. (45) Additional studies are underway.

2. **Reduce infectious and inflammatory complications.** Another mechanistically-based therapy is glutamine supplementation. L-glutamine may decrease treatment-induced metabolic deficiencies and promote healing. Studies of L-glutamine oral rinses for mucositis have not shown efficacy, likely due to poor absorption when administered topically. AES-14, a proprietary vehicle which enhances mucosal uptake of L-glutamine and the amino acid, reduced the incidence of mucositis in a placebo-controlled phase 3 trial in patients at risk for mucositis secondary to anthracycline-based chemotherapy. (46) Antimicrobials are largely used for the treatment of associated or secondary infections. Iseganan, an analog of protegrin-I, has broad spectrum anti-microbial activity. Early studies suggest its use reduces mucositis, though more data are needed.
3. **Modify epithelial proliferative capabilities.** Keratinocyte growth factor, a member of the fibroblast growth factor family, is an epithelial mitogen which acts through a subset of fibroblast growth factor receptors expressed predominantly on epithelial cells. Keratinocyte growth factor is upregulated after epithelial injury and plays a role in tissue repair. A double blind, randomized placebo controlled study of recombinant human keratinocyte growth factor (rHuKGF-I, palifermin) in patients undergoing high dose chemotherapy and hematopoietic stem cell transplantation demonstrated a reduction in the severity and duration of oral mucositis, improvement in quality of life, and a decrease in opioid usage and days of total parenteral nutrition in the patients who received rHuKGF-I. Additional studies are underway.
4. **Reduce and inhibit pro-inflammatory cytokines.** A topical, nonsteroidal anti-inflammatory agent, benzydamine, has recently been shown to reduce the frequency and severity of oral ulcerations and the associated oral pain in patients with radiation-induced oral ulcers.² Benzydamine, in addition to its analgesic and antimicrobial activities, inhibits the production and effects of proinflammatory cytokines.

Treatment

Once mucositis begins, treatment is supportive. Little has been shown to change the overall course of mucositis. General measures such as oral hygiene and dietary modification, topical local anesthetics, and systemic analgesics have been recommended. Other options are currently being studied.

Oral hygiene—Good oral hygiene appears to reduce the severity of oral mucositis. Patients should:

- Brush gently with a soft-bristled toothbrush using fluoride containing toothpaste two or three times daily.
- Floss gently, daily to remove food build-up.
- Rinse the mouth every 4 hours with a dilute saline and baking soda solution (½ teaspoon salt plus ½ teaspoon baking soda in a cup of warm water). Chlorhexidine appears no better than sterile saline. In patients with radiotherapy related mucositis, data suggests that chlorhexidine made them worse.
- Remove dentures at night.

Limit food contact—Limit the amount of time food is allowed to come into contact with the oral mucosa. Recommend foods that require little or no chewing. Advise against foods that are irritating, eg, acidic, spicy, salty, coarse, or dry.

Pain relief is challenging. Local anesthetics provide some pain relief. Systemic analgesics are frequently used. Patient-controlled analgesia with an opioid is recommended. Follow standard opioid dosing guidelines (see EPEC-O Module 2: Cancer Pain Management).

Summary

Mucositis is a mucosal barrier injury, characterized by oral erythema, ulceration, and pain. Preventive approaches include: diminish mucosal delivery of anti-cancer agents, antimicrobial/anti-inflammatory interventions, modification of the underlying pathobiology, and reduction/inhibition of pro-inflammatory cytokines. Once mucositis is present, treatment focuses on good oral hygiene and comfort measures.

Nausea

Nausea is an unpleasant subjective sensation of being about to vomit (47,48). Vomiting is the reflex expulsion of gastric contents through the mouth. Nausea may be present without vomiting or vice versa. The awareness of nausea, the inability to keep food or fluids down, the associated acid and bitter tastes, and the unpleasant smells associated with vomitus can be very distressing for patients, families, and caregivers.

