CME CREDIT ***EDUCATIONAL OBJECTIVE:*** Readers will recognize the importance of assessment and palliation of symptoms in cancer patients

**LAURA K. SHOEMAKER, DO**
The Harry R. Horvitz Center for Palliative Medicine, Taussig Cancer Institute, Cleveland Clinic

**BASSAM ESTFAN, MD**
Department of Hematology and Medical Oncology, Cleveland Clinic

**RAGHAVA INDURU, MD**
The Harry R. Horvitz Center for Palliative Medicine, Taussig Cancer Institute, Cleveland Clinic

**T. DECLAN WALSH, MD**
The Harry R. Horvitz Center for Palliative Medicine, Taussig Cancer Institute, and Department of Hematology and Medical Oncology, Cleveland Clinic

# Symptom management: An important part of cancer care

## ABSTRACT

Physicians can do a better job of palliating symptoms and improving the quality of life of cancer patients if they understand the principles of symptom management. We review the general principles of symptom management for fatigue, anorexia, constipation, dyspnea, nausea, and vomiting.

## KEY POINTS

Patients with advanced cancer typically suffer from multiple concurrent symptoms, which they rate as moderate or severe.

The principles of symptom management include taking an aggressive detailed approach, prioritizing, and identifying symptom pathophysiology.

Prescribed regimens should be specific and simple; physicians should consider the patient's age and fragility, the cost of the treatment, and anticipated drug side effects.

To ensure optimal palliation with the fewest possible adverse effects, reassess frequently, make one change at a time, and use rescue doses.

doi:10.3949/ccjm.78a.10053

Cancer patients experience many distressing symptoms during the course of their illness. In addition to pain, they commonly suffer from fatigue, anorexia, constipation, dyspnea, nausea, and vomiting.[1]

*See related commentary, page 24.*

Although it is important to diagnose and manage the cancer itself, it is also the physician's duty to recognize and effectively treat associated symptoms, regardless of the outcome of the underlying disease.

Some of the symptoms are due to the underlying disease, but some are iatrogenic, as many medical interventions have predictable adverse effects, such as nausea and vomiting with chemotherapy or constipation with opioids.

Symptoms of advanced cancer become chronic, and patients usually rate them as moderate or severe.[1] Unrelieved suffering causes demoralization and may quickly impair quality of life.[2]

Understanding the principles of symptom management may help optimize palliation and improve quality of life. In this paper, we outline an approach to the management of cancer-related symptoms.

## A HEAVY BURDEN OF SYMPTOMS

In patients with advanced cancer, the prevalence rates of various symptoms are approximately as follows[1,3]:

- Pain 89%
- Fatigue 69%
- Weakness 66%
- Anorexia 66%
- Lack of energy 61%
- Nausea 60%

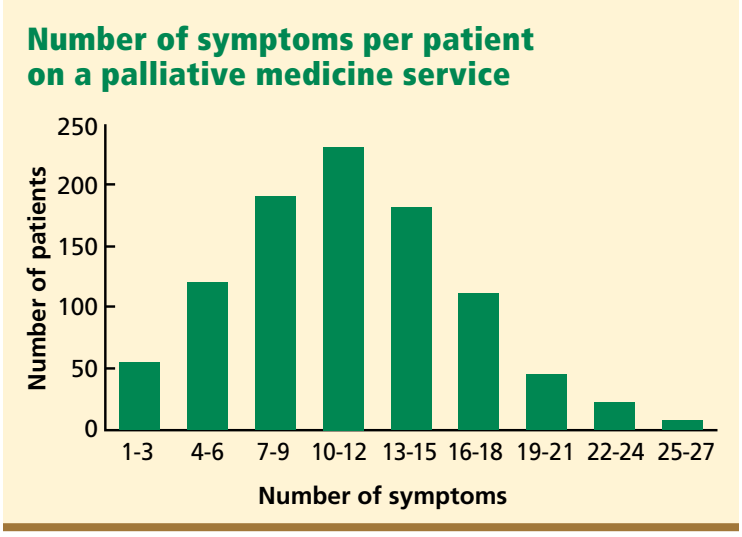


**FIGURE 1**

DATA FROM HOMSI J, WALSH D, RIVERA N, ET AL. SYMPTOM EVALUATION IN PALLIATIVE MEDICINE: PATIENT REPORT VS SYSTEMATIC ASSESSMENT. SUPPORT CARE CANCER 2006; 14:444–453.

- Dry mouth 57%
- Constipation 52%
- Early satiety 51%
- Dyspnea 50%
- Vomiting 30%.

Furthermore, patients with advanced cancer typically have multiple concurrent symptoms. In a survey of patients in a palliative medicine service at our hospital,[4] we found that the median number of symptoms per patient was 10 (range 0–25) (FIGURE 1).

**Patients may underreport their symptoms or may not mention them if not asked directly**

## PRINCIPLES OF SYMPTOM MANAGEMENT

**Show an interest in the patient's symptoms.** Many patients with advanced cancer believe that suffering is an inevitable part of the disease or of its treatment.

Ask patients about their symptoms in a positive and detailed fashion, starting with open-ended questions and following up with specific questions. Patients may underreport their symptoms or may not mention them if not asked directly. In the survey of palliative care patients at our hospital mentioned above,[4] the median number of *volunteered* symptoms was only 1 (range 0–6), whereas a median of 10 were found by systematic assessment.

