

Nonpain Symptom Management in the Dying Patient

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The dying process can be a time of untold loss and suffering, particularly unrelieved physical suffering. The obligation of physicians to relieve physical suffering is universal, particularly when death is imminent and the indignities of illness consume patients' final days and hours of life. Although pain is the most frequent symptom of dying patients, nonpain symptoms can generate significant suffering and precipitate a horrific death for patients and an unsettling and troublesome bereavement period for surviving family members. Consequently, the management of debilitating physical symptoms, particularly among terminally ill patients, is integral to good palliative care and is a moral, ethical, and professional obligation of physicians. Nausea and vomiting, dyspnea, death rattle, and cough are four of the most common nonpain symptoms among terminally ill patients and mandate competent, appropriate, and efficacious management to ensure patient dignity and familial equanimity.

NAUSEA AND VOMITING

Nausea and vomiting occur in 62% of terminally ill patients with cancer, with a prevalence rate of 40% among those in the last 6 weeks of life. Nausea and vomiting occur more commonly in women, in persons younger than 65 years of age, and in patients with gastric and breast cancer.

Little was known about the pathophysiology of nausea and vomiting until 1949, when Borison and Wang identified an area in the lateral reticular formation of the medulla that precipitated emesis in a decerebrate cat.¹ This area was labeled the emetic or vomiting center and is now considered the final common pathway for emesis.^{2,3} The vomiting center contains histamine and acetylcholine receptors and receives afferent impulses from 5 other areas that play a role in provoking nausea and vomiting: (1) the chemoreceptor trigger zone, (2) the pharynx and gastrointestinal tract, (3) the cerebral cortex, (4) the vestibular system, and (5) intracranial pressure receptors (**Table 1**).²⁻⁶

Although the cause of nausea and vomiting in terminally ill patients is usually multifactorial (**Table 2**),

physicians should attempt to ascertain the underlying cause to facilitate the selection of an antiemetic medication, unless the patient is near death. A basic evaluation can be accomplished by a brief and concise history and physical examination coupled with minimal laboratory studies that include measurement of serum creatinine, blood urea nitrogen, electrolyte, and calcium levels.^{2,7} If a cause is identified, corrective measures should be instituted; however, empiric palliative therapy is usually necessary, particularly in actively dying patients. Nine basic categories of antiemetic agents are used for nausea and vomiting in terminally ill patients (**Table 3**).²⁻⁷ In general, however, physicians are less likely to prescribe antiemetics for elderly patients and those with an impaired level of consciousness.⁸

Most antiemetic agents can be administered on an as-needed basis, although persistent and refractory nausea and vomiting mandate around-the-clock administration. Oral and rectal preparations are available; however, in severe cases, parenteral (ie, intravenous and subcutaneous) medications may be necessary (**Table 3**). A unique rectal preparation can be compounded that is quite successful in abating nausea and vomiting of diverse etiologies; ingredients usually include various combinations of diphenhydramine, metoclopramide, lorazepam, dexamethasone, haloperidol, and benztropine.

In addition to antiemetics, several nonpharmacologic interventions are available. They include the following: eating small, frequent meals or liquid meals; consuming boiled or baked foods instead of fried foods; eating food at room temperature; avoiding sweet, salty, fatty, and spicy foods, as well as foods with a strong odor; limiting the sights, sounds, and smells that precipitate emesis; drinking carbonated beverages;

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Table 1. Characteristics of Emetic Areas of the Body

| Emetic Area | Receptors | Stimulants |
|-------------------------------------|--------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------|
| Chemoreceptor trigger zone | Histamine, dopamine, 5-HT ₃ , acetylcholine | Opioids, digoxin, chemotherapy agents, uremia, radiation toxicity |
| Pharynx and gastro-intestinal tract | 5-HT ₃ (possible) | Gastroparesis, medications (eg, NSAIDs, corticosteroids), extrinsic compression of the stomach (eg, from hepatomegaly), gastric involvement by tumor |
| Cerebral cortex | Not known | Fear, anxiety, odors, visual images, sounds |
| Vestibular system | Histamine, acetylcholine | Motion changes, dehydration, tumors and metastases to the base of the skull |
| Intracranial pressure receptors | Not known | Increased intracranial pressure |

5-HT₃ = type 3 serotonin; NSAIDs = nonsteroidal anti-inflammatory drugs.

