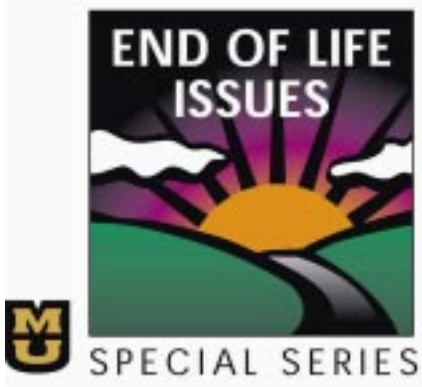
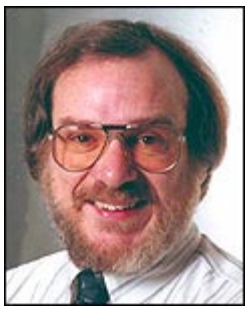


Relieving Non-Pain Suffering at the End-of-life

by David D. Cravens, MD, Clay M. Anderson, MD

Symptoms such as nausea and vomiting cause distress to dying patients and their families, and should be treated as aggressively as pain.



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Abstract

We discuss non-pain problems at end-of-life in this paper. Management of these problems is key to ensuring relief of suffering. Much of this paper is a reiteration of the material on common physical symptoms, which is presented in module 10 of the Education for Physicians on End-of-life Care (EPEC) project of the American Medical Association in conjunction with the Robert Wood Johnson Foundation.

Introduction

The compassionate physician treats disease and manages patients' symptoms to minimize suffering and maximize comfort. This begins with the inception of treatment and continues throughout the disease process. At the end-of-life, when disease-modifying treatments are no longer available, not advisable, or not desired by the patient, care becomes focused on the patient's physical comfort and meeting their emotional and spiritual needs.

Treatment becomes focused on symptom management, often independent of the cause of the symptoms. Symptoms can be caused by the underlying disease process, other associated diseases or conditions, prior treatment, or psychological and emotional factors. The treatments are usually the same regardless of the etiology. Patients near the end-of-life may develop many distressing symptoms. This article will discuss the evaluation and management of the most common end-of-life symptoms: dyspnea, nausea, vomiting, constipation, diarrhea, anorexia, edema, skin ulcers, fatigue and insomnia.

It is worth noting that dying people fear pain the most, but they also fear other symptoms and loss of control and dignity. Comprehensive care based on the uniqueness of the individual, their goals and values are just as important as specific symptom-focused interventions. The principles and practice of this care are discussed in this issue in the articles in the Nov/Dec 2002 issue of Missouri Medicine entitled "Spiritual and Psychological Suffering at the End-of-life," and pain management is discussed in "Pain Relief at the End-of-life."

While pain management is often foremost in the mind of physicians providing end-of-life care, the above-mentioned symptoms can be equally distressing to patients and their caregivers. When disease can no longer be cured or diminished, treatment of symptoms becomes the primary goal. Learning the pathophysiology and appropriate treatment of symptoms is important in helping the patient remain comfortable at end-of-life.

The basic approach to managing symptoms is the same as that used to

Table 1. Benzodiazepines for Dyspnea

MEDICATION	DOSE	ROUTE OF ADMINISTRATION	FREQUENCY
Lorazepam	0.5—2.0 mg	P.O., SL, or IV	q 1h until effect, then q4—6h
Diazepam	5—10 mg	P.O., or IV	q 1h until effect, then q 6—8h
Clonazepam	0.25—2.0 mg	P.O.	q 12h
Midazolam	0.5 mg	IV	q 15min until effect, then continuous SQ or IV

manage any illness: an accurate history, a thorough physical examination and appropriate laboratory or imaging investigations. When the cause and pathophysiology are identified, therapeutic interventions can be implemented to treat the symptom and its underlying cause. Often goals of care may preclude aggressive disease management or the patient may be in the last hours of life. Imaging studies and laboratory investigations may then not be appropriate.

It is important to become comfortable with "treating without diagnosing" in these circumstances. Initiating therapeutic trials based on inference and monitoring patient's responses can provide both symptom relief and additional information regarding symptom pathophysiology.