The examiner should clarify when necessary and recognize that a layperson's language may not directly translate to medical language. For example, a patient may not understand the term "anorexia." Furthermore, "loss of appetite" may mean nausea, vomiting, constipation, or early satiety. "Numbness" may mean a loss of sensation or a pins-and-needles sensation. Symptoms should also be quantified using a consistent measure (ie, numerical or categorical) to facilitate monitoring.

**Prioritize the symptoms.** Advanced cancer is accompanied by multiple symptoms. Assess which ones are most bothersome, and where therapy should be directed first.

**Try to understand the pathophysiology behind the symptom.** When possible, choose a drug treatment that targets the likely underlying cause. Nausea and vomiting, for example, can be secondary to gastric outlet obstruction, hypercalcemia, increased intracranial pressure, esophagitis, opioid use, or constipation.

**Be specific about the drug, dosing, timing, and route, and keep it simple.** If a regimen is cumbersome, compliance suffers. It is better to start one medication for the most bothersome symptom or symptoms and make some progress than it is to overwhelm the patient with a complex list of drugs. Sustained-release formulations are often useful. It is unrealistic to expect most patients to take a medication every 4 hours around the clock. Try the most cost-effective remedies first, and attempt to use one drug that may address multiple symptoms. For example, dexamethasone may have positive effects on energy, pain, and appetite.

**Use 'rescue dosing.'** Rescue drugs are important for expected symptom exacerbations in those on sustained medication. This approach increases efficacy and minimizes adverse effects. In most cases, the rescue medication should be the same as the regularly scheduled one. For example, a prescription to treat nausea may read "metoclopramide (Reglan) 10 mg by mouth before meals and at bedtime and every 4 hours as needed to treat nausea or vomiting."

**Consider the patient's age and fragility, the cost of the drug, and anticipated adverse effects.** Oral or transdermal preparations are preferable to parenteral ones with regard to convenience and compliance, although many transdermal preparations are costly. If parenteral dosing is necessary, the subcutaneous route is

an alternative to the intravenous route.

**Discontinue drugs that are ineffective or unnecessary.** This may help compliance and diminish adverse effects.

**Make one change at a time** so the response to that change is clear. Titrate one drug to its effective dose, to its maximum dose, or to a level of intolerability before considering another. If one drug of a class is ineffective, another drug in the same class may work.

**Reassess often.** A follow-up phone call or office visit in 1 to 2 weeks is appropriate. The symptoms of advanced cancer are often progressive, so regular evaluation is important, even if symptoms are controlled on stable drug regimens. Instructions should be both verbal and written and should be communicated to patients and any involved caregiver to ensure compliance. Have a "plan B" if the first plan is ineffective.

A challenging and important part of symptom management is to assess the goals of care. Every intervention is not appropriate for every patient. Which therapies are used depends on the stage of the disease, the available disease-modifying treatments, and the patient's condition and preferences. Patients and their loved ones should be engaged in discussions about goals of care early in the disease and should be included in medical decision-making. Both curative treatment and palliative treatment are important, but palliation plays a bigger role towards the later stages of advanced cancer (FIGURE 2).

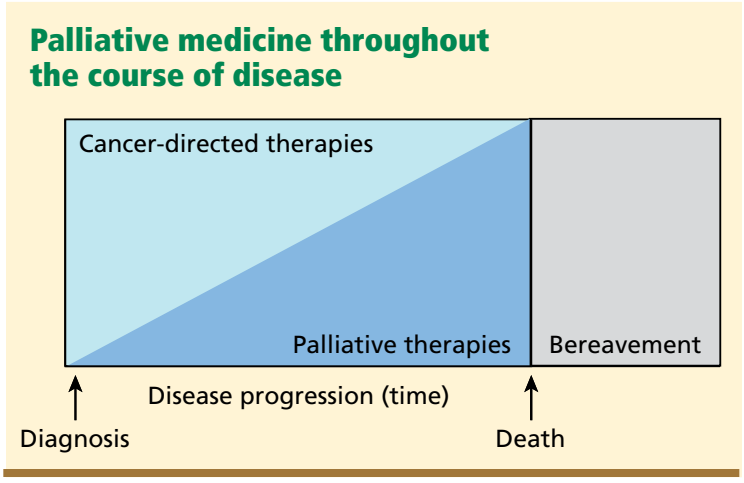


**FIGURE 2.** During the course of progressive cancer, proportionally more attention is directed to relieving symptoms and less to treating the underlying disease.

## CANCER-RELATED FATIGUE: COMMON BUT NOT INEVITABLE

Most cancer patients report fatigue. Although it is one of the most common symptoms in advanced cancer,[5] it is not necessarily inevitable or untreatable.[6]

Cancer-related fatigue is multidimensional and develops over time, diminishing energy, mental capacity, and psychological condition.[7] Patients may report feeling tired or being unable to complete their activities of daily living. People who were previously very active may be frustrated by their inability to participate in favorite leisure activities, which has a big impact on quality of life. Fatigue can be physical, emotional, or mental. It is important to distinguish physical weakness from dyspnea on exertion, which is commonly reported as fatigue. Depression may also cause or exacerbate fatigue.

Unlike fatigue in the general population, cancer-related fatigue does not improve with rest, and patients often report large amounts of unrestorative sleep.

**Cancer-related fatigue may not improve with rest, and patients often report large amounts of unrestorative sleep**

### Look for reversible causes of fatigue

First, conduct a thorough assessment to identify any reversible causes, such as:

- Anemia
- Insomnia, sleep disturbance
- Malnutrition
- Pain
- Depression
- Medical comorbidities: renal, cardiac, or pulmonary disease
- Hypothyroidism
- Hypogonadism.