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Table 2. Common Causes of Nausea and Vomiting in Terminally Ill Patients

| | |
|-------------------------------------------------------------------------------------|----------------------------------------------|
| Chemical/pharmacologic causes | Radiation |
| Chemotherapeutic agents | Abdominal and pelvic irradiation |
| Medications (eg, digoxin, theophylline, nonsteroidal anti-inflammatory drugs, iron) | Vestibular causes |
| Tumor-generated toxins | Body motion (eg, motion sickness) |
| Fluid/electrolyte abnormalities | Skeletal metastases to the base of the skull |
| Dehydration/volume depletion | Tumors |
| Hypercalcemia | Visceral causes |
| SIADH | Biliary/genitourinary disease |
| Neurologic causes | Constipation/fecal impaction |
| Increased intracranial pressure | Esophageal disease (eg, tumors, GERD) |
| Meningitis (eg, chemical, infectious, carcinomatous) | Gastroparesis |
| Primary and metastatic brain tumors | Hepatic malignancies |
| Psychologic causes | Intestinal obstruction |
| Anxiety | Intra-abdominal tumors |
| Fear | Oropharyngeal inflammation (eg, stomatitis) |
| | Renal failure |

GERD = gastroesophageal reflux disease; SIADH = syndrome of inappropriate antidiuretic hormone secretion.

providing fresh air through an open window; providing mental distractions; and using relaxation techniques such as rhythmic breathing.^{2,3,9}

DYSPNEA

Dyspnea occurs in 29% to 90% of terminally ill patients and is frequently the most common severe symptom a patient experiences at the end of life. Although dyspnea is more common in patients with lung or pleural disorders, 24% of patients with this symptom in the National Hospice Study did not exhibit cardiac, lung, or pleural disease.¹⁰

The pathophysiology of dyspnea varies with the underlying disorder. Dyspnea can be caused by (1) existing disease (eg, asthma, chronic obstructive pulmonary disease [COPD], congestive heart failure [CHF], anemia); (2) acute superimposed conditions (eg, pneumonia, pulmonary embolus); (3) cancer-induced complications (eg, bronchial obstruction, pleural effusion, lymphangitis carcinomatosa, replacement of lung tissue with tumor); (4) effects of cancer therapy (eg, radiation fibrosis, pneumothorax); and (5) miscellaneous factors (eg, uremia, ascites, anxiety, depression).^{2,3,11}

The treatment of dyspnea should address the underlying cause. Bronchodilators may be useful in COPD, diuretics in CHF, pleural aspiration and pleurodesis for pleural effusions, and radiotherapy for obstructing lesions. Important considerations in deciding on a treatment regimen include the life expectancy of the patient and the invasiveness and potential complications of the therapeutic intervention being considered^{2,3}; all potential side effects must be weighed before a therapeutic regimen is implemented.

Table 3. Pharmacologic Palliative Treatment of Nausea and Vomiting in Terminally Ill Patients

