# Management of Intractable Nausea and Vomiting in Patients at the End of Life

## "I Was Feeling Nauseous All of the Time . . . Nothing Was Working"

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**Nausea and vomiting, symptoms that occur commonly near the end of life, represent a substantial source of physical and psychological distress for patients and families. In the context of the case of Mr Q, a 50-year-old man with metastatic esophageal cancer admitted to the hospital with intractable nausea and vomiting, we review the evaluation and treatment of this symptom complex. A thorough history and physical examination are essential first steps in the management of these patients because they define the severity of the symptoms and clues to their underlying etiology. Once the most likely cause is determined, the clinician discerns the mechanism, specific transmitters, and receptors by which this etiology is triggering nausea and vomiting. Subsequent pharmacological management focuses on prescribing the appropriate antagonist to the implicated receptors. If symptoms are refractory despite adequate dosage and around-the-clock prophylactic administration, an empirical trial combining several therapies to block multiple emetic pathways should be attempted. Less traditional agents are also discussed, although evidence for their use is limited. Often, oral administration of medication is not feasible and alternate routes such as rectal suppositories, subcutaneous infusions, and orally dissolvable tablets should be considered. Using this stepwise approach, nausea and vomiting can be successfully managed in most patients at the end of life.**

*JAMA. 2007;298(10):1196-1207* www.jama.com

### THE PATIENT'S STORY

Mr Q is a 50-year-old electronics designer with metastatic esophageal cancer treated with third-line palliative chemotherapy. Recently, he has spent more than half of his time in bed due to a general lack of energy, although he walks without assistance or dyspnea. He was admitted to a university hospital in May 2006 for intractable nausea and vomiting.

His medical history was remarkable for migraine headaches, depression, and ulcerative colitis during childhood. He was diagnosed with esophageal cancer by endoscopic biopsy in October 2005. Thoracic computed tomography (CT) scans at the time showed circumferential thickening of the distal esophagus and an enlarged gastrohepatic lymph node. In December 2005, he began presurgical chemotherapy with docetaxel and capecitabine. In February 2006, he underwent an exploratory laparotomy but the tumor was found to be unresectable. A 20 × 20-mm stent was inserted in the gastroesophageal junction for impending obstruction and a jejunostomy feeding tube (J-tube) was placed. In March 2006, CT scans showed evidence of liver metastases.

Mr Q had experienced intermittent nausea and vomiting throughout his course of chemotherapy and reported a painful burning sensation in the chest and epigastrium since the esophageal stenting. Ten days before admission he had begun palliative chemotherapy with capecitabine. Afterwards, his nausea and vomiting worsened considerably, with vomiting episodes occurring up to 10 times a day, consisting of both dry heaves and emesis of bilious fluid. There was no apparent temporal relation of these symptoms to oral in-



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**Perspectives on Care at the Close of Life** is produced and edited at the University of California, San Francisco, by Stephen J. McPhee, MD, Michael W. Rabow, MD, and Steven Z. Pantilat, MD; Amy J. Markowitz, JD, is managing editor.
**Perspectives on Care at the Close of Life Section Editor:** Margaret A. Winker, MD, Deputy Editor.

take or J-tube feedings. Normal daily bowel movements were noted and a trial of ondansetron was not effective. He and his wife became worried about his inability to keep down food or water so they came to the emergency department.

On admission to the hospital, Mr Q received intravenous fluids and nothing by mouth; however, his nausea and vomiting persisted. At that time, his antiemetic regimen consisted of 8 mg of ondansetron intravenously twice a day; a scopolamine patch, 1.5 mg topically; lorazepam, 1 mg intravenously every 4 to 6 hours as needed; and promethazine, 12.5 to 25 mg intravenously every 4 to 6 hours as needed. Additional medications included oral morphine elixir as needed, bupropion, docusate, potassium chloride, and transdermal and transmucosal fentanyl. Upon physical examination, his mucus membranes were moist, with no oral thrush. His abdominal examination revealed no tenderness or distention, no hepatosplenomegaly, and normoactive bowel sounds. Laboratory studies were unremarkable including a normal complete blood count, electrolyte panel, liver function tests, amylase, lipase, and urinalysis. An abdominal and pelvic CT scan showed no abnormally dilated bowel loops. A palliative care consultant, Dr O, was asked to assist with management of the patient's nausea and vomiting.

## PERSPECTIVES

A Perspectives editor interviewed Mr Q and Dr O in May and June 2006.

MR Q: *I was just feeling terrible. . . . I was nauseous all of the time and throwing up. My energy level was really low, and I was dropping weight. What prompted me to go into the hospital was . . . I really just couldn't eat or drink anything. Even feeding through a J-tube . . . was making me nauseous. My wife and I were afraid that I was starving. . . . [W]e went to the emergency department and did the long wait there. . . . They couldn't tell me to go home without figuring out how to give me food and liquids.*

DR O [PALLIATIVE CARE PHYSICIAN]: *We were called to consult on [Mr Q] by the primary medical team for symptom management. . . . He [was] not eating much and feeling weaker as a result.*

Nausea and vomiting are common symptoms at the end of life, occurring in 62% of terminally ill cancer patients with a prevalence of at least 40% during the last 6 weeks of life.[1] Although most extensively studied in the cancer setting, nausea and vomiting also occur frequently in other terminal illnesses such as congestive heart failure and AIDS.[2,3] In a retrospective review of 100 consecutive patients with varying diagnoses admitted to a palliative care unit, 71% reported nausea during their stay.[4] Nausea often presents with a cluster of symptoms[5]; in one study, 25% of cancer patients treated for pain also reported nausea.[6] Nausea and vomiting cause substantial psychological distress for patients and families near the end of life,[7] with poorly controlled symptoms contributing to fears about starvation, dehydration, and even disease progression.

Using the case of Mr Q, this article reviews a general approach to caring for patients with nausea and vomiting near the end of life, relying on empirical evidence, and in its absence, our clinical experience. The approach involves: (1) careful evaluation to determine the etiology of the presenting symptoms; (2) using pathophysiology to determine the mechanism and, subsequently, receptors underlying the patient's nausea and vomiting; and (3) choosing an antiemetic to block the implicated receptors. Because of its importance at the end of life, this article places a special emphasis on how to approach intractable nausea, defined herein as nausea and vomiting that is not adequately controlled after multiple antiemetics are used in series and/or in combination. Although we believe a mechanism-based approach is applicable to any patient with nausea and vomiting, this article's focus may not be generalizable to populations with less limited life expectancies.