Dyspnea

Dyspnea may be caused by anemia, airway obstruction, anxiety, bronchospasm, hypoxemia, pleural effusion, pneumonia, pulmonary edema, pulmonary embolism, metabolic disturbances or social and environmental causes. Often it will not be possible to determine or correct the underlying cause. Pharmacological management of dyspnea consists of oxygen, opioids and anxiolytics. Nonpharmacologic measures can greatly ease the suffering of breathlessness. If pneumonia is suspected, it should be treated in a manner consistent with the patient's wishes.

It is important to note the most patients who report breathlessness are not hypoxemic. Pulse oximetry is not as reliable or helpful as is the patient's self-report. Cool air moving across a patient's face may eliminate dyspnea as well as supplemental oxygen. However, a trial of supplemental oxygen may be beneficial; oxygen supplementation is often viewed as symbolic of optimal contemporary medical practice.

Opioids relieve breathlessness in many patients, possibly by both central and peripheral mechanisms. Doses lower than those required to achieve pain control are often successful. While anecdotal reports abound, nebulized opioids have not been shown to have advantage over oral or parenteral regimens. When dosing guidelines are followed, respiratory depression, hastened death or abusive behaviors are not likely.

Opioids alone do not reliably relieve anxiety in many breathless patients; some may require additional treatment. Benzodiazepines are effective, preferably using relatively longer half-life preparations to avoid pronounced peak/trough effects. They are safe to use in conjunction with opioids. See Table 1 for suggested doses of some benzodiazepines.

Non-pharmacologic measures may be beneficial in relieving dyspnea and can be effective as the sole therapy. A cool but comfortable room is ideal, with adequate humidity and free of environmental irritants such as dust or cigarette smoke. A window, open if possible, with an unobstructed pleasing view to the outside is desirable. Limit the number of people in the room to avoid crowding. Relaxation, distraction or hypnotic therapy may be beneficial.

Nausea and vomiting

Nausea is a subjective sensation related to cortical responses or stimulation of either the gastrointestinal lining, the chemoreceptor trigger zone in the brain, or the vestibular apparatus. Neurotransmitters involved include serotonin, dopamine, acetylcholine and histamine. Cortical responses, such as anticipatory nausea associated with chemotherapy, seem to be learned responses and are not associated with specific neurotransmitters. The causes of nausea and vomiting can be thought of as the "*Eleven M's*": metastases, meningeal irritation, movement, mental anxiety, medications, mucosal irritation, mechanical obstruction, motility, metabolic, microbes and myocardial.

Different causes will require different measures for ideal symptom control. Helpful medications include: antacids, anticholinergics, antihistamines, cyto-protective agents, dopamine antagonists, prokinetic agents, and serotonin antagonists

The most common form of nausea is probably dopamine-mediated. Haloperidol is the least sedating dopamine antagonist. See Table 2 for recommended doses of dopamine antagonists for treatment of

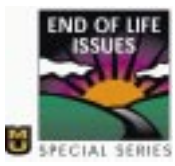


Table 2. Dopamine Agonist for Nausea & Vomiting

MEDICATION	DOSE	ROUTE OF ADMINISTRATION	FREQUENCY
Haloperidol	0.5—2.0 mg	P.O., IV, SC	q 6h, then titrate
Prochlorperazine	10—20 mg	P.O., P.R.	q 6h, q 12h respectively
Prochlorperazine	5—10 mg	IV	q 6h
Droperidol	2.5—5.0 mg	IV	q 6h
Thiethylperizine	10—20 mg	P.O.	q 6h
Promethazine	12.5—25 mg	P.O., P.R., IV	q 4—6h
Perphenazine	2—8 mg	P.O., IV	q 6h
Trimethobenzamide	200—250 mg	P.R., P.O.	q 6—8h,
Metoclopramide	10—20 mg	P.O.	q 6h

dopamine-mediated nausea. Antihistamines having anticholinergic activity may be beneficial. Examples are diphenhydramine, meclizine or hydroxyzine. Doses of 25—50 mg p.o. q 6hrs are usually effective.

Anticholinergics can diminish opioid or anesthetic related nausea that is acetylcholine mediated via the vestibular apparatus. Scopolamine may be used: suggested doses are 0.1—0.4 mg subcutaneous (SQ) or intravenous (IV) q 4hrs, or 1 to 3 transdermal patches q 72hrs, or 10—80 mcg/hr continuous IV or SC infusion.