In many cases, however, a reversible cause cannot be found.

### Treating cancer-related fatigue

**Nonpharmacologic interventions** have been evaluated for this application, but evidence of efficacy is limited and mixed. The National Cancer Comprehensive Network guidelines[8] suggest that energy conservation and education about cancer-related fatigue are central to management. Patients should be advised that fatigue has a fluctuating course and

that they have a limited pool of energy, which they should conserve and use judiciously.

In a meta-analysis by Schmitz et al,[9] physical activity interventions were found to be beneficial. Sixty-three percent of those studied were undergoing active treatment, so whether this population reflects advanced cancer is unclear. A small pilot study in advanced cancer found a trend toward benefit with exercise.[10]

**Comment.** The strategies of rest and exercise are complementary. The key point is to plan them per personal preference.

**Psychostimulants** include methylphenidate (Ritalin). A randomized placebo-controlled trial in patients with acquired immunodeficiency syndrome (AIDS) found methylphenidate 15 to 60 mg/day to have a positive effect.[11] Prospective studies have shown similar results in cancer patients,[12] and a Cochrane review in 2008 showed a small but significant benefit in cancer-related fatigue.[13]

Methylphenidate is usually started at a dose of 5 mg given at 8:00 AM and at noon, and then titrated. Benefit, when experienced, is typically noted within 24 to 48 hours. Possible adverse effects include anorexia, insomnia, anxiety, confusion, tremor, and tachycardia.

Stimulants should be used with caution in patients with cardiac disease or delirium.

**Modafinil** (Provigil), a nonstimulant agent, has been less studied, but it may also help.[14,15] The usual dosage is 50 to 200 mg daily.

**Corticosteroids** may have a role in advanced cancer, as suggested by anecdotal reports.[16] They should be used judiciously, as their adverse effects (insomnia, muscle wasting, edema) are themselves burdensome and may outweigh their benefits.

**Tube feeding and parenteral nutrition do not improve survival or comfort in terminally ill patients**

## ANOREXIA CAN BE DISTRESSING TO THE FAMILY AND THE PATIENT

Most patients with advanced cancer experience anorexia, which is a marker of poor prognosis.[1]

Appetite loss may occur in isolation or as a part of the anorexia-cachexia syndrome. This syndrome is a wasting state seen in chronic, advanced diseases including cancer, AIDS, chronic obstructive pulmonary disease, chronic renal insufficiency, and congestive heart failure.[17] The associated weight loss is involuntary and includes both muscle and fat.

Appetite loss alone is usually not bothersome. In fact, anorexia frequently causes more distress to the family than to the patient.[18] The ramifications of decreased appetite, on the other hand, can be devastating. Decreased caloric intake coupled with the hypermetabolic state of malignancy leads to rapid, dramatic changes in body habitus. This outward sign of the ravages of cancer can be psychologically damaging to patients and their loved ones as they contemplate advanced disease and limited life expectancy. They may be concerned about starvation, in which case education about and attempts to normalize the anorexia-cachexia syndrome are essential.

### Look for reversible causes of anorexia

The first step in the management of anorexia is to identify any reversible causes, such as:

- Stomatitis
- Constipation
- Uncontrolled severe symptoms such as pain or dyspnea
- Delirium
- Nausea, vomiting
- Depression
- Gastroparesis.

### Managing cancer-related anorexia

**Nonpharmacologic measures** include nutritional counseling and increased physical activity. Patients may be counseled to eat calorie-dense foods and supplemental high-calorie, high-protein, high-fat drinks. Some may be able to take advantage of a diurnal variation in appetite, usually an increased appetite in the morning.

**Megestrol acetate** (Megace) improved appetite and induced weight gain when used in a dosage of 800 mg daily in a randomized controlled trial in AIDS patients.[19] Case studies have shown doses as low as 80 to 160 mg daily to be beneficial.[20] Most of the added weight is fat, not lean muscle mass. Unfortunately, the addition of testosterone to megestrol did not increase the accumulation of lean muscle mass in another randomized trial.[21] But the addition of olanzapine (Zyprexa) to megestrol was associated with improved appetite and weight gain in a significant percentage of advanced cancer patients.[22] Rates of adverse effects with megestrol are low; the most significant adverse

effect is thromboembolism.

**Corticosteroids.** While much of the support for corticosteroids is anecdotal, a prospective study of dexamethasone 4 to 16 mg daily showed improvement in several symptoms, including appetite.[23] Because of the multiple adverse effects of corticosteroids, careful attention to dose, duration, and tolerability is essential. Corticosteroids should be discontinued if the desired positive effects are not observed within 3 to 5 days. If prolonged survival is expected, wean to the lowest effective dose.

**Cannabinoids.** Dronabinol (Marinol), a synthetic formulation of delta-9-tetrahydrocannabinol (THC), the active agent of marijuana, has been beneficial in AIDS anorexia. Fewer studies have been done in advanced cancer.

In a small, open-label case series, doses of 7.5 to 15 mg of dronabinol daily improved appetite and were well tolerated.[24] On the other hand, in a multicenter, randomized, double-blind, placebo-controlled trial, neither cannabis extract nor THC (5 mg daily) significantly improved appetite over a 6-week period.[25]

A large randomized study found megestrol acetate 800 mg to be superior to dronabinol 5 mg daily for treating anorexia.[26]

Neurotoxicity, anxiety, nervousness, dizziness, euphoria, and somnolence from dronabinol can be severe and intolerable for some.