## EVALUATION

A history and physical examination represent essential first steps in the evaluation of nausea and vomiting, for they provide a measure of symptom severity[8] and clues to the underlying etiology. Careful evaluation permitted physicians in one study to confidently establish the cause of nausea and vomiting for about 45 (75%) of 61 hospice patients.[9] The most frequently cited etiologies were chemical abnormalities (metabolic, drugs, infection; 33%), impaired gastric emptying (44%), and visceral and serosal causes (bowel obstruction, gastric bleed, enteritis, constipation; 31%).[9] A study of 40 patient-episodes of nausea, vomiting, or both on a palliative care unit identified 59 reversible etiologies, with medications (51%) and constipation (19%) presenting most commonly.[10]

The history should focus on characterizing the nausea and vomiting as well as any associated symptoms (**TABLE 1**).[11,12] Special attention should be paid to complaints of anorexia because it may represent a constant low-grade nausea. Although Mr Q did not have a history of constipation, given its frequency near the end of life,[10] constipation must be ruled out in every patient.[11,13] This includes a detailed history of the frequency and consistency of stools because many patients with limited oral intake mistakenly believe it is normal to have infrequent bowel movements. Mr Q reported esophageal burning consistent with gastroesophageal reflux, a common complication after esophageal stent placement.[14]

Obtaining a complete medication history is essential, including a thorough evaluation of new and recently discontinued prescription and over-the-counter drugs. Chemotherapeutics, opioids, antidepressants, and antibiotics are frequent contributors to nausea and vomiting near the end of life.[15] Recent and/or rapid discontinuation of corticosteroids or high-dose progesterones may cause nausea due to adrenal insufficiency.[16]

Nonpharmacological therapies must also be considered in the evaluation. Radiation therapy, especially to the ab-

domen or lumbosacral spine, can trigger nausea and vomiting.[17] Any recent surgery, particularly abdominal surgery, can also produce symptoms.[18] In the case of Mr Q, the esophageal stent placement, palliative capecitabine (though a low emetic risk agent), and opioid therapy could all be contributing to his nausea. Bupropion and potassium chloride can be emetogenic, but represent long-standing therapies for Mr Q and, as such, are less likely causes of his symptoms.

The past medical history provides additional critical clues. Peptic ulcer disease, gastroesophageal reflux, or both may explain symptoms. Diabetes mellitus, alcoholism, chronic renal failure, advanced cancer, autoimmune disorders, amyloidosis, and Parkinson disease are all associated with autonomic dysfunction and delayed gastric emptying.[19] For cancer patients, the type of malignancy, its site of origin, and location of metastases are dispositive. For example, liver metastases, malignant bowel obstruction, and peritoneal carcinomatosis can all cause nausea and vomiting.[12] External compression of the stomach or duodenum by tumor or massive ascites is associated with nausea and vomiting through the "squashed-stomach syndrome."[12] Primary or metastatic brain or leptomeningeal tumor can be emetogenic as well.[12] Finally, a patient's psychological state, particularly anxiety or depression, may be associated with nausea.[20] Mr Q's past medical history of migraines and ulcerative colitis can cause nausea but currently appear quiescent. Esophageal cancer, through direct extension, may irritate the esophageal or gastric mucosa, causing nausea and vomiting. Mr Q does not appear to have any distant contributory metastases.

The physical examination provides additional clues to the etiology of a patient's nausea and vomiting with important findings listed in Table 1. Mr Q, however, presented with a normal abdominal, rectal, and neurological examination.

Laboratory and radiology testing may provide diagnostic insights, but for patients in the home setting an exhaustive workup often distracts from minimizing symptom burden and optimizing management.[11] A laboratory evaluation may reveal renal failure, hyponatremia, liver failure, pancreatitis, or hypercalcemia, all of which may cause or contribute to nausea and vomiting. Drug toxicity from digoxin or anticonvulsants can precipitate symptoms and, if suspected, may warrant checking a serum level. A supine abdominal film helps identify constipation,[13] and is espe-

**Table 1.** History and Physical Examination: Clues to Specific Etiologies of Nausea and Vomiting[a]

| Element of History or Physical Examination | Suggested Etiology of Nausea and Vomiting |
|---|---|
| History | |
| Pattern | |
| Large, infrequent vomitus that relieves nausea | Complete or partial bowel obstruction |
| Small-volume emesis | Gastric stasis |
| Associated symptoms | |
| Vertigo and symptom association with movement | Vestibular dysfunction |
| Morning symptoms with morning headache and neurological symptoms | Increased intracranial pressure |
| Polyuria, polydipsia | Hyperglycemia or hypercalcemia |
| Altered mental status | Uremia, hyponatremia, or increased intracranial pressure |
| Neck stiffness | Meningeal disease |
| Syncopal episodes, early satiety | Autonomic insufficiency |
| Decreased frequency of bowel movements, abdominal fullness, hard stools, straining with defecation | Constipation |
| Obstipation, crampy abdominal pain | Bowel obstruction |
| Bloating, early satiety | Gastric stasis |
| Esophageal burning, sour taste in mouth, worse with lying down | Gastroesophageal reflux disease |
| Right upper-quadrant pain | Gallbladder or liver disease |
| Epigastric pain radiating to back | Pancreatitis |
| Fever, diarrhea | Gastroenteritis |
| Worry, emotional responses | Anxiety |
| Physical examination | |
| Orthostatic blood pressure and pulse changes or absence of heart rate variation with Valsalva maneuver | Autonomic insufficiency |
| Papilledema, neurological signs | Increased intracranial pressure |
| Thrush or herpetic lesions | Oropharyngeal, esophageal irritation |
| Abdominal distention and abnormal bowel sounds | Bowel obstruction, ileus, or constipation |
| Succussion splash | Gastric outlet obstruction |
| Abdominal masses or ascites | Abdominal malignancy |
| Marked splenomegaly | Direct bowel compression by spleen |
| Fecal impaction on rectal examination | Constipation |

[a] See text for comorbidities and therapies that may directly contribute to nausea.

cially useful in patients with delirium or dementia who are unable to give an accurate history of recent bowel movements. Finally, an upright abdominal film can identify air-fluid levels if gastrointestinal (GI) tract obstruction is suspected. Mr Q's laboratory studies were unremarkable, and a CT scan did not show evidence of bowel obstruction.