Serotonin antagonists can be very effective but are extremely expensive. They are usually tried only when other medications have failed. These medications include: Ondansetron 8 mg p.o. tid or Granisetron 1 mg p.o. qd or bid.

Prokinetic agents may be beneficial for nausea related to the sluggish bowel of carcinomatosis, opioid therapy, other medications, pseudo-obstruction from hepatomegaly, ascites or peritoneal disease. Prokinetic medications include: metoclopramide 10—20 mg p.o., q 6hrs or cisapride10—20 mg p.o. q 6hrs (cisapride is no longer commercially available, but physicians interested in enrolling patients in the investigational limited-access program should call toll-free: 1-877-795-4247.)

Nausea related to hyperacidity, esophageal reflux, gastric or duodenal ulceration or erosions may be treated with 15—30 cc of antacid q 2hrs PRN, histamine$_2$ receptor antagonists such as cimetidine, ranitidine or famotidine, or proton pump inhibitors such as omeprazole, lansoprazole, or esomeprazole.

Other medications that have uncertain mechanisms of action but potential benefits in some patients include: dexamethasone 6—20 mg p.o. qd, dronabinol 2.5—5 mg p.o. tid, or lorazepam 0.5—2.0 mg p.o. q 4—6hrs.

Constipation

Constipation may be caused by medications, decreased motility, ileus, mechanical obstruction, dehydration, metabolic abnormalities, spinal cord compression, autonomic dysfunction or malignancy. Unmanaged constipation leads to suffering from abdominal pain, bloating, nausea, vomiting, overflow incontinence, tenesmus, fecal impaction and bowel obstruction. General measures that can be helpful include regular toileting based on the patient's normal bowel habits and utilizing the gastrocolic reflex that occurs after eating.

Cathartics may be required in constipated patients with advanced disease, poor mobility and diminished oral intake. Stimulant laxatives should always be initiated along with opioid therapy to prevent the inevitable opioid-associated constipation. Stimulant laxatives that irritate the bowel and increase peristalsis are helpful. Osmotic agents draw water into the bowel lumen, maintaining or increasing the moisture content and overall volume of stool. Stool softeners are detergent laxatives that facilitate the dissolution of fat in water and increase the water content of stool. See Table 3 for listing of these agents. Lubricant stimulants both lubricate the stool and irritate the bowel creating increased peristalsis. Examples are glycerin suppositories, and mineral or peanut oil. Large volume enemas add water to stool and distend the bowel, inducing peristalsis. Soap suds added to a water enema creates more bowel irritation stimulating additional peristalsis.

Diarrhea

Infections, gastrointestinal bleeding, malabsorption, medications, obstruction, overflow incontinence, stress, or lack of absorptive surface may cause diarrhea. Keys to conservative management involve determining normal function for the patient, and then making dietary adjustments to eliminate gas-producing foods and to

Table 3. Treatments for Constipation

AGENT	DOSE	ROUTE OF ADMINISTRATION	FREQUENCY
STIMULANT LAXATIVES			
Prune Juice	120-240 cc	P.O.	qd or bid
Senna	2 tablets	P.O.-titrate to effect (9 or more per day)	q hs,
Casanthranol	2 tablets	P.O.-titrate to effect (9 or more per day)	q hs
Bisacodyl	5 mg	P.O., P.R.- titrate to effect	q hs
OSMOTIC AGENTS			
Lactulose	30 cc initially	P.O. - then titrate to effect	q 4—6 h
Sorbitol 70%	30 cc initially	P.O. - then titrate to effect	q 4—6 h
Kristalose	20 gm initially	in juice or water P.O. then titrate to effect	q 4—6 h
Magnesium citrate	1—2 bottles	P.O.	PRN
STOOL SOFTENERS			
Sodium docusate	1-2 tablets	P.O., titrate to effect	qd—bid
Calcium docusate	1-2 tablets	P.O., titrate to effect	qd—bid
Phosphosoda	enema	P.R.	qd

increase bulk. Pharmacologic therapy will be required when diarrhea is moderate to severe or has become chronic.