Management

In the management of nausea and vomiting, it is frequently not possible to identify or specifically correct the underlying etiology. Time-limited therapeutic trials may provide both relief and clues to underlying causes. Correction of dehydration, hypokalemia and metabolic alkalosis will sometimes resolve the symptom.

Few high-quality therapeutic trials have compared the efficacy of different drugs in specified types of nausea and vomiting outside of chemotherapy. There are five classes of antiemetics drugs: antidopaminergic drugs, antiserotonergic drugs, antihistamines, anticholinergics, and neurokinins (49). In addition, there are a group of adjunctive drugs that, while not directly antiemetics, treat specific causes of nausea (such as hyperacidity or gut dysmotility) or whose mechanism of action is poorly understood.

Empiric therapy with antiemetics usually begins with a single medication targeting the presumed mechanism of nausea/vomiting. The dose should be optimized before a second medication with a different mechanism of action is added rather than substituted. Sequential combination therapy may be required in some patients. (50)

Chemotherapy-associated nausea and vomiting

Three distinct types of chemotherapy-associated nausea and vomiting have been defined: acute, delayed and anticipatory (49).

Acute nausea/vomiting occurs within the first 24 hours after chemotherapy. It usually starts within 1–2 hours and peaks at 4–6 hours. Several groups have classified the emetogenic potential of chemotherapy programs in 5 categories and identified effective oral antiemetic therapy. (See table 1).

Delayed nausea/vomiting occurs more than 24 hours after chemotherapy. With cisplatin, this peaks 48–72 hours after therapy, then gradually subsides for 2–3 days. It is also seen with carboplatin, cyclophosphamide and the anthracyclines. The antiserotonergic and antidopaminergic medications have minimal effect on delayed nausea. The antineurokinin class is the first to show definitive, albeit small, effect on this syndrome.

Anticipatory nausea/vomiting is a conditioned response to previous experiences. If acute and delayed nausea are prevented, anticipatory nausea does not occur. Once it occurs, it is a learned response—it is not mediated by the usual emetic neurotransmitters. Once established, benzodiazepines for their anxiolytic and amnestic properties are most useful. Psychotherapy with a focus on cognitive/behavioral interventions may be adjunctive.

Opioid-induced nausea/vomiting

Opioids have been associated with acute nausea in up to 30% of patients, particularly young women. This is thought to be due to direct effects in the chemoreceptor trigger zone and the vestibular apparatus. Antidopaminergics (such as prochlorperazine) can be given as a premedication in patients at high risk. Antihistamines, anticholinergic and antiserotonergic drugs have all been observed to be effective (8). Fortunately, patients generally develop pharmacological tolerance to this side effect within 5–7 days of initiating therapy, and the antiemetics can be discontinued. For some patients, changing to a different opioid is also effective.

Nausea that emerges after chronic use is most likely mediated through diminished gut motility and/or constipation causing pseudo obstruction. Management is best directed at increasing gut motility and relieving constipation.

Dopamine antagonists

Dopamine-mediated nausea is probably the most common form of nausea, and the most frequently targeted for initial symptom management outside of the chemotherapy setting. These medications are phenothiazines or butyrophenone neuroleptics and have the potential to cause drowsiness and extrapyramidal symptoms, particularly in young women. Haloperidol is less sedating. Medication dosing options include:

- Haloperidol, 0.5–2.0 mg PO, IV, SC q 6 h, then titrate
- Metoclopramide, 10–20 mg PO q 6 h
- Olanzapine 5 – 10 mg daily
- Perphenazine, 2–8 mg PO, IV q 6 h
- Prochlorperazine, 10–20 mg PO q 6 h or 25 mg pr q 12 h or 5–10 mg IV q 6 h

Histamine antagonists (antihistamines)

All antihistamines typically used to control nausea may also cause sedation (9). Because the antihistamines also have anticholinergic properties, they may do “double duty” as a single agent and cover both mechanisms. Consider using:

- Diphenhydramine, 25–50 mg PO q 6 h
- Hydroxyzine, 25–50 mg PO q 6 h
- Meclizine, 25–50 mg PO q 6 h

Acetylcholine antagonists (anticholinergics)