## MECHANISM

### The 4 Pathways

DR O: *I went down a lengthy list of the . . . causes of intractable nausea and vomiting. . . . It's important to have an etiologic diagnosis, so you know which treatments are going to be most helpful.*

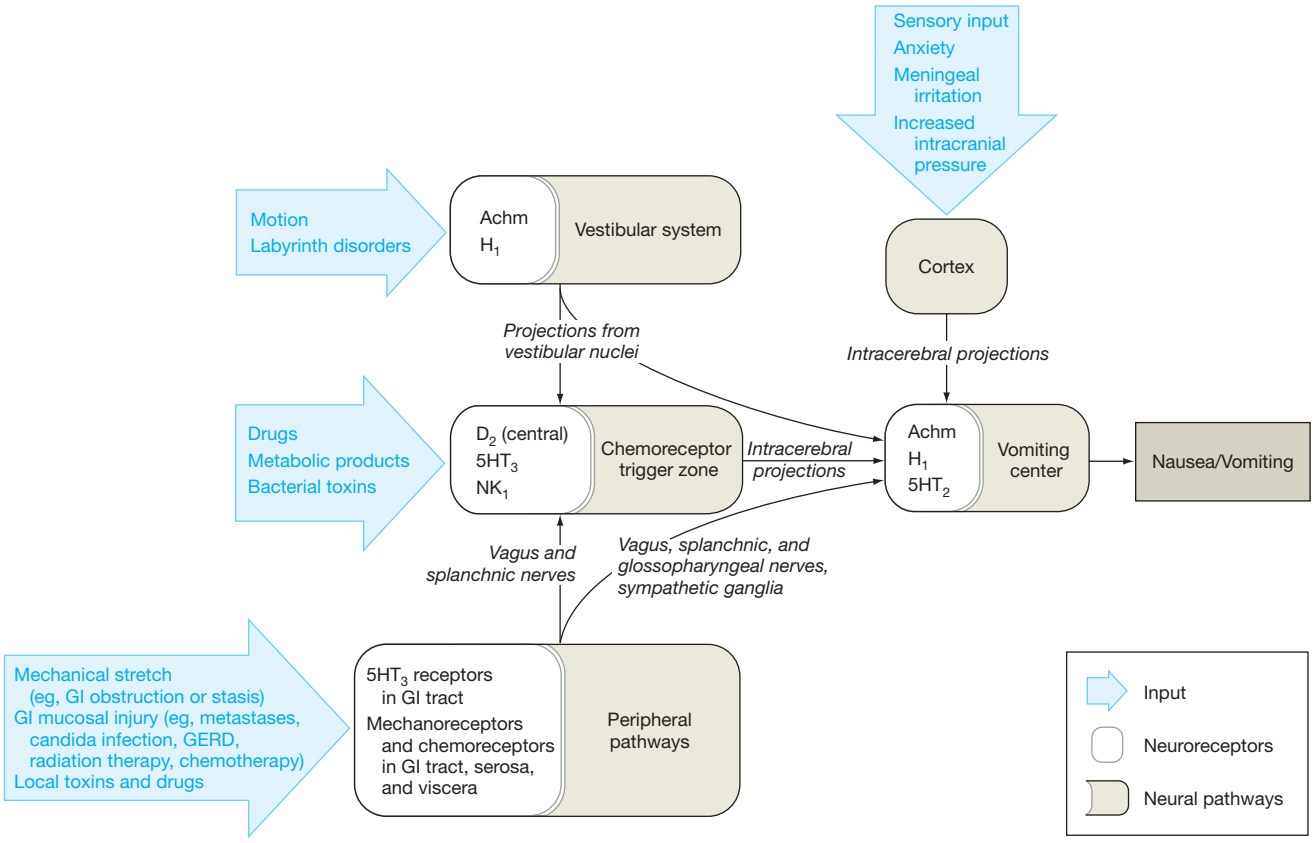
After elucidating the most likely etiology of nausea and vomiting, the next step is to determine which mechanism is triggering symptoms to guide therapy. Nausea and vomiting are caused by the stimulation of at least 1 of the 4 pathways. Each of these provides input into the vomiting center in the brainstem, which produce nausea or vomiting when the minimum thresholds are reached (FIGURE). The 4 pathways are[12,21-24]

1. Chemoreceptor trigger zone (CTZ): functionally outside the blood-brain barrier, the CTZ is exposed to toxins in the bloodstream and cerebrospinal fluid that can stimulate vomiting.
2. Cortex: thought to cause nausea due to input from the 5 senses, anxiety, meningeal irritation, and increased intracranial pressure, the cortex supplies many afferents to the vomiting center.
3. Peripheral pathways: the main emetogenic input from the periphery, these are triggered by mechanoreceptors and chemoreceptors in the GI tract, serosa, and viscera and transmitted via the vagus and splanchnic nerves, sympathetic ganglia, and glossopharyngeal nerves.
4. Vestibular system: mediated through labyrinthine inputs into the vomiting center via the vestibulocochlear nerve, nausea and vomiting are triggered by motion.

### Pathophysiology of Common Etiologies

**Opioid-Induced Nausea and Vomiting.** Up to 40% of opioid-treated patients experience nausea and vomiting,[25] triggered by constipation, stimulation of the CTZ, gastropare-

**Figure.** Interrelationships Between Neural Pathways That Mediate Nausea and Vomiting




Achm indicates muscarinic acetylcholine receptor; $D_2$, dopamine type 2 receptor; GERD, gastroesophageal reflux; GI, gastrointestinal; $H_1$, histamine type 1 receptor; $NK_1$, neurokinin type 1 receptor; $5HT_2$, 5-hydroxytryptamine type 2 receptor; and $5HT_3$, 5-hydroxytryptamine type 3 receptor.

sis, and sensitization of the labyrinth.[26] The effects in the CTZ are largely mediated through central dopamine type 2 ($D_2$) receptors, whereas the gastroparesis is mediated through peripheral $D_2$ receptors. Although early studies attributed opioid-induced nausea and vomiting to the accumulation of metabolites, particularly morphine-6 glucuronide,[27] more recent studies do not support this theory.[28]

