Symptom Control in Palliative Care—Part I: Oncology as a Paradigmatic Example

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ABSTRACT

Achieving the best quality of life for patients and their families when a disease becomes progressive and no longer remains responsive to curative therapy is the primary goal of palliative care. A comprehensive care plan focusing on control of physical symptoms as well as psychological, social, and spiritual issues then becomes paramount in that context. Symptom assessment and treatment are a principle part of palliative care. This paper is the first of three in a series addressing non-pain symptoms, which are frequently encountered in the palliative care populations. The most frequent non-pain symptoms are constipation, chronic nausea and vomiting, anorexia, dyspnea, fatigue, and delirium. As symptoms are subjective, their expression varies from patient to patient, depending on the individual patient's perception and on other factors such as psychosocial issues. While symptoms are addressed individually, patients frequently have multiple coexisting symptoms. Generally told, once the intensity of a symptom has been assessed, it is necessary to assess the symptom in the context of other symptoms such as pain, appetite, fatigue, depression, and anxiety. Given that fact, adopting a multidimensional assessment allows for formulation of a more effective therapeutic strategy. More pertinently, this paper highlights the management of non-pain symptoms as an integral part of patient care and reviews the pathophysiologies, causes, assessment, and management of constipation, chronic nausea, and vomiting, each of which is common among the palliative care population.

INTRODUCTION

PATIENTS EXPERIENCE a number of devastating physical and psychosocial symptoms before they die. Our task is to identify and treat these symptoms so that patients with advanced illness may have the best possible quality of life. Studies have shown a wide variation in the reported frequency of the various symptoms evaluated.[1–8]

Patients with advanced cancer account for approximately half of all admissions to hospice programs. The remainder comprises patients with cardiac disease, dementia, respiratory disease, stroke, motor neuron disease, renal failure, hepatic failure, and human immunodeficiency virus (HIV). There is a trend for an increased number of noncancer admissions to hospice.[9] The mechanism of symptoms in chronic illness is shown in Figure 1.

Because symptom control research has traditionally focused on the cancer population, the use of cancer as the paradigmatic example for treatment of nonpain symptoms is an imperfect but necessary approach. It should be noted that the

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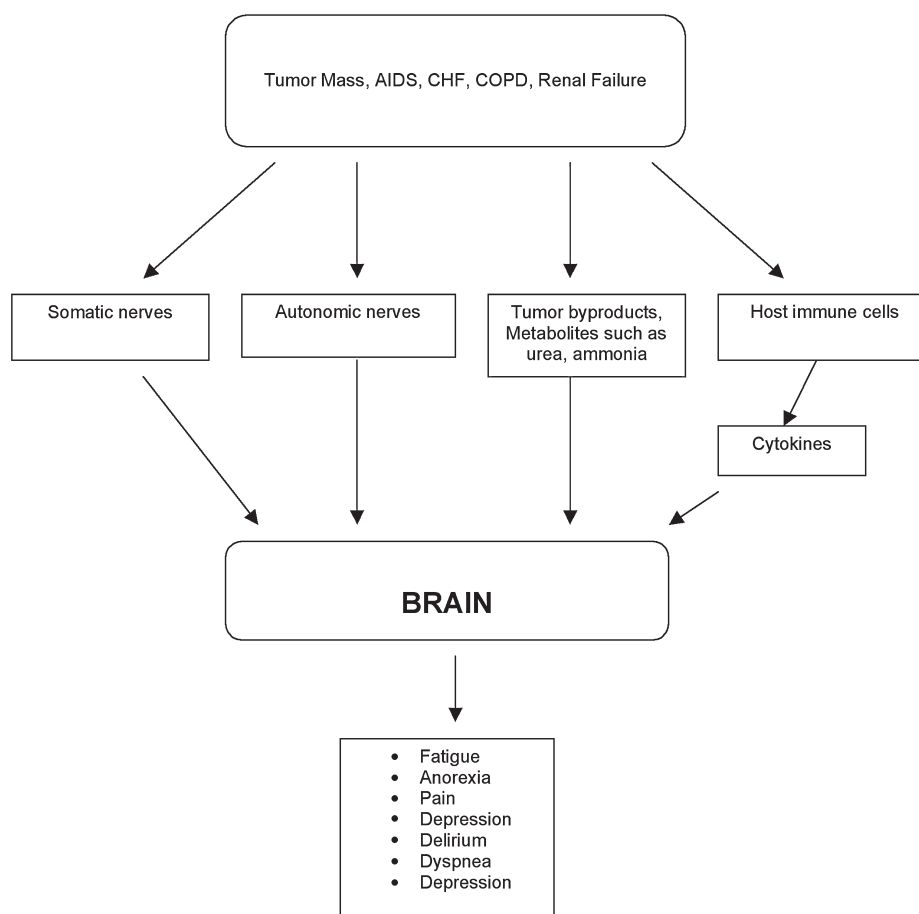
FIG. 1. Mechanisms of symptoms in chronic illness.