**Enteral tube feeding and parenteral nutrition** do not improve survival or comfort in terminally ill patients.[27] On the contrary, they are associated with complications, including aspiration pneumonia, sepsis, abdominal pain, vomiting, and diarrhea. Nevertheless, in some patients with mechanical impediments to nutrition (eg, esophageal fistula, obstruction, or proximal small bowel obstruction) or in those who are hungry and unable to take food by mouth, tube feeding may be appropriate.

## CONSTIPATION SHOULD BE ANTICIPATED, AND PREVENTED IF POSSIBLE

Constipation is variably defined by patients and health care professionals, but it usually includes components of the Rome II criteria, ie, two or more of the following symptoms[28]:

- Straining at least 25% of the time
- Hard stools at least 25% of the time
- Incomplete evacuation at least 25% of the time
- Two or fewer bowel movements per week.

These criteria were intended to describe functional constipation in a healthy population.[27]

More than 50% of patients with advanced cancer report constipation,[1] and in those on opioids, the scope of the problem is larger. In addition to binding central nervous system receptors to mediate pain perception, opioids bind systemic receptors including those in the gut. As a result, opioids interfere with smooth muscle tone and contractility, lengthen transit time, promote dry stools, and increase anal sphincter tone.[29] A nursing study found that when patients taking opioids were screened for constipation, 95% identified it as the major adverse effect of their pain regimen.[30]

### Multiple causes of constipation

Factors that can cause or contribute to constipation include:

- Dietary factors such as a generally low intake of food, and specifically of fiber
- Inactivity
- Confusion
- Dehydration
- Intestinal obstruction
- Cormorbidities such as diabetes mellitus, hypothyroidism, hypercalcemia
- Uncomfortable toilet arrangements
- Drugs such as opioids (as noted above), anticholinergics, antihypertensives, antacids, diuretics, and iron supplements.

**Constipation prophylaxis should be started at the initiation of any regular opioid regimen**

### Take a proactive approach to constipation

Constipation is expected in a number of clinical scenarios, such as with the use of opioids or with limited mobility. Patients often attribute constipation to diminished oral intake. But despite low oral intake, regular, smaller-caliber bowel movements are important to ensure that sloughed bowel endothelium and bacteria are eliminated.

Although little evidence supports the use of one standard bowel regimen, prevention is essential. The goal is a soft bowel movement every 1 to 2 days. Constipation prophylaxis should be started at the initiation of any regular opioid regimen. Encouraging physical activity and oral fluid intake and creating a fa-

**TABLE 1**

**Commonly used laxatives and their mechanisms of action**

**Stool softeners**
Docusate sodium (Colace)
Surfactant, increases water penetration in stool

**Laxatives**
Lactulose
Osmotic, retains water in gut lumen

**Saline laxatives**
Magnesium hydroxide, magnesium citrate (milk of magnesia)
Osmotic, retains water in gut lumen
Stimulates peristalsis at higher doses

**Stimulants**
Senna (Senokot)
Alters electrolyte transport of intestinal mucosa
Increases peristalsis

Bisacodyl (Dulcolax)
Alters electrolyte transport of intestinal mucosa
Increases peristalsis

**Opioid antagonists**
Methylnaltrexone (Relistor)
Blocks peripheral opioid receptors in the gut

**Common causes of nausea and vomiting in advanced cancer: impaired gastric emptying, chemical and metabolic factors, bowel obstruction**

vorable environment for elimination may also help manage constipation.

Commonly used laxatives and their mechanisms of action are listed in TABLE 1.

In our practice, we use a softening agent such as docusate sodium (Colace) 100 mg twice daily, and add a laxative agent such as senna (Senokot) or a magnesium-based osmotic agent as needed. Bulking agents such as over-the-counter fiber supplements should be used with caution in opioid-related constipation. If there has been no bowel movement for 48 hours, a rectal suppository or enema is used. Suppositories or enemas can be scheduled regularly for bedbound patients with chronic constipation.

**Methylnaltrexone** (Relistor), a mu-opioid antagonist, is a new agent that blocks peripheral opioid receptors in the gut. In a randomized study of 133 patients, methylnaltrexone produced laxation within 4 hours of administration in 48%.[31] This methylated, charged compound does not significantly cross the blood-brain barrier and therefore does not interfere with analgesia or cause opioid withdrawal. The dose is 8 mg or 12 mg subcutaneously (based on weight), which can be repeated in 48 hours. If laxation does not occur after one to three doses, other causes of constipation should be explored.

Methylnaltrexone is contraindicated in patients with bowel obstruction, even if the obstruction is thought to be secondary to opioids. Adverse effects include abdominal pain, flatulence, and nausea.

## NAUSEA AND VOMITING: NOT ALWAYS DUE TO CHEMOTHERAPY

Nausea (the sensation of the need to vomit) and vomiting (the forceful expulsion of gastric contents) are common symptoms in advanced cancer and are not necessarily related to chemotherapy or radiation therapy. About 60% of cancer patients have nausea, and about 30% vomit.[32] Both symptoms are very distressing and diminish quality of life.

### Look for potentially reversible causes of nausea and vomiting

Identifying the cause, which is sometimes reversible, may help direct treatment. Potentially reversible causes include:

- Drugs
- Uremia
- Infection
- Anxiety
- Constipation
- Gastric irritation
- Proximal gastrointestinal obstruction.