**Chemotherapy-Induced Nausea and Vomiting.** Chemotherapy causes nausea and vomiting by a complex set of mechanisms.[29] First, chemotherapy is thought to directly stimulate the CTZ. This effect appears to be mediated by 5-hydroxytryptamine type 3 ($5HT_3$) and neurokinin type 1 ($NK_1$) receptors. Second, chemotherapy is thought to damage the GI mucosa and cause release of neurotransmitters including $5HT_3$. This stimulates nausea and vomiting via peripheral pathways mediated by vagal and splanchnic nerves. Third, there appears to be some neurohormonal etiology to these symptoms via alteration in arginine vasopressin and prostaglandin levels.[29] Finally, chemotherapy-induced nausea and vomiting may be mediated by anxiety, which can trigger symptoms via central pathways.[30,31]

**Malignant Bowel Obstruction.** Malignant bowel obstruction can occur with any malignancy but is most commonly associated with advanced ovarian and colorectal cancer.[32] Peripheral pathways are stimulated because of the stretch of bowel wall, pain, and colic associated with accumulating food and fluids proximal to the obstruction. Additionally, the CTZ is likely triggered by inflammatory mediators and bacterial toxins.[24]

**Impaired GI Tract Motility of Advanced Cancer.** Autonomic dysfunction may play a central role in chronic nausea and vomiting in patients with advanced cancer as a result of gastroparesis and constipation.[33] Symptoms are likely triggered by activation of peripheral pathways due to stretch of the gastric or esophageal wall from this poor motility. The etiology of autonomic failure in patients with advanced cancer is multifactorial, including malnutrition and cachexia, chemotherapy and other drugs, radiation therapy, paraneoplastic phenomena, nerve invasion by tumor, and comorbidities such as diabetes mellitus.[12]

Mr Q's esophageal irritation due to tumor burden and poststent reflux is likely triggering nausea via vagal input into the vomiting center. The opioids he is receiving may be activating central $D_2$ receptors in the CTZ, and the capecitabine chemotherapy may be activating $NK_1$ receptors in the CTZ and $5HT_3$ receptors in the GI tract and the CTZ.

## TREATMENT

Dr O: *We generated a list of possible etiologies and tried to rank them. . . . We recommended adding* [*prochlorperazine*] *to cover the possibility that the opiates were producing the nausea. Because of the possibility that he was having esophageal candidiasis, we recommended nystatin. Because of the stent and the possibility that reflux was creating irritation in his esophagus and upper GI tract, we thought about [adding sucralfate].*

Mr Q: *They started me on different* [*combinations of*] *pain and antinausea medications. The thing that made the most difference, I think, is when they put me on an antacid called* [*lansoprazole*]. . . . [*t*]*he acid reflux got better 2 or 3 days later. It was in conjunction with other anti-nausea medications. . . . By the second day, I wasn't taking in anything orally, but I wasn't throwing up.*

Thoughtful evaluation to determine both the etiology of the symptoms and the pathophysiological mechanism by which they are triggered allows directed therapy to begin. Therapy should not only include antiemetics, but also measures to alleviate the cause of the symptoms, such as the proton pump inhibitor for Mr Q.

### Nonpharmacological Therapy

Nonpharmacological therapy is an important first consideration in the management of intractable nausea. Simple recommendations like avoiding strong smells or other nausea triggers, eating small, frequent meals, and limiting oral intake during periods of extreme emesis are helpful.[34,35] Psychological techniques, especially those that promote relaxation, can be helpful.[36,37] Acupuncture and acupressure may provide some benefit in the setting of chemotherapy or surgery. A systematic review found benefit to P6 stimulation (just above the wrist) in 11 of 12 randomized placebo-controlled trials.[38] Acupressure wrist bands, however, have not been shown to be effective.[39] Medical devices including gastric electrical stimulation[40] and transcutaneous electrical nerve stimulation units[41] are currently under investigation, but a lack of convincing evidence and substantial cost currently limit their use.

### Pharmacological Therapy

A mechanism-based treatment scheme administering the most potent antagonist to the implicated receptors has been shown to be effective in up to 80% to 90% of patients near the end of life.[9,10,42] It should be noted that some practitioners recommend starting an empirical antiemetic regimen, typically with a $D_2$ antagonist, regardless of the presumed etiology.[43] To date, no head-to-head comparisons between mechanism-based and empirical therapy exist.[44] We advocate and practice a mechanism-based management paradigm because it facilitates a systematic approach to caring for the patient, identifies all potential symptomatic contributors, directs therapy, and minimizes the risk of overmedicating a vulnerable population.

In practice, multiple etiologies are often at play and patients are acutely symptomatic on presentation, requiring empirical treatment and numerous interventions while evaluation is ongoing. All potential underlying causes, such as constipation, opioids, and electrolyte abnormalities should be addressed simultaneously to provide the greatest chance of rapidly resolving symptoms. When choosing antiemetics for these patients, we favor initiating medications that target the $D_2$ receptor, such as metoclopramide, prochlor-

perazine, or haloperidol, which are the foundation of many of the empirical schemes.[43,45-47] Choosing one of these agents makes mechanistic sense because $D_2$ antagonists block CTZ-mediated nausea, a common cause of symptoms in patients near the end of life.

Another important consideration when selecting an antiemetic is the medication's adverse-effect profile. For example, a patient with nausea due to stimulation of the CTZ may benefit from either a $5HT_3$ or $D_2$ antagonist. If the patient is concerned about excessive sedation, the clinician might avoid the $D_2$ antagonist, whereas, if constipation has been particularly problematic, the $D_2$ antagonist might be the better choice.