Mild or transient diarrhea can be managed with attapulgite (Kaopectate) 30cc or 2 tablets PRN, or bismuth salts (e.g., Pepto-Bismol) 15—30cc bid—qid. Persistent diarrhea is best managed with agents that slow peristalsis. Treatment options are listed in Table 4. Severe, secretory diarrhea may be managed with octreotide 50 mcg SC q 8—12 hrs; titrate to 500 mcg or higher q 8hrs. Provide parenteral fluid support if necessary and appropriate.

Bowel obstruction

Bowel obstruction, usually from metastatic cancer, causes nausea, vomiting, belching, distention, abdominal cramping, abdominal pain, constipation, and diarrhea. This can be a major challenge for the dying patient, and is difficult to manage medically. Mechanical interventions include surgical bypass or resection, gastrostomy, or nasogastric tube drainage. While these interventions may be appropriate in incurable patients early in the course of their illness, their appropriateness declines over time as harm begins to outweigh benefits. Bowel obstruction managed medically usually requires aggressive intervention and frequent reassessments. Bowel rest (no oral intake) is not obligatory, but will usually help, even if it is only partial. The patient will usually have to be sedated to varying degrees in order to achieve symptomatic relief. A balanced approach using opiates, antispasmodics, benzodiazepines, and antipsychotics is most effective. Corticosteroids may also treat any suspected inflammatory component. Rectal, subcutaneous, or intravenous routes of administration are often required. Bowel obstruction may remit spontaneously for a time, allowing temporary removal of medications and an improved level of alertness and perhaps resumption of some oral intake.

Anorexia

Loss of appetite and loss of weight are commonly encountered in the end stages of many diseases. Caregivers and patients often mistakenly believe they must be doing something wrong in these circumstances. It is important to provide education that these symptoms usually represent natural progression of disease and are not reversible. However, it is reasonable to search for potentially correctable problems that may be adding to the patient's suffering e.g., dysphagia, odynophagia, medication effects, or infections.

Although therapies that improve appetite or stimulate weight gain do not add to longevity, some patients and caregivers may appreciate the semblance of normalcy associated with eating. The patient who is not hungry should not be coerced into eating, as enjoyment of food is the primary goal. Beneficial measures include: 1) eliminate any dietary restrictions. 2) offer favorite foods and supplements if desired. 3) offer an alcoholic beverage such as a glass of

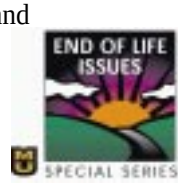


Table 4. Treatments for Diarrhea

MEDICATION	DOSE	ROUTE OF ADMINISTRATION	FREQUENCY
Loperamide	2—4 mg	P.O.	q 6h or higher
Diphenoxalate	2.5—5.0 mg	P.O.	q 6h or higher
Tincture of opium	0.7 cc	P.O.	q 4h and titrate

Table 5. Medications for Insomnia

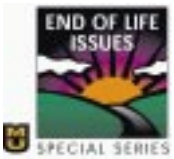
MEDICATION	DOSE	ROUTE OF ADMINISTRATION/FREQUENCY
Diphenhydramine	25—50 mg	P.O. q hs
Meclizine	25—50 mg	P.O. q hs
Lorazepam	0.5—2.0 mg	P.O. q hs
Zolpidem	5—10 mg	P.O. q hs
Risperidone or Haloperidol	1 mg	P.O. q hs
Chlorpromazine	10—100 mg	P.O. q hs
Trazodone	25—200 mg	P.O. q hs
Temazepam	15—45 mg	P.O. q hs

wine. 4) dexamethasone 2—20 mg p.o. qd. 5) megestrol acetate 200 mg p.o. q 6—8 hrs and titrate. 6) dronabinol (Marinol)—begin with small doses and titrate to effect. 7) androgens (oxandrolone, nandrolone)

Fatigue and weakness

Fatigue and weakness are frequently two of the most bothersome symptoms for patients at end-of-life. Management begins with helping patients and caregivers alter activities to promote energy conservation. Transfusion for anemia early in the course of illness can be beneficial. Physical therapists and occupational therapists can help evaluate the situation, educate the patient and caregivers in energy conservation, and provide appropriate assistive devices.

Stopping regular medications, which may no longer be appropriate, for chronic illness at the end-of-life may help diminish fatigue. This is one area where physical assistance (two caregivers assisting a person to their garden or a wheelchair used for a short day trip to a favorite outdoor spot) can allow patients to achieve their goals without making the symptom better.