In a prospective study of 121 patients with advanced cancer, the most common causes of nausea and vomiting were impaired gastric emptying, chemical and metabolic factors (drugs, organ failure, electrolyte disturbance, infection), and bowel obstruction.[33–35]

### Management of nausea and vomiting

Management of nausea and vomiting may require multiple antiemetics, which may need to be given intravenously or subcutaneously.[33]

### The choice of drugs depends on the cause of the nausea

The evidence-based choice of drugs for nausea depends on the cause[33–35]:

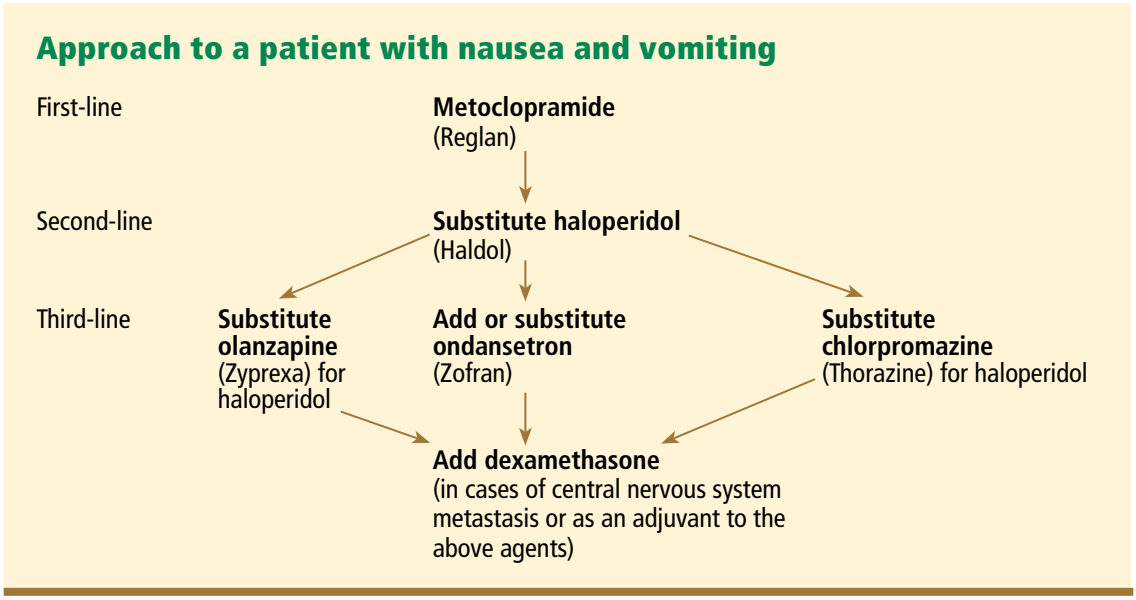


FIGURE 3

- Nausea due to chemical or metabolic factors: haloperidol (Haldol), levomepromazine (another antipsychotic drug, not available in the United States), cyclizine (Marezine)
- Nausea due to gastric stasis, outlet obstruction: metoclopramide, domperidone (a similar drug, not available in the United States), levomepromazine
- Nausea due to regurgitation: metoclopramide, cyclizine, haloperidol, levomepromazine
- Nausea due to bowel obstruction: metoclopramide (if obstruction is not complete), domperidone, cyclizine, levomepromazine, octreotide (Sandostatin), hyoscyamine (Levsin)
- Nausea due to cranial disease: cyclizine, levomepromazine
- Movement-related nausea: cyclizine, levomepromazine, hyoscyamine
- Cause unclear or multiple causes: cyclizine, haloperidol, levomepromazine
- Cortical nausea: lorazepam (Ativan).

If a cause cannot be found or an extensive diagnostic evaluation is not indicated, an empiric approach to management is appropriate (FIGURE 3). For patients who are dying, for example, prompt symptom control is the priority. A systematic review of the efficacy of antiemetics in advanced cancer demonstrated that the empiric approach was as efficacious as the etiologic approach.[36]

**Metoclopramide.** If complete bowel obstruction is not suspected, oral metoclopramide, a dopamine antagonist, is our choice for first-line drug therapy.[32] Adverse effects include abdominal pain, diarrhea, and sedation.

**Haloperidol**, another dopamine antagonist, can also be used.[32] Haloperidol may cause sedation and is associated with a prolonged QTc interval. Care should be taken in those at risk for dysrhythmia or arrhythmia.

**Olanzapine** (Zyprexa) is an alternative antipsychotic for patients who cannot tolerate or do not respond to metoclopramide and haloperidol.

**Ondansetron** (Zofran), a serotonin 5-HT3 receptor antagonist, is usually reserved for nausea and vomiting associated with chemotherapy or radiation, but it can be used in advanced cancer if the above agents fail.[37]

**Dexamethasone.** Those with central nervous system metastasis can be treated with dexamethasone as an adjuvant to the above therapies (TABLE 2).

**Increasing the rate of a continuous opioid infusion does not provide the prompt relief of dyspnea a bolus dose delivers**

## DYSPNEA IS COMMON, EVEN WITHOUT LUNG DISEASE

Dyspnea is the subjective perception of impaired breathing, which may include the sensation of breathlessness, chest tightness, air hunger, suffocation, or increased work of breathing.