| Drug | Starting Dosage | Drug | Starting Dosage |
|-------------------------|-------------------------------------------------------------------------------------------------------------------|-----------------------------------------|-----------------------------------------------------------------------------------|
| Antihistamines | | Dopamine antagonists[†] | |
| Diphenhydramine | 25 mg PO, IV, or IM* q 4 hours prn | Haloperidol | 0.5–2 mg PO, IM*, IV, or SQ q 4–6 hours prn <i>or</i> 5–15 mg as a CSI q 24 hours |
| Cyclizine | 50 mg PO or IM* q 6 hours prn <i>or</i> 50–100 mg as a CSI q 24 hours | Prochlorperazine | 5–20 mg PO, IM*, or IV q 4–6 hours prn <i>or</i> 25 mg PR q 4 hours prn |
| Meclizine | 25–50 mg PO q 4–6 hours prn | Promethazine | 25 mg PO or PR q 4–6 hours prn <i>or</i> 12.5–25 mg IV q 4–6 hours prn |
| Anticholinergics | | Droperidol | 2.5–5 mg IV q 4–6 hours prn |
| Scopolamine | 250–800 µg PO prior to emetic-producing activity <i>or</i> TDP q 72 hours <i>or</i> 0.8–20 mg as a CSI q 24 hours | Substituted benzamide | |
| Hyoscyamine | 0.125–0.250 mg PO or SL q 4 hours prn <i>or</i> 0.25–0.5 mg SQ q 4 hours prn <i>or</i> 1–2 mg as a CSI q 24 hours | Metoclopramide [‡] | 5–20 mg PO, IM*, IV, or SQ q 6 hours prn <i>or</i> 20–80 mg as a CSI q 24 hours |
| Corticosteroids | | Serotonin antagonists | |
| Dexamethasone | 1–4 mg PO, IV, or SQ qd–q 6 hours prn <i>or</i> 2–12 mg as a CSI q 24 hours | Ondansetron | 8 mg PO, IV, or SQ q 8 hours prn <i>or</i> 8–24 mg as a CSI q 24 hours |
| Prednisone | 5–20 mg PO q 6 hours prn | Granisetron | 0.5–1 mg PO, IV, or SQ q 12 hours prn |
| Methylprednisolone | 5–20 mg SQ qd–qid | Miscellaneous | |
| Cannabinoids | | ABHR, ABHRD, or ABHRDC [§] | 1 PR q 4–6 hours prn |
| Dronabinol | 2.5–7.5 mg PO bid–tid | Octreotide | 150 µg SQ tid <i>or</i> 0.2–0.9 µg as a CSI q 24 hours |
| Benzodiazepines | | | |
| Lorazepam | 0.5–2 mg PO, SL, SQ, IM*, or IV q 4 hours prn | | |

bid = twice a day; CSI = continuous subcutaneous infusion; IM = intramuscularly; IV = intravenously; PO = by mouth; PR = per rectum; prn = as needed; q = every; qd = every day; qid = 4 times a day; SL = sublingually; SQ = subcutaneously; TDP = transdermal patch; tid = 3 times a day.

*If possible, avoid intramuscular injections because they can cause significant pain.

[†]Different dopamine antagonists generally should not be prescribed concurrently (ie, promethazine with prochlorperazine), because the potential for extrapyramidal reactions are increased without any real increase in antiemetic effect.

[‡]Metoclopramide is a serotonin antagonist at high doses.

[§]Needs to be prepared by a pharmacist; may variously contain lorazepam (Ativan), diphenhydramine (Benadryl), haloperidol (Haldol), metoclopramide (Reglan), dexamethasone (Decadron), and benztropine (Cogentin).

^{||}Useful when bowel obstructions are present; helps reduce intestinal secretions and motility.

For most terminally ill patients, efficacious palliation can be achieved by the empiric use of opioids, benzodiazepines, and corticosteroids (Table 4).^{2,3,9,12} Opioids are safe and effective for dyspnea^{13–15}; they ostensibly decrease respiratory distress by altering the perception of breathlessness,¹⁴ decreasing ventilatory response to hypoxia and hypercapnia,^{14,16} and reducing oxygen con-

sumption at rest and with exercise.^{14,17} Oral preparations of morphine are preferred. However, if oral morphine cannot be tolerated, rectal, subcutaneous, intravenous, and nebulized morphine can be used.² Other opioids are equally efficacious in reducing dyspnea and may be used when patients are allergic to morphine or are otherwise unable to tolerate it. Nebulized opioids are an

Table 4. Pharmacologic Palliative Treatment of Dyspnea in Terminally Ill Patients