A recent development is the incorporation of $5HT_3$ antagonists such as ondansetron. Evidence supports the use of these agents for chemotherapy-induced nausea and vomiting,[48] radiation therapy-induced nausea,[49] and postoperative nausea.[50] Smaller studies suggest efficacy of $5HT_3$ antagonists in nausea and vomiting due to opioids[51] and uremia.[52] However, the literature does not support using these agents empirically outside of the noted clinical scenarios. Moreover, for the most common etiologies of nausea and vomiting at the end of life, $5HT_3$ antagonists are no more effective than the less expensive $D_2$ antagonists.[53,54]

Despite evidence supporting its use, a mechanism-based monotherapy approach may not reduce nausea and vomiting to an acceptable level.[9] Before changing regimens, practitioners should ensure that the prescribed therapy was properly administered. A common management pitfall is that first-line antiemetics are prescribed on an as-needed basis instead of scheduled around-the-clock.[11] If nausea and vomiting continue despite effective blocking of the targeted pathway, a second agent that antagonizes other implicated neurotransmitters should be added. Adding a second agent is preferred to switching agents because nausea is often multifactorial and several neurotransmitters are active at each receptor site. This approach has proved effective in chemotherapy[48] and for patients at the end of life.[43,55-57]

Prophylactic dosing prior to known emetogenic triggers has value particularly with chemotherapy,[48] radiation therapy,[17] in the postoperative setting,[58] or in patients with known prior adverse reactions to, eg, opioids.[59] Prevention of nausea is particularly important if the stimulus is likely to be repeated, such as with chemotherapy, because of the high potential for developing learned responses.[30]

In the case of Mr Q, a careful evaluation revealed several possible contributory etiologies. As such, Dr O recommended prochlorperazine to block $D_2$ receptors in the CTZ to counteract nausea and vomiting due to opioids. In addition, Dr O recommended lansoprazole and sucralfate to treat Mr Q's gastroesophageal reflux.

In the following section, we apply the mechanistic approach to the management of some of the most common etiologies of nausea and vomiting in patients near the end of life (**TABLE 2**). **TABLE 3** provides a list of frequently used antiemetics, their mechanism of action, dosage, common adverse effects, and cost. **TABLE 4** reviews selected studies supporting the use of these agents in patients near the end of life.

**Table 2.** Common Clinical Scenarios Associated With Nausea and Vomiting at the End of Life

| Clinical Scenario | References | Mechanism of Nausea and Vomiting | Typical First-line Antiemetics |
|---|---|---|---|
| Opioid-induced nausea and vomiting | 26, 46, 59, 61, 62 | Stimulation of CTZ ($D_2$)<br>Gastroparesis ($D_2$)<br>Constipation ($H_1$, muscarinic acetylcholine receptor)<br>Sensitization of labyrinth ($H_1$, muscarinic acetylcholine receptor) | Metoclopramide, haloperidol, and prochlorperazine |
| Chemotherapy-induced nausea and vomiting | 29, 48, 81 | $5HT_3$ released in gut, stimulating peripheral pathways<br>Stimulation of CTZ ($D_2$, $5HT_3$, $NK_1$)<br>Anxiety | $5HT_3$ antagonists (such as ondansetron), dexamethasone, and aprepitant |
| Malignant bowel obstruction | 32, 78 | Stimulation of CTZ ($D_2$)<br>Stimulation of peripheral pathways ($H_1$, muscarinic acetylcholine receptor) | Metoclopramide (if incomplete obstruction), haloperidol, and dexamethasone (also consider octreotide or hyoscyamine, nasogastric tube, venting gastrostomy tube) |
| Impaired GI tract motility of advanced cancer | 33, 110 | Gastroparesis ($D_2$) | Metoclopramide |
| Radiation-associated nausea and vomiting | 17, 49 | Stimulation of peripheral pathways via $5HT_3$ released from enterochromaffin cells in GI tract | $5HT_3$ antagonists |
| Brain tumor | 24 | Increased ICP or meningeal irritation activate meningeal mechanoreceptors, which stimulate the vomiting center | Dexamethasone |
| Motion-associated nausea and vomiting | 26 | Stimulation via vestibulocochlear nerve (muscarinic acetylcholine receptor, $H_1$) | Scopolamine, diphenhydramine, and promethazine |

Abbreviations: CTZ, chemoreceptor trigger zone; $D_2$, dopamine type 2 receptor; GI, gastrointestinal; $H_1$, histamine type 1 receptor; ICP, intracranial pressure; $NK_1$, neurokinin type 1 receptor; $5HT_3$, 5-hydroxytryptamine type 3 receptor.

### Opioid-induced Nausea and Vomiting

Generally, opioid-induced nausea and vomiting occurs with initiation of opioids or with dose escalation and resolves within 3 to 5 days of continued use. If nausea develops, antiemetics targeting $D_2$ receptors should be prescribed around-the-clock for several days and then tapered as tolerated.[24,70] Haloperidol, droperidol,[46,59,71] and metoclopramide[59,72] all have demonstrated efficacy. Limited evidence suggests that promethazine may potentiate the effects of opioids.[73] Although some clinicians see this interaction with opioids as a therapeutic advantage, others avoid promethazine due to sedation and the increased risk of respiratory depression.[74]

A small number of patients develop persistent nausea that may improve with an opioid dose-reduction or rotation. A 10% to 20% reduction in daily opioid dose often alleviates nausea without a loss in analgesia.[75] However, if dose reduction is not feasible or is ineffective, opioid rotation demonstrates efficacy in both prospective and retrospective studies.[76,77]

### Chemotherapy-Induced Nausea and Vomiting

The patient's goals of care are paramount when considering the use of chemotherapeutic agents near the end of life. Management of chemotherapy-induced nausea and vomiting is preventive and based on the emetogenicity of the prescribed agent (TABLE 5).[48]

Some of the nausea associated with chemotherapy may also be anxiety-related or "anticipatory" because patients associate receiving chemotherapy with becoming nauseated.[37] This may partially explain the observed decreasing efficacy of antiemetics in patients undergoing multiple cycles of chemotherapy.[78] Although not strictly classifiable as antiemetics, benzodiazepines such as lorazepam are effective in preventing anticipatory nausea.[79,80] Outside of this set-