TABLE 2

**Dosing strategies for commonly used antiemetics**

| DRUG | AROUND-THE-CLOCK DOSING | AS-NEEDED DOSING | MAXIMUM DOSE |
|---|---|---|---|
| **Metoclopramide** (Reglan) | 10 mg by mouth before meals and at bedtime<br>40–60 mg/24 hours subcutaneously or by continuous intravenous infusion | 10 mg by mouth, subcutaneously, or intravenously every 4 hours | 120 mg/24 hours |
| **Haloperidol** (Haldol) | 1 mg by mouth every 12 hours<br>5–15 mg/24 hours subcutaneously or by continuous intravenous infusion | 1 mg by mouth, subcutaneously, or intravenously every 4 hours | 20 mg/24 hours |
| **Olanzapine** (Zyprexa) | 2.5–5 mg sublingually every 12 hours | 2.5–5 mg sublingually every 6 hours | |
| **Ondansetron** (Zofran) | 4–8 mg by mouth or intravenously every 12 hours | 4 mg by mouth or intravenously every 6 hours | 32 mg/24 hours |
| **Dexamethasone** | 8 mg by mouth or intravenously at 8 AM and at noon | Not applicable | |

**We do not recommend writing opioid infusion orders with a 'titrate to comfort' clause in the terminally ill**

At least half of patients with advanced cancer complain of dyspnea.[1] Most have primary pulmonary malignancies or metastatic lung disease, but almost 25% have no documented lung involvement or underlying cardiopulmonary diagnosis to which to attribute it.[38]

Dyspnea is often very distressing. Palliative sedation is used more frequently for the relief of intractable dyspnea than for pain.[39]

### Opioids are effective but underutilized for dyspnea

Although opioids are effective in both oral and parenteral formulations for the symptomatic management of dyspnea,[40] the exact mechanism by which they improve dyspnea is unknown. Central control of respiration occurs in the medulla, and perception of dyspnea is mediated by the sensory cortex.

Opioids are underutilized by physicians other than palliative medicine specialists because of concern about respiratory depression. Appropriately titrated, opioids are safe and do not cause clinically significant respiratory depression.[41]

Allen et al[42] showed that an opioid in low doses (diamorphine 2.5 mg subcutaneously) was effective and well tolerated in elderly patients with advanced pulmonary fibrosis who had not received opioids before.

**Start low and go slow.** An appropriate starting dose for a patient who has not been on opioids before may be morphine sulfate 2 mg intravenously (or a 5-mg immediate-release tablet by mouth) every 2 hours as needed for dyspnea. After 24 to 48 hours of an as-needed regimen, one can evaluate the patient's response, tolerance, and dose requirement. If needed, parenteral infusion or a long-acting opioid preparation can be started with continued as-needed bolus dosing for breakthrough dyspnea.

We do not recommend writing opioid infusion orders with a "titrate to comfort" clause in the terminally ill. Increasing the rate of a continuous infusion does not provide the prompt symptomatic relief a bolus dose deliv-

ers. Dose accumulation and adverse effects are more likely when opioids are titrated in this fashion.

A Cochrane review showed that nebulized opioids are ineffective for dyspnea.[43]

### Oxygen paradoxically does not improve dyspnea

Oxygen is commonly prescribed, although the literature does not indicate that it improves the sensation of breathlessness.[44]

A study by Clemens et al[45] showed no correlation between dyspnea and oxygen saturation. It also found morphine to be superior to oxygen in subjective dyspnea, even in hypoxia.

A double-blind crossover study showed that ambient air delivered via nasal cannula was as effective as oxygen for dyspnea.[46] The inexpensive and simple practice of a fan to blow ambient air on the patient's face may help relieve dyspnea.