Few medications are beneficial in treating fatigue and weakness at end-of-life. Steroids and/or psychostimulants may be beneficial. Possible treatments and suggested doses: 1) dexamethasone 2—20 mg p.o. qd. 2) methylphenidate 2.5—5 mg p.o q am and q noon; titrate to 10—30 mg/dose. 3) pemoline 25—100 mg bid. 4) dextroamphetamine 5 mg q am and q noon; titrate to 10—20 mg/dose.

Fluid balance and Edema

Edema that has an easily identifiable and reversible cause should be treated appropriately. Judicious use of diuretics is reasonable. However, patients with advanced disease and hypoalbuminemia will be unable to maintain normal intravascular volume. Albumin infusions are inappropriate; they are expensive, ineffective, and frequently exacerbate problems with edema. A small amount of edema is expected in patients with hypoalbuminemia—lack of edema usually signifies significant dehydration in this setting. Patients and caregivers should be reassured that urine output of 300 cc/day or less is adequate.

Patients should be encouraged to eat and drink as they normally would, but supplemental fluids should be avoided. Some salt-containing fluids (e.g., soups, sports drinks, vegetable juices) should be encouraged in place of free water drinks such as water, tea, coffee and soft drinks. Maximize comfort by paying careful attention to keeping mucous membranes (lips, mouth, eyes, nose) moist and well lubricated. Family and caregivers should be told it is normal to lose thirst in the last hours of life. Providing unwanted fluids can increase secretions that may further impair breathing, add to misery from incontinence in debilitated patients, and can worsen edema states.

Some patients may be more comfortable with compression bandages applied to edematous limbs. Leg elevation and/or compression stockings are other options.

Skin ulcers

Skin ulcers are more easily prevented than treated. Family and caregivers should be instructed regarding the importance of keeping skin clean and dry. Pressure points can be covered with hydrocolloid dressings. Fragile skin at risk for breakdown can be covered with clear occlusive dressings such as Tegaderm. Foam pads, air mattresses, gel mattress, or air-flotation beds may be necessary to minimize pressure points on cachectic patients.

When pressure ulcers do occur they should be appropriately staged and treated. The reader is referred to treatment guidelines for pressure ulcers (Agency for Healthcare Research and Quality: *www.ahcpr.gov/clinic/cpgsix.htm)*.

Odors from superficial infection of ulcers or exophytic malignancies are usually the result of anaerobic infections and/or poor hygiene. Topical metronidazole or silver sulfadiazine bid or tid can be effective. Dakin's solution, a dilute bleach solution—¼ percent sodium hypochlorite—can also be effective in limiting odors from anaerobic infections. Other measures that may be effective in controlling odors include placing a pan of kitty litter or activated charcoal under the bed, improving room ventilation, placing an open cup of vinegar or burning candle in the room. Adding additional fragrances in attempt to mask odors should be avoided as it often simply leads to a noxious concoction of odors.

Insomnia

Insomnia is a bothersome symptom for both patients at the end-of-life and their families or caregivers. General management principles consist fore mostly of good sleep hygiene. This includes, if possible, avoiding staying in bed when awake, avoiding caffeine late in the day, alcohol at bedtime, and avoiding overstimulation in the hours before bedtime. Pain management is essential—long acting medications are preferred to control pain through the night. Some patients may benefit from using relaxation and imagery.

Pharmacologic agents that are beneficial include antihistamines, benzodiazepines, neuroleptics, and sedating antidepressants. Some examples and suggested doses are listed in Table 5. Chlorpromazine is a more sedating agent than risperidone or haloperidol.

Summary

Along with a "whole-istic" approach to the general care of the dying person focusing on the individual's values and goals, careful attention to symptom control and alleviating suffering is rewarding, albeit challenging at times. It is important to educate both patients and their families and caregivers about potential symptoms and their amenability to treatment as end-of-life approaches. Minimizing or eliminating symptoms maximizes comfort and can help patients feel better is spite of progressive disease and gradual decline as they approach death.

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A primary source for this material is the Education for Physicians on End-of-life Care project of the American Medical Association in conjunction with the Robert Wood Johnson Foundation, Module 10: Common Physical Symptoms.

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