**Table 3.** Antiemetics

| Antiemetic | Trade Name | Presumed Primary Receptor Site of Action | Dosage/Route | Major Adverse Effects | Cost, $[b] |
|---|---|---|---|---|---|
| Metoclopramide | Reglan | $D_2$ (primarily in GI tract) or $5HT_3$ (only at high doses) | 5-20 mg Orally or subcutaneously or IV before every meal and before bed | Dystonia, akathisia, esophageal spasm, and colic in GI tract obstruction | 1.21 per 10-mg pill |
| Haloperidol | Haldol | $D_2$ (primarily in CTZ) | 0.5-4 mg Orally or subcutaneously or IV every 6 h | Dystonia and akathisia | 0.10 per 1-mg pill |
| Prochlorperazine | Compazine | $D_2$ (primarily in CTZ) | 5-10 mg Orally or IV every 6 h or 25 mg rectally every 6 h | Dystonia, akathisia, and sedation | 0.43 per 10-mg pill |
| Chlorpromazine | Thorazine | $D_2$ (primarily in CTZ) | 10-25 mg Orally every 4 h, 25-50 mg IM or IV every 4 h, or 50-100 mg rectally every 6 h | Dystonia, akathisia, sedation, and postural hypotension | 0.30 per 25-mg pill |
| Promethazine | Phenergan | $H_1$, muscarinic acetylcholine receptor or $D_2$ (primarily in CTZ) | 12.5-25 mg Orally or IV every 6 h or 25 mg rectally every 6 h | Dystonia, akathisia, and sedation | 0.39 per 25-mg pill |
| Diphenhydramine | Benadryl | $H_1$ | 25-50 mg Orally or IV or subcutaneously every 6 h | Sedation, dry mouth, and urinary retention | 0.13 per 25-mg pill |
| Scopolamine | Transderm scop | Muscarinic acetylcholine receptor | 1.5 mg Transdermal patch every 3 d | Dry mouth, blurred vision, ileus, urinary retention, and confusion | 7.80 per patch |
| Hyoscyamine | Levsin | Muscarinic acetylcholine receptor | 0.125-0.25 mg Sublingually or orally every 4 h or 0.25-0.5 mg subcutaneously or IV every 4 h | Dry mouth, blurred vision, ileus, urinary retention, and confusion | 0.82 per 0.125-mg tablet |
| Ondansetron[a] | Zofran | $5HT_3$ | 4-8 mg Orally by pill or dissolvable tablet or IV every 4-8 h | Headache, fatigue, and constipation | 38.93 per 8-mg tablet |
| Mirtazapine | Remeron | $5HT_3$ | 15-45 mg Orally every night | Somnolence at low dose, dry mouth, and increased appetite | 3.20 per 15-mg tablet |

Abbreviations: CTZ, chemoreceptor trigger zone; $D_2$, dopamine type 2 receptor; GI, gastrointestinal; $H_1$, histamine type 1 receptor; IM, intramuscular; IV, intravenous; $5HT_3$, 5-hydroxytryptamine type 3 receptor.

[a] Ondansetron is included as an example of $5HT_3$ antagonists because it was the first agent of this class and adopted in many hospital formularies. Its inclusion is not meant to indicate superiority over other members of the class, such as dolasetron, granisetron, and palonosetron.

[b] Cost per pill was calculated from prices listed on epocrates.com.

ting, however, the use of benzodiazepines for nausea is generally discouraged.[81]

### Malignant Bowel Obstruction

Management of malignant bowel obstruction often involves both pharmacologic and nonpharmacologic interventions. Surgery is generally not recommended for persons with a life expectancy of less than 2 months[82,83] because it does not improve survival, rarely palliates symptoms, and is associated with a high complication rate.[84] Gastrointestinal tract stents may have a role, depending on the location of the obstruction, but have been associated with complications.[85] Nasogastric tubes can relieve symptoms but should only be used temporarily while other treatment is pursued given the complications and discomfort associated with their long-term use.[32]

Fortunately, medical management provides very effective symptom control.[86] Recommended pharmacologic therapy in-

**Table 4.** Selected Studies Supporting Use of Common Antiemetics[a]

| Source | Intervention | Design | No. of Participants | Setting | Outcomes | Length of Follow-up | Results | Adverse Events |
|---|---|---|---|---|---|---|---|---|
| Robbins and Nagel,[60] 1975 | Haloperidol 1 mg IM × 1 vs placebo | RCT | 28 | Nursing home residents with nausea and vomiting due to GI tract disorders | Failure: vomiting after antiemetic | 12 h | 86% Haloperidol group completed study vs 43% placebo[b]<br>Less nausea and vomiting observed in haloperidol group[b] | None |
| Barton,[61] 1975 | Haloperidol 1 mg IM × 1 vs placebo | RCT | 62 | Postoperative patients who developed nausea | Vomiting and report of nausea | 3 h | Haloperidol more effective (83% vs 29% with no vomiting at 1 h, 71% vs 20% with no nausea)[b] | No serious adverse effects |
| Bruera et al,[62] 2000 | Controlled-release metoclopramide 40 mg orally every 12 h vs placebo | RCT | 26 | >1 mo of cancer-associated dyspepsia syndrome | Nausea and vomiting self-report on 100 mm VAS in daily journal | 4 d in each arm of cross-over design | 5-Point lower nausea score in cohort receiving controlled-release metoclopramide[b] | No difference from placebo |
| Gralla et al,[63] 1981 | Metoclopramide 10 mg/kg vs prochlorperazine 50 mg vs placebo over study period | RCT | 41 | Patients with advanced cancer receiving cisplatin | Episodes of emesis, volume of emesis, duration of nausea | 9 h | Fewer vomiting episodes with metoclopramide (10.5) vs placebo (1)[b] and metoclopramide (12) vs prochlorperazine (1)[b]<br>Reduced emesis volume and nausea duration with metoclopramide[b] | Mild sedation with metoclopramide; 1 patient in the motoclopramide group had brief extrapyramidal reaction |
| Ernst et al,[64] 2000 | Prochlorperazine 10 mg IV vs promethazine 25 mg IV | RCT | 84 | Adults treated at emergency department for gastritis or gastroenteritis | Patient report of nausea on 100 mm VAS, time to complete relief | 60 min | Scores: Prochlorperazine baseline, 65; 30 min, 29; and 60 min, 4.5;<br>Promethazine baseline, 73; 30 min, 46; and 60 min, 26[b]<br>Prochlorperazine was also superior in time to complete relief[b] | 14% Akathisia or extrapyramidal reactions in both groups<br>Less sedation in prochlorperazine (38% vs 71%) |
| Bardfeld,[65] 1966 | Trimethobenzamide 200 mg IM vs prochlorperazine 10 mg IM vs placebo | RCT | 126 | Mostly ambulatory patients with nausea and vomiting | Patient self-report | 24 h | Prochlorperazine superior: no relief in 21% of placebo, 18% of trimethobenzamide, and 7% of prochlorperazine (*P* value range, .07-.08) | Drowsiness and pain at injection site in 12 of 41 patients receiving prochlorperazine |
| Pykko et al,[66] 1985 | Transdermal scopolamine (1 patch delivering 5 µg/h vs 2 patches delivering 10 µg/h) vs dimenhydrinate 100 mg with 50 mg of caffeine vs placebo | RCT | 16 | Experimentally induced motion sickness in healthy volunteers | Self-report of nausea on 0-100 numerical scale | Duration of experimental induction of nausea | Mean score for scopolamine 1 patch (40), 2 patches (23), and dimenhydrinate (18), all superior to placebo (61)[b] | Dry mouth more often than placebo with all 3 treatments, vertigo and gait disturbances in 3 participants treated with 2 scopolamine patches |
| Marty et al,[67] 1990 | Ondansetron 8 mg IV before cisplatin then 1 mg/h for 24 h vs metoclopramide 3 mg/kg before cisplatin then 0.5 mg/kg for 8 h then placebo for 16 h | RCT | 76 | Cancer patients receiving cisplatin | Observed emesis, self-report of nausea by graded scale, VAS, and patient preference | 24 h | 2 or fewer episodes of vomiting in 75% of patients treated with ondansetron vs 42% treated with metoclopramide[b]<br>Ondansetron also superior for nausea control[b] | Dystonic reactions in 3 patients treated with metoclopramide, more sedation with metoclopramide (12 vs 5 patients) |
| Theobald et al,[68] 2002 | Mirtazapine 15 and 30 mg orally as needed | Open-label crossover trial | 20 | Cancer patients taking opioids for pain | Self-report of nausea on 1-10 scale | 6 wk | Nausea decreased from 2.4 to 0.9 (*P* = .10) | Not reported |