assessment instruments and management of symptoms may differ in noncancer patients. Some of these differences will be discussed in the text. In Part I symptom assessment, constipation, and nausea are covered.

SYMPTOM PHASES

Symptom expression by the patient involves three steps: production, perception, and expression (Fig. 2). Production is caused mostly by the disease process itself and cannot be measured directly. Examples of symptom production include nociceptive input from bone metastases, or the stimulation of "J" receptors in the lung producing dyspnea.

Perception takes place at the level of central nervous system and, similar to symptom production, cannot be measured directly. Perception is influenced by the action of endorphins, inhibitory, and facilitatory pathways. As an exam-

ple: one "perceives" a limb to be present and painful even after amputation—the "phantom limb" syndrome.

Symptom expression is the visible aspect of assessment and guides therapy. Patients with the same level of production may have a different expression of symptoms. Symptom expression is not only related to the disease pathology, but is also influenced by other factors such as learned responses to coping and prior experiences, family support, religious and personal beliefs, and the presence of delirium or depression. For example, when one is a child, a scraped knee from a fall will result in a high expression of pain (crying, screaming), but as one ages and cortical inhibition develops, the same level of injury (symptom production) will result in a muted expression. Similarly, in patients with delirium, disinhibition causes symptoms to be highly expressed. The degree to which different dimensions influence the expression of a symptom must be recognized in order to deliver effective tar-
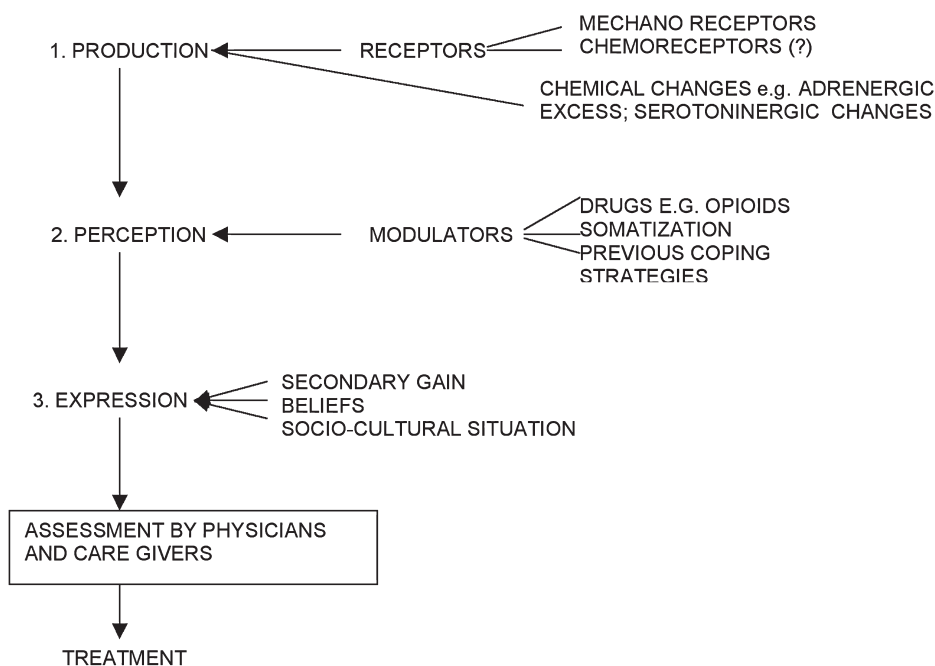
FIG. 2. Production, perception, and expression of symptoms.

geted treatment. Two patients may have identical fatigue scores of 8 of 10, but the relative contribution of the different factors involved could vary significantly (Table 1).