## REFERENCES


1. **Donnelly S, Walsh D**. The symptoms of advanced cancer. Semin Oncol 1995; 22(2 suppl 3):67–72.
2. **Walsh D, Rybicki L, Nelson KA, Donnelly S**. Symptoms and prognosis in advanced cancer. Support Care Cancer 2002; 10:385–388.
3. **Komurcu S, Nelson KA, Walsh D, Donnelly SM, Homsi J, Abdullah O**. Common symptoms in advanced cancer. Semin Oncol 2000; 27:24–33.
4. **Homsi J, Walsh D, Rivera N, et al**. Symptom evaluation in palliative medicine: patient report vs systematic assessment. Support Care Cancer 2006; 14:444–453.
5. **Donnelly S**. Quality-of-life assessment in advanced cancer. Curr Oncol Rep 2000; 2:338–342.
6. **Stone P, Richardson A, Ream E, Smith AG, Kerr DJ, Kearney N**. Cancer-related fatigue: inevitable, unimportant and untreatable? Results of a multi-centre patient survey. Cancer Fatigue Forum. Ann Oncol 2000; 11:971–975.
7. **Portenoy RK, Itri LM**. Cancer-related fatigue: guidelines for evaluation and management. Oncologist 1999; 4:1–10.
8. **Berger AM, Abernethy AP, Atkinson A, et al**. NCCN Clinical Practice Guidelines in Oncology Cancer-related fatigue—v.1.2010. www.nccn.org/professionals/physician_gls/PDF/fatigue.pdf. Accessed November 15, 2010.
9. **Schmitz KH, Holtzman J, Courneya KS, Mâsse LC, Duval S, Kane R**. Controlled physical activity trials in cancer survivors: a systematic review and meta-analysis. Cancer Epidemiol Biomarkers Prev 2005; 14:1588–1595.
10. **Porock D, Kristjanson LJ, Tinnelly K, Duke T, Blight J**. An exercise intervention for advanced cancer patients experiencing fatigue: a pilot study. J Palliat Care 2000 Autumn; 16:30–36.
11. **Breitbart W, Rosenfeld B, Kaim M, Funesti-Esch J**. A randomized, double-blind, placebo-controlled trial of psychostimulants for the treatment of fatigue in ambulatory patients with human immunodeficiency virus disease. Arch Intern Med 2001; 161:411–420.
12. **Sarhill N, Walsh D, Nelson KA, Homsi J, LeGrand S, Davis MP**. Methylphenidate for fatigue in advanced cancer: a prospective open-label pilot study. Am J Hosp Palliat Care 2001; 18:187–192.
13. **Minton O, Richardson A, Sharpe M, Hotopf M, Stone P**. A systematic review and meta-analysis of the pharmacological treatment of cancer-related fatigue. J Natl Cancer Inst 2008; 100:1155–1166.
14. **Kaleita TA, Wellisch DK, Graham CA, et al**. Pilot study of modafinil for treatment of neurobehavioral dysfunction and fatigue in adult patients with brain tumors (abstract). J Clin Oncol 2006; 24(suppl):58s.
15. **Morrow GR, Jean-Pierre P, Roscoe JA, et al**. A phase III randomized, placebo-controlled, double-blind trial of a eugeroic agent in 642 cancer patients reporting fatigue during chemotherapy: a URCC CCOP study (abstract). J Clin Oncol 2008; 26(suppl):504s.
16. **Tannock I, Gospodarowicz M, Meakin W, Panzarella T, Stewart L, Rider W**. Treatment of metastatic prostatic cancer with low-dose prednisone: evaluation of pain and quality of life as pragmatic indices of response. J Clin Oncol 1989; 7:590–597.
17. **Morley JE, Thomas DR, Wilson MM**. Cachexia: pathophysiology and clinical relevance. Am J Clin Nutr 2006; 83:735–743.
18. **Poole K, Froggatt K**. Loss of weight and loss of appetite in advanced cancer: a problem for the patient, the carer, or the health professional? Palliat Med 2002; 16:499–506.
18. **Von Roenn JH**. Randomized trials of megestrol acetate for AIDS-associated anorexia and cachexia. Oncology 1994; 51(suppl 1):19–24.
20. **Donnelly S, Walsh TD**. Low-dose megestrol acetate for appetite stimulation in advanced cancer. J Pain Symptom Manage 1995; 10:182–183.
21. **Mulligan K, Zackin R, Von Roenn JH, et al; ACTG 313 Study Team**. Testosterone supplementation of megestrol therapy does not enhance lean tissue accrual in men with human immunodeficiency virus-associated weight loss: a randomized, double-blind, placebo-controlled, multicenter trial. J Clin Endocrinol Metab 2007; 92:563–570.
22. **Navari RM, Brenner MC**. Treatment of cancer-related anorexia with olanzapine and megestrol acetate: a randomized trial. Support Care Cancer 2010; 18:951–956.
23. **Mercadante S, Fulfaro F, Casuccio A**. The use of corticosteroids in home palliative care. Support Care Cancer 2001; 9:386–389.
24. **Walsh D, Kirkova J, Davis MP**. The efficacy and tolerability of long-term use of dronabinol in cancer-related anorexia: a case series. J Pain Symptom Manage 2005; 30:493–495.
25. **Cannabis-In-Cachexia-Study-Group; Strasser F, Luftner D, Possinger K, et al**. Comparison of orally administered cannabis extract and delta-9-tetrahydrocannabinol in treating patients with cancer-related anorexia-cachexia syndrome: a multicenter, phase III, randomized, double-blind, placebo-controlled clinical trial from the Cannabis-In-Cachexia-Study-Group. J Clin Oncol 2006; 24:3394–3400.
26. **Jatoi A, Windschitl HE, Loprinzi CL, et al**. Dronabinol versus megestrol acetate versus combination therapy for cancer-associated anorexia: a North Central Cancer Treatment Group study. J Clin Oncol 2002; 20:567–573.
27. **Winter SM**. Terminal nutrition: framing the debate for the withdrawal of nutritional support in terminally ill patients. Am J Med 2000; 109:723–726.
28. **Drossman DA, Sandler RS, McKee DC, Lovitz AJ**. Bowel patterns among subjects not seeking health care. Use of a questionnaire to identify a population with bowel dysfunction. Gastroenterology 1982; 83:529–534.
29. **McMillan SC**. Assessing and managing opiate-induced constipation in adults with cancer. Cancer Control 2004; 11(suppl 3):3–9.
30. **Robinson CB, Fritch M, Hullett L, et al**. Development of a protocol to prevent opioid-induced constipation in patients with cancer: a research utilization project. Clin J Oncol Nurs 2000; 4:79–84.
31. **Thomas J, Karver S, Cooney GA, et al**. Methylnaltrexone for opioid-induced constipation in advanced illness. N Engl J Med 2008; 358:2332–2343.
32. **Davis MP, Walsh D**. Treatment of nausea and vomiting in advanced cancer. Support Care Cancer 2000; 8:444–452.
33. **Stephenson J, Davies A**. An assessment of aetiology-based guidelines for the management of nausea and vomiting in patients with