| Drug | Starting Dosage |
|------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Opioids | |
| Morphine | 5–10 mg PO, SL, IM, IV, SQ, or PR q 1–4 hours prn; IV and SQ doses should be adjusted by using a 3:1 oral-to-parenteral ratio; patients already on morphine may need to increase their regular dose by 25% to 50%; if dyspnea is severe and acute, use 2–5 mg IV q 15 minutes or 5 mg SQ q 20 minutes until dyspnea is improved |
| Oxycodone | 5–10 mg PO, SL, or PR q 1–4 hours prn |
| Hydromorphone | 1–2 mg PO, SL, IM, IV, SQ, or PR q 1–4 hours prn; IV and SQ doses should be adjusted by using a 5:1 oral-to-parenteral ratio |
| Nebulized morphine* | 5 mg in 2 mL of normal saline q 1–4 hours prn via nebulizer, may titrate to 20 mg q 2–4 hours prn; hydromorphone may be substituted for morphine and started at 1 mg q 1–4 hours prn |
| Corticosteroids | |
| Dexamethasone | 4–8 mg PO, SL, IM, IV, SQ, or PR qd prn |
| Prednisone | 20–40 mg PO or SL qd prn |
| Benzodiazepines | |
| Lorazepam | 0.5–2 mg PO, SL, IM, IV, SQ, or PR q 1–4 hours prn |
| Diazepam | 5–10 mg PO, SL, IM, IV, or PR q 1–4 hours prn |
| Midazolam | 0.5 mg IV q 15 minutes prn until patient is sedated <i>or</i> 2.5–5 mg SQ, then 10–30 mg as a CSI q 24 hours |
| Phenothiazine | |
| Chlorpromazine | 12.5–25 mg IV q 2–4 hours prn <i>or</i> 25 mg PO or PR q 2–4 hours prn |

CSI = continuous subcutaneous infusion; IM = intramuscularly; IV = intravenously; PO = by mouth; PR = per rectum; prn = as needed; q = every; qd = every day; SL = sublingually; SQ = subcutaneously.

*Nebulized morphine may cause histamine-mediated bronchospasm, particularly in opioid-naïve patients or during the first nebulization.

innovative approach to opioid delivery that have anecdotally shown success.^{18,19} Although they are thought to exert a local effect on pulmonary opioid receptors, the exact mechanism of action is unknown.⁹

Benzodiazepines are useful when anxiety complicates dyspnea and may help reduce the vicious cycle of dyspnea leading to anxiety, and anxiety leading to increasing dyspnea. However, some authorities question the value of anxiolytics in terminally ill patients with dyspnea and have voiced concern about their sedating effects.²⁰ Nevertheless, benzodiazepines are valuable adjuncts in the pharmacologic management of dyspnea in the terminally ill patient, particularly when agitation and anxiety occur during the final days of life. Although not a benzodiazepine, chlorpromazine, a phenothiazine, has been used in dyspnea refractory to opioids, benzodiazepines, and corticosteroids.^{21,22} It appears to reduce breathlessness with minimal side effects and has been particularly efficacious during the end of life.²

Corticosteroids reduce dyspnea by anti-inflammatory activity and are useful in dyspnea associated with airway obstruction, lymphangitis carcinomatosa, superior vena cava syndrome, COPD, and radiation pneumonitis.^{3,23,24} Although side effects limit their long-term use, they are relatively safe and efficacious for short-term use in terminally ill patients.

Although oxygen is frequently prescribed for patients with dyspnea, it has little objective benefit. However, it may be of some value in hypoxemic maladies such as COPD and pulmonary fibrosis,¹³ as well as in some nonhypoxemic disorders (through a placebo effect that engenders psychological benefit regardless of the results of pulse oximetry or blood gas analysis).² A bedside fan is also useful to assuage dyspnea; apparently, the fan improves dyspnea by stimulating receptors in the trigeminal nerve located in the cheek and nasopharynx, altering the perception of breathlessness.²⁵ The fan should be set on low speed and directed at the patient's face.

DEATH RATTLE

During the last 24 to 48 hours of life, many patients retain secretions in the back of the throat that produce a gurgling type of sound frequently referred to as the *death rattle*.^{2,3} A patient with death rattle is usually lethargic or comatose and unaware of the noise; however, it can be very disturbing to family members. Oropharyngeal suctioning is usually provided, but gagging and coughing may generate patient discomfort and further distress family members. Instead, treatment with anticholinergic medications is recommended to dissipate secretions and abolish the need for suctioning (Table 5). Clinicians should be aware that anticholinergic agents do not dry up secretions already present, so these drugs should be used at the first sign

Table 5. Pharmacologic Treatment of Death Rattle

| Drug | Starting Dosage |
|----------------|-----------------------------------------------------------------------------------------------------------------------|
| Scopolamine | 0.4–0.6 mg SQ q 2–4 hours prn <i>or</i> 0.8–2 mg as a CSI q 24 hours <i>or</i> TDP q 72 hours |
| Hyoscyamine | 0.125–0.250 mg SL q 2–4 hours prn <i>or</i> 0.25–0.5 mg SQ q 2–4 hours prn <i>or</i> 1–2 mg as a CSI q 24 hours |
| Glycopyrrolate | 0.2 mg SL <i>or</i> SQ q 2–4 hours prn |
| Atropine | 0.4 mg SQ q 2–4 hours prn <i>or</i> 2 mg via nebulizer q 2–4 hours prn |