For clinicians, symptoms present both diagnostic clues and therapeutic challenges; for the patient, the symptoms and the distress they produce are inextricably linked to disease experience. Symptom-related distress, which includes physical, emotional, and spiritual distress, is influenced by diverse psychological and cultural factors.

In clinical practice, patients often present with multiple symptoms requiring simultaneous assessment and management. Frequently, management of one symptom may lead to aggravation of another. For example, the management of pain with opioids may also improve insomnia and anxiety, but can exacerbate sedation, constipation, and nausea. An effective strategy requires a multidimensional assessment of the patient with formulation of an individualized management plan, in accordance with treatment goals and the wishes of the patient. Reassessment is essential, because treatment strategies that control symptoms at one stage may be inappropriate or ineffective at another stage of the disease. The multidimensional nature of symptoms is best managed via a multidisciplinary approach in order to address the complex needs of patients and their families. The multidisciplinary team may include psychologists, chaplains, occupational therapists, physical therapists, nutritionists, nurses, social workers, and case managers.

TABLE 1. RELATIVE CONTRIBUTION OF DIFFERENT ETIOLOGIES OF FATIGUE IN TWO PATIENTS REPORTING IDENTICAL INTENSITY OF 8 OF 10 ON ESAS

	Patient 1	Patient 2
Cachexia	50%	0%
Depression	0%	60%
Anemia	30%	0%
Deconditioning	20%	10%
Pain	0%	10%
Drugs	0%	20%
	100%	100%

ESAS, Edmonton Symptom Assessment System.

INSTRUMENTS FOR ASSESSMENT OF SYMPTOMS

At present there is no gold standard for symptom assessment in palliative care. Rapid, efficient instruments to assess for the presence of multiple symptoms include the Edmonton Symptom Assessment System (ESAS), the Condensed Memorial Symptom Assessment Scale (CMSAS), and the Symptom Distress Scale (SDS). Assessment tools allow for the identification of many more
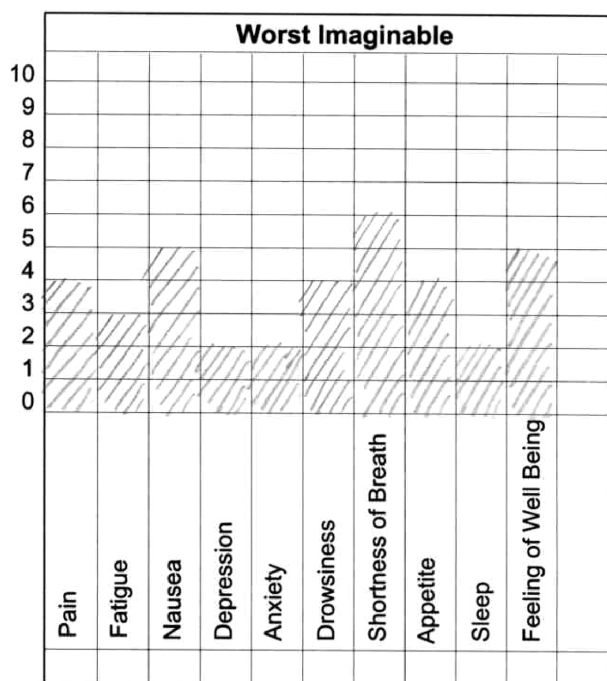
FIG. 3. Edmonton Symptom Assessment Scale (visual analogue).

symptoms than a simple unstructured evaluation.[10,11] Lengthier assessment instruments, such as the Memorial Symptom Assessment Scale (MSAS), are best used for research purposes.