*(continued)*

**Table 4.** Selected Studies Supporting Use of Common Antiemetics[a] (cont)

| Source | Intervention | Design | No. of Participants | Setting | Outcomes | Length of Follow-up | Results | Adverse Events |
|---|---|---|---|---|---|---|---|---|
| Mystakidou et al,[57] 1998 | Chlorpromazine 25 mg 2/d + dexamethasone 2 mg daily vs chlorpromazine 25 mg 2/d + tropisetron 5 mg/d vs chlorpromazine 25 mg 2/d + tropisetron 5 mg/d + dexamethasone 2 mg/d vs tropisetron 5 mg/d | RCT | 160 | Terminally ill patients with cancer with no readily identifiable cause of nausea and vomiting | Patient report of nausea and vomiting with total control defined as no nausea and vomiting | 15 d | Total control nausea/vomiting in 18 (33.9%) of chlorpromazine + dexamethasone, 74.4 (84.6%) of chlorpromazine + tropisetron, 85 (92.5%) of chlorpromazine + tropisetron + dexamethasone, 65.8 (78.9%) of tropisetron<br>All tropisetron-containing regimens superior to chlorpromazine + dexamethasone[b] | No difference in adverse effects and none that forced discontinuation of therapy |
| Braude, et al,[69] 2006 | Droperidol 1.25 mg vs metoclopramide 10 mg vs prochlorperazine 10 mg vs placebo<br>All received IV fluids | RCT | 97 | Adults in emergency department with nausea | 100 mm VAS | 60 min | Droperidol (–54.5 mm), metoclopramide (–40.2 mm), prochlorperazine –40.5 mm), and placebo (–38.7 mm)[b] | Droperidol (71.4%) caused more self-reported anxiety or restlessness than all others (23.5%) |

Abbreviations: IM, intramuscular; IV, intravenous; RCT, randomized controlled trial; VAS, visual analog scale.
[a]Study selection based primarily on quality of evidence and secondarily on how well the study population approximates patients near the end of life.
[b]Statistically significant at $P < .05$.

**Table 5.** American Society of Clinical Oncology Guidelines for Management of Chemotherapy-Induced Nausea and Vomiting[a]

| Emetic Risk Category | Incidence of Emesis Without Antiemetics, % | Antiemetic Regimen |
|---|---|---|
| High | >90 | $5HT_3$ antagonist day 1<br>Dexamethasone day 1-4<br>Aprepitant day 1-3 |
| Moderate | 30-90 | $5HT_3$ antagonist day 1<br>Dexamethasone day 1-3 (may omit day 2 and 3 if aprepitant given)<br>(Aprepitant day 1-3 if patients given combination of an anthracycline and cyclophosphamide) |
| Low | 10-30 | Dexamethasone day 1 |
| Minimal | <10 | Prescribe on as needed basis |

Abbreviation: $5HT_3$, 5-hydroxytryptamine type 3 receptor.
[a]Based on Kris et al.[48]

cludes analgesics, antisecretory agents, and antiemetics.[32] Opioids are used for pain control. Anticholinergics such as hyoscyamine and a somatostatin analogue (octreotide) diminish secretions and potentially reduce pain and nausea by decreasing mucosal distention and peristalsis. Octreotide can be administered subcutaneously beginning at 50 to 100 µg 3 times daily (to a maximum of 900 µg per day). Some palliative care units will administer octreotide via continuous infusion at much higher doses, although evidence to support this practice is scarce. Metoclopramide is recommended for patients with nausea and a partial obstruction without colic. In patients with complete obstruction, metoclopramide can induce colic through its peripheral $D_2$ receptor stimulation of GI motility, although this concern may be overstated.[87] For these patients, the recommended agents are central $D_2$ antagonists, such as haloperidol, which work primarily at the CTZ. Antihistamines that work through peripheral pathways and the vomiting center may also be effective. Corticosteroids, such as dexamethasone, are generally included in most antiemetic regimens for their potential effect on tumor-associated inflammation. A recent Cochrane review found a nonsignificant ($P>.05$) trend suggesting that corticosteroids may be effective in helping resolve the obstruction.[88]

If medical therapy provides insufficient relief, a venting gastrostomy tube may be placed. With this, gastrointestinal and oral secretions are removed without a nasogastric tube, and the patient may continue liquid oral intake as desired.[89]