CSI = continuous subcutaneous infusion; prn = as needed; q = every; SL = sublingually; SQ = subcutaneously; TDP = transdermal patch.

of noisy respirations. In addition, placing the patient in a lateral recumbent position with the head slightly elevated may help reduce pooling of secretions and reduce noisy respirations.

COUGH

Cough can be a troublesome symptom; it occurs in 29% to 83% of terminally ill patients.^{2,26} Although a defense mechanism to protect pulmonary airways, cough can aggravate nausea and vomiting, dyspnea, and musculoskeletal pain.² Cough can be precipitated by numerous causes, which can be classified into 4 categories: (1) cardiopulmonary (eg, asthma, COPD, CHF, tumors); (2) esophageal (eg, gastroesophageal reflux disease); (3) drug-induced (eg, angiotensin-converting enzyme inhibitors); and (4) aspirational (eg, in multiple sclerosis).²⁶

As with the treatment of nausea, vomiting, and dyspnea, the treatment of cough in terminally ill patients should address the underlying cause. Bronchodilators and corticosteroids may be useful for COPD, diuretics and vasodilators for CHF,² and antihistamines and decongestants for postnasal drainage.⁹ Various pharmacologic treatments for cough in palliative therapy are listed in **Table 6**.

When cough is refractory, management depends on whether the cough is productive or nonproductive.²⁷ If the cough is productive and the patient is able to expectorate without causing pain (eg, when there are no bone metastases), an expectorant such as guaifenesin may be indicated but may aggravate nausea and vomiting in terminally ill patients.²⁴ If the cough is nonproductive or productive with an inability to expectorate, suppression of cough is indicated.

Opioids remain the most efficacious cough suppressants²³ and are the preferred agents for terminally ill

Table 6. Pharmacologic Palliative Treatment of Cough in Terminally Ill Patients

| Drug | Dosage |
|------------------------|----------------------------------------------|
| Opioids | |
| Morphine | 5 mg q 2–4 hours prn |
| Oxycodone | 5 mg q 2–4 hours prn |
| Codeine | 15–30 mg q 4 hours prn |
| Corticosteroids | |
| Dexamethasone | 4–8 mg qd |
| Prednisone | 20–40 mg qd |
| Anesthetic | |
| Lidocaine | 2 mL of nebulized lidocaine q 6 hours prn |
| Miscellaneous | |
| Dextromethorphan | 15–30 mg q 4 hours prn |

prn = as needed; q = every; qd = every day.

patients. All opioids exert antitussive activity; therefore, the choice of a drug is dependent on physician preference. If the patient is already taking an opioid, the dose should be gradually increased until the cough is suppressed or side effects of the medication become intolerable.² Codeine, frequently prescribed for cough, has no benefit over other opioids and may actually cause more gastrointestinal discomfort. Dextromethorphan, an antitussive that acts centrally through nonopioid receptors, is as effective as codeine when prescribed in dosages of 15 mg to 30 mg every 4 hours.^{27,28} If pulmonary tumor enlargement contributes to cough, a trial of corticosteroids may be beneficial in reducing peritumor edema and malignant obstruction. In addition, palliative radiotherapy may be useful in decreasing tumor burden and should be considered in cough nonresponsive to pharmacologic interventions.²

Nebulized anesthetics have also been used as antitussives in cough refractory to standard suppressants; the nebulized anesthetics are able to block J receptors, which generate sensitivity to bronchial irritants.^{2,11,23} Lidocaine is the preferred agent, with 2 mL of a 1%, 2%, or 4% solution given by nebulizer every 6 hours as needed.⁹ Because numbness of the oral cavity may persist after anesthetic inhalation, patients should refrain from eating for 30 minutes to avoid aspiration and worsening of cough.²

CONCLUSION

Symptom management is cardinal to good palliative care, particularly as patients approach death. Nausea