The ESAS consists of nine visual analog scales (VAS) or numerical rating scales (NRS) that evaluate a combination of physical and psychological symptoms (Fig. 3).[12] The ESAS has been validated for internal consistency, criterion validity, and concurrent validity[13] and is widely used in palliative care research.[14] Ease of use and visual representation make it an effective practical tool that can be used at bedside[15–17] and allows for symptoms to be tracked over time with regards to intensity, duration, and responsiveness to therapy. In a study of patients with delirium and pain, the ESAS accurately captured the "crescendo" of symptom expression that occurs in the presence of delirium.[18] The MSAS measures patient rated severity, frequency, and distress associated with 32 variables of physical and psychological symptoms. Specific subscales incorporated within it capture physical, psychological, and global distress symptoms.[19] A new abbreviated version, the short form MSAS[20] (MSAS-SF) captures patient-rated distress associated with 26 physical symptoms and the frequency of 4 psychological symptoms. The Condensed MSAS[21] (CMSAS) takes 2–4

minutes to complete and contains both quality of life and survival information approximately equivalent to the original 32 items. The SDS is a patient-rated instrument that assesses 9 physical and 2 psychological symptoms as to their intensity, frequency, and distress level.[22]

INSTRUMENTS FOR ASSESSMENT OF SYMPTOMS IN THE COGNITIVELY IMPAIRED

Impaired cognition, whether caused by delirium or dementia, hinders the accurate measurement of symptoms. A systematic review[23] found a high prevalence of delirium superimposed on dementia, few well-controlled studies, and frequent underrecognition of the phenomenon. Assessment tools for cognitive impairment and delirium are discussed in the section on delirium.

Patients with mild to moderate cognitive impairment can usually respond to a self reported instrument evaluating pain.[24] A recent study[25] of the available instruments for assessing pain in cognitively impaired individuals found good consistency between scores on five different pain assessment scales for those with moderate cognitive impairment. Another study showed that one third of patients, with a mean MMSE of 15.7, were not able to complete any of the three pain assessment tools studied,[26] and caregiver and patient agreement about pain intensity occurred in only 67%. In patients with severely impaired cognition, behavioral and verbal[27,28] cues have to be used for clinical assessment.

INSTRUMENTS FOR ASSESSMENT OF FUNCTION AND PROGNOSIS

Symptoms, function and prognosis are dynamic interrelated dimensions. (A full description of assessment tools for function and prognosis is outside the scope of this review). Functional status is important for planning the setting of care, which can be at home, hospice or hospital,[29] and is an independent predictor of survival.[30]

The Karnofsky Performance Status (KPS) scores and the Eastern Co-operative Oncology Group (ECOG) score are the most widely used performance status assessment scales in oncology

practice for treatment planning and research, and are reliable prognostic parameters.[31–34] However, one systematic review of physicians' clinical predictions of survival showed that performance status, anorexia and dyspnea added limited information to that contained in the physician's prediction. Physicians typically tended to overestimate survival.[35]

Two complementary tools, the Edmonton Functional Assessment Tool (EFAT) and Functional Independence Measure (FIM), can be used to evaluate functional status of patients with advanced cancer over time. The EFAT is a validated tool that allows a physiotherapist or trained nurse to determine the functional performance of patients with advanced cancer, as well as the evaluation of factors that contribute to the functional impairment, such as communication, mental status, pain, and dyspnea, among others.[36,37] The functional status of advanced cancer patients can be assessed in the research setting using the FIM.[38,39] The FIM includes 18 items covering independence in self-care, sphincter control, mobility, locomotion, communication, and social cognition.

The Katz index of activities of daily living (ADL)—eating, bathing, dressing, toileting, transferring, and continence—can be used as appropriate proxies for a patient's level of physical impairment. A scale of Instrumental Activities of Daily Living (IADL) captures more complex life activities, such as light housework, laundry, meal preparation, transportation, grocery shopping, using the telephone, medication management, and money management. The IADL may identify individuals with cognitive impairment if they are unable to manage medications, manage finances, or use the telephone.