If a motion-related component is elicited, the vestibular apparatus is implicated. In addition, opioids and anesthetics can trigger acetylcholine-mediated nausea in the vestibular apparatus.³ A medication from this class may be added to other antiemetics in empiric therapy. Consider (10):

- Scopolamine, 0.1–0.4 mg SC, IV q 4 h or
1–3 transdermal patches q 72 h or
10–80 µg/h by continuous IV or SC infusion

Serotonin antagonists

Serotonin (hydroxytryptophan) subtype 3 (commonly abbreviate HT-3) has been particularly implicated in chemotherapy-associated nausea. This class of medications can be exceedingly effective if serotonin is a mediator, but they are very expensive. For each drug, there is a plateau in therapeutic efficacy; titration beyond gives no improvement in outcome. Outside the setting of prophylaxis before chemotherapy and before radiotherapy to the abdomen (that stimulates serotonin release from the gut lining), and postoperative nausea, they can be useful for refractory nausea of diverse types but are typically tried only when other medications have failed (11). They should be promptly stopped if they are not effective after a short trial. Medication and dosing options include:

- Dolasetron, 200 mg PO or 50 mg IV
- Granisetron, 1 mg PO q d or bid
- Ondansetron, 8 mg PO tid
- Palonosetron 0,25 mg IV

Neurokinin antagonists

The newest class of antiemetic, neurokinin-1 receptor antagonists, is used in combination with a serotonin inhibitor and dexamethasone for highly emetogenic chemotherapy with significant potential for delayed nausea and vomiting.

- Aprepitant 125 mg day 1 followed by 80 mg days 2 and 3

Prokinetic agents

A “sluggish” or dyskinetic gut, due to carcinomatosis, opioid therapy, other medications, etc., may be a profound source of nausea and vomiting in patients with advanced disease (12,13). A large liver may be causing a “squashed stomach.” Ascites or peritoneal disease may be causing pseudo-obstruction. Constipation can be an exacerbating factor. Medication and dosing options include:

- Erythromycin 250 mg PO q 6 h (ac & HS)
- Metoclopramide, 10–20 mg PO q 6 h (ac & HS)

Antacids

Hyperacidity, with or without gastroesophageal reflux and/or gastric or duodenal erosions, may produce considerable nausea, heartburn, acidity, or bitter taste. Possible therapies include:

- Antacids, 1–2 tablespoons q 2 h PRN
- H₂ Receptor Antagonists (e.g. cimetidine 800 mg hs, famotidine 40 mg hs, ranitidine 150 mg hs)
- Proton pump inhibitors (omeprazole 20 mg daily, lansoprazole 30 mg daily, pantoprazole 40 mg daily)

Other medications

This heterogeneous class of medications has unclear mechanisms of action, but uncontested benefits in some patients (13–15). Consider:

- Dexamethasone, 6–20 mg daily
- Lorazepam, 0.5–2 mg PO q 4–6 h
- Tetrahydrocannabinol, 2.5–5 mg PO tid

Summary

Acute and chronic nausea are associated with misery, poor quality of life, and can impair comprehensive cancer care. Management requires 3 things: a solid knowledge of the pathophysiology, including neurotransmitters; a careful evaluation to target likely etiologies; and skillful administration of medications, frequently in combination and titrated to effect.

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Table 1

Antiemetic Regimens Based on Emetogenic Potential of Chemotherapy (6,7)

Emetogenic Class	Acute Vomiting (incidence)	Regimen to prevent acute chemotherapy- associated nausea
I	Minimal (< 10 %)	PRN antidopaminergic
II	Low (10–30%)	Dexamethasone 20 mg orally once
III	Mild (30–60%)	5 HT-3 inhibitor + Dexamethasone 20 mg orally once
IV	Moderate (80–90%)	5 HT-3 inhibitor + Dexamethasone 20 mg orally once
V	High (>90%)	5 HT-3 inhibitor + Dexamethasone 20 mg orally once + Aprepitant (NK1 inhibitor), eg, Emend®