## Intractable Nausea and Vomiting

MR Q: *We tried these little dots [ondansetron ODT] for nausea. But nothing was working. It wasn't until we went into the hospital and just started experimenting that I really got some relief.*

In some cases, nausea and vomiting may persist despite a mechanism-based approach using several medications at appropriate dosages taken around-the-clock targeting multiple pathways. In these situations, less traditional agents can be considered, but evidence supporting their use remains limited. For instance, dexamethasone, is widely used for its antiemetic effects in palliative care, even though a recent study demonstrated no greater effect than placebo when added to metoclopramide for patients with chronic nausea of advanced cancer.[90] Despite this study's results, corticosteroids have well-described antiemetic properties,[91] and in our experience are extremely effective at decreasing symptom severity. Mirtazapine, an antidepressant that antagonizes the $5HT_3$ receptor, is also frequently used to

alleviate intractable symptoms. To date, evidence supporting its use is limited to small trials and case reports.[68,92] Cannabinoid agents, such as dronabinol, can be effective antiemetics in patients with AIDS[93,94] and cancer[95,96] but should be used with caution in older adults or cannabinoid-naive patients because adverse effects, including confusion and hallucinations, may be pronounced. Olanzapine, an atypical antipsychotic, blocks several receptors associated with nausea and vomiting including dopamine, acetylcholine, histamine, and serotonin receptors. Larger studies are needed to better define its role.[97-99] Megestrol acetate and thalidomide decreased nausea in patients enrolled in clinical trials for appetite stimulation,[100,101] but they are rarely used solely for their antiemetic properties. The ABHR suppository, a combination preparation of lorazepam (Ativan), diphenhydramine (Benadryl), haloperidol (Haldol), and metoclopramide (Reglan), is often used for home hospice patients, although there are no data to support its benefit. It is well tolerated,[102] but, in our experience, exerts its effect mainly through sedation. Herbal medicines have been used to treat chemotherapy-induced[103] and pregnancy-induced[104] nausea and vomiting, but little evidence exists to support their use in end-of-life populations.[105] Finally, $5HT_3$ antagonists are sometimes used to treat intractable nausea and vomiting,[106-108] but, as noted above, there is little justification for their use outside of circumscribed clinical scenarios.

Refractory nausea and vomiting may make oral administration of medication unfeasible so alternate routes must be considered. Many of the most common antiemetics are available in several preparations, such as rectal suppositories, subcutaneous infusions,[109] and orally dissolvable tablets (Table 3), allowing patients to be treated at home.

### Polypharmacy and Drug-Drug Interactions

DR O: *Ordinarily, I like to do things one at a time. If you do a bunch of things at once, you never know what the useful things were. . . . I was a little nervous that the medical team was using such a variety of antinausea medicines.*

Avoiding polypharmacy is a critical aspect of nausea and vomiting management for the reasons Dr O observes. If patients are taking multiple medications, it may be difficult to identify the effective agent, and the patient is at increased risk for adverse effects as well as for drug-drug interactions.[110] Precipitating delirium in patients near the end of life is of particular concern as they exhibit diminished cognitive reserve, and most antiemetic agents are centrally acting.[111-113] Standardized tools such as the Confusion Assessment Method[114] are effective and should routinely be incorporated into clinical practice to screen for delirium in patients with advanced life-limiting diseases.

One common misstep in the management of nausea and vomiting is the coadministration of multiple antiemetics that antagonize the same receptor, resulting in adverse effects at lower than expected doses. For example, if a patient is taking prochlorperazine and haloperidol, both of which work on the $D_2$ receptor, the risk of a dystonic reaction or akathisia increases. A mechanism-based approach helps avoid this pitfall and facilitates a step-wise introduction of medications that exert their effects at different receptor sites.

### Palliative Sedation

If nausea and vomiting remain intractable despite aggressive, multimodal attempts at control, palliative sedation may be considered for patients with a limited life expectancy.[115,116] Although symptoms of nausea and vomiting are rarely the primary indication for palliative sedation,[117] they are commonly noted secondary symptoms of patients choosing palliative sedation for other reasons (36%-44% of cases).[115] No standard regimen exists for sedation of patients with intractable nausea; however, propofol has been proposed as an ideal agent because it blocks $5HT_3$ receptors, resulting in an antiemetic effect in addition to its sedative effects.[118]

## CONCLUSIONS

A step-wise, mechanism-based approach to treatment of nausea and vomiting has proved effective for a majority of patients experiencing these symptoms toward the end of life. A thorough assessment to ascertain potential etiologies, pathways, and respective transmitters and receptors allows the clinician to prescribe the most appropriate antagonist to the offending receptor. If monotherapy is ineffective, a trial combining several therapies to block multiple emetic pathways is recommended. Further research will refine palliative care management strategies that minimize adverse effects and maximize control of these highly distressing symptoms.

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**Financial Disclosures:** None reported.
**Funding/Support:** The Perspectives on Care at the Close of Life section is made possible by a grant from the Archstone Foundation.
**Role of the Sponsor:** The funding source had no role in the preparation, review, or approval of the manuscript.
**Other Sources:** For a list of relevant Web sites, see the article on the *JAMA* Web site at http://www.jama.com.

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# Web Resources for End-of-Life Care

### End of Life/Palliative Education Resource Center

http://www.eperc.mcw.edu/

Online site with peer-reviewed educational resources, including materials on communication and end-of-life decision making.

### PALLIATIVE CARE LEADERSHIP CENTERS (PCLC)

http://www.capc.org/pclc

The Center to Advance Palliative Care has funded 6 Palliative Care Leadership Centers throughout the nation to provide health care institutions intensive training and assistance tailored to that individual institution's needs.

### AMERICAN SOCIETY OF CLINICAL ONCOLOGY (ASCO) GUIDELINE FOR ANTIEMETICS IN ONCOLOGY: UPDATE 2006

http://www.asco.org/guidelines/antiemetics

Online site from the American Society of Clinical Oncology with access to the society's complete guidelines for the management of chemotherapy-induced nausea and vomiting.

### NATIONAL CANCER INSTITUTE (NCI) SUPPORTIVE CARE: NAUSEA AND VOMITING

http://www.cancer.gov/cancertopics/pdq/supportivecare

Online site with educational resources for patients and health care professionals. Numerous topics in supportive care, including nausea and vomiting, can be accessed through this site.