An excellent resource for further study of assessment tools is a website maintained by Joan Teno, M.D., M.S.: ⟨www.chcr.brown.edu/pcoc/toolkit.htm⟩.

CONSTIPATION AND CHRONIC NAUSEA

Constipation

Constipation is defined as the infrequent and difficult passage of hard stool. It can be a difficult condition to assess and treat because of the wide variety of presenting symptoms. Most patients define constipation by one or more of the following symptoms: hard stools, infrequent stools, sense of incomplete bowel evacuation, and need for excessive straining[40]; others may report bloating, decreased appetite, nausea, or generalized abdominal discomfort. Atypical symptoms include overflow diarrhea or urinary retention. There is a wide variation in normal bowel patterns, with normal frequency defined as anywhere between 3 stools per day to 3 stools per week. It is a common cause of morbidity in the palliative care setting, occurring in approximately 40% of patients referred to palliative care service,[41] and it is thought to affect the overwhelming majority (>95%) of patients who are treated with opioids for relief for cancer related pain.[42]

Mechanisms

The common causes of constipation in the palliative care setting are shown in Figure 4. Of these, the two most common etiologies are related to the side effects of opioids and the effects of progressive disease. Physiologic factors include inadequate oral intake, dehydration, and lack of exercise. In the palliative care setting, careful attention must be given to the multifactorial nature of constipation.

Although constipation is often overlooked in the setting of other comorbid conditions, it is not necessarily a benign condition and some of the complications of unrelieved constipation can indeed be life-threatening.[43] Severe constipation can lead to bowel obstruction with attendant issues of severe morbidity. In patients who are neutropenic, severe constipation can lead to bacterial transfer across the colon, with bacteremia and sepsis as a result.

Assessment

Patients with advanced disease have many risk factors for severe constipation and should be carefully assessed for this complication. A thorough history of the patient's bowel pattern, fluid intake, dietary habits, and recent changes, a medication review and a thorough physical examination can identify potential causes of constipation.

History. The assessment of constipation begins with a careful history of bowel habits. Was there a history of constipation prior to the cancer (or other chronic illness)? What was the normal
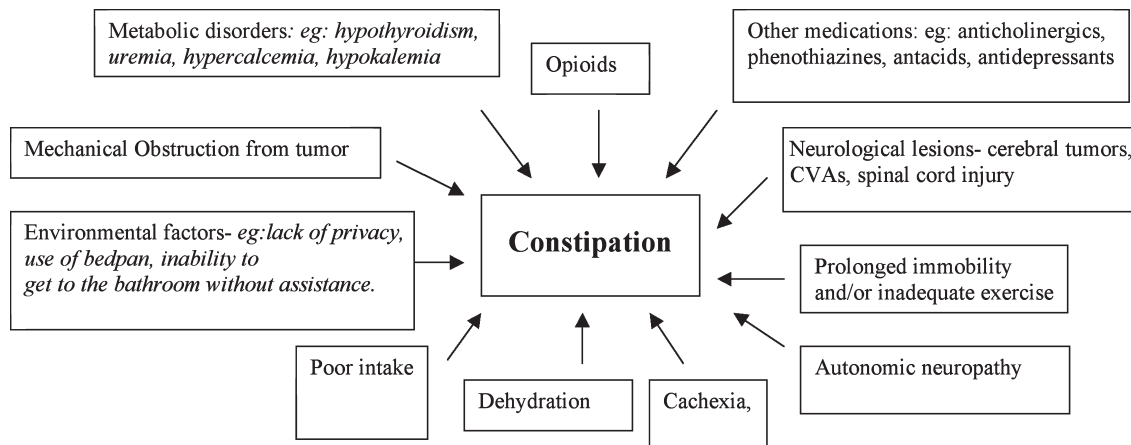
FIG. 4. Common causes of constipation in palliative care.

bowel pattern (frequency, amount) and the characteristics of the stool (hard versus soft, loose versus formed, "ribbon-like" versus "pellet-like")? Further questioning should include the date of the last bowel movement, the degree of straining and pain involved, whether the movement felt complete, or whether there was no