advanced cancer. Support Care Cancer 2006; 14:348–353.
34. **Lichter I**. Results of antiemetic management in terminal illness. J Palliat Care 1993; 9:19–21.
35. **Bentley A, Boyd K**. Use of clinical pictures in the management of nausea and vomiting: a prospective audit. Palliat Med 2001; 15:247–253.
36. **Glare P, Pereira G, Kristjanson LJ, Stockler M, Tattersall M**. Systematic review of the efficacy of antiemetics in the treatment of nausea in patients with far-advanced cancer. Support Care Cancer 2004; 12:432–440.
37. **Currow DC, Coughlan M, Fardell B, Cooney NJ**. Use of ondansetron in palliative medicine. J Pain Symptom Manage 1997; 13:302–307.
38. **Reuben DB, Mor V**. Dyspnea in terminally ill cancer patients. Chest 1986; 89:234–236.
39. **Fainsinger RL, Waller A, Bercovici M, et al**. A multicentre international study of sedation for uncontrolled symptoms in terminally ill patients. Palliat Med 2000; 14:257–265.
40. **Jennings AL, Davies AN, Higgins JP, Broadley K**. Opioids for the palliation of breathlessness in terminal illness. Cochrane Database Syst Rev 2001; CD002066.
41. **Estfan B, Mahmoud F, Shaheen P, et al**. Respiratory function during parenteral opioid titration for cancer pain. Palliat Med 2007; 21:81–86.
42. **Allen S, Raut S, Woollard J, Vassallo M**. Low dose diamorphine reduces breathlessness without causing a fall in oxygen saturation in elderly patients with end-stage idiopathic pulmonary fibrosis. Palliat Med 2005; 19:128–130.
43. **Polosa R, Simidchiev A, Walters EH**. Nebulised morphine for severe interstitial lung disease. Cochrane Database Syst Rev 2002; CD002872.
44. **Currow DC, Agar M, Smith J, Abernethy AP**. Does palliative home oxygen improve dyspnoea? A consecutive cohort study. Palliat Med 2009; 23:309–316.
45. **Clemens KE, Quednau I, Klaschik E**. Use of oxygen and opioids in the palliation of dyspnoea in hypoxic and non-hypoxic palliative care patients: a prospective study. Support Care Cancer 2009; 17:367–377.
46. **Philip J, Gold M, Milner A, Di Iulio J, Miller B, Spruyt O**. A randomized, double-blind, crossover trial of the effect of oxygen on dyspnea in patients with advanced cancer. J Pain Symptom Manage 2006; 32:541–550.

***ADDRESS**: Declan Walsh, MD, MSc, Hematology and Medical Oncology, M76, Cleveland Clinic, 9500 Euclid Avenue, Cleveland, OH 44195; e-mail walsht@ccf.org.*

## CME CALENDAR

# 2011

## JANUARY

**7TH ANNUAL MINIMAL ACCESS GYNECOLOGY**
January 21–24
Ritz-Carlton
Fort Lauderdale, FL
www.ccf.org/florida/cme

**ARAB HEALTH CONGRESS: THE WORLD'S LARGEST MULTI-TRACK MEDICAL CONGRESS**
January 24–27
Dubai, UAE

## FEBRUARY

**A CASE-BASED APPROACH TO CONTROVERSIES IN CARDIOVASCULAR DISEASE: A CLEVELAND CLINIC–MAYO CLINIC PARTNERSHIP, IN COLLABORATION WITH THE EMIRATES CARDIAC SOCIETY AND THE SAUDI HEART ASSOCIATION**
February 3–5
Raffles Dubai, UAE
www.infomedweb.com/cardiovascular

**PRECEPTORSHIP IN CAROTID ULTRASOUND INTERPRETATION**
February 7–11
Cleveland Clinic
Cleveland, OH
www.ccfcme.org/Carotid10

**22ND ANNUAL INTERNATIONAL COLORECTAL DISEASE SYMPOSIUM**
February 17–19
Harbor Beach Marriott
Fort Lauderdale, FL
www.ccf.org/florida/cme

**14TH DIASTOLOGY AND NEW ECHO TECHNOLOGIES, FEATURING HEART VALVE AND CONTRAST ECHO MINISYMPOSIUM**
February 23–26
Westin Hotel
Fort Lauderdale, FL
www.ccfcme.org/echo11

**RHEUMATOLOGY HIGHLIGHTS REPORT *LIVE*, FEATURING ADVANCES IN B CELL BIOLOGY: RA, SLE, AND VASCULITIS**
February 25–26
Westin Hotel
Fort Lauderdale, FL
www.ccfcme.org/RHR11

## MARCH

**6TH ANNUAL PERIOPERATIVE MEDICINE SUMMIT**
March 3–5
Eden Roc Hotel
Miami, FL
www.cme.med.miami.edu

**13TH ANNUAL PAIN MANAGEMENT SYMPOSIUM**
March 5–9
Hyatt Regency Sarasota Hotel
Sarasota, FL
www.ccfcme.org/pain11

**14TH ANNUAL PALLIATIVE MEDICINE AND SUPPORTIVE ONCOLOGY**
March 10–12
Fort Lauderdale, FL

**RHEUMATOLOGY HIGHLIGHTS REPORT *LIVE*, FEATURING ADVANCES IN B CELL BIOLOGY: RA, SLE, AND VASCULITIS**
March 11–12
Scottsdale Conference Center
Scottsdale, AZ
www.ccfcme.org/RHR11

## MAY

**PRECEPTORSHIP IN CAROTID ULTRASOUND INTERPRETATION**
May 2–6
Cleveland Clinic
Cleveland, OH
www.ccfcme.org/Carotid10

**NEW DIRECTIONS IN SMALL-VESSEL VASCULITIS—ANCA, TARGET ORGANS, TREATMENT, AND BEYOND**
May 4
Cleveland Clinic
Cleveland, OH

**FOR SCHEDULE UPDATES AND TO REGISTER ONLINE, VISIT: WWW.CCFCME.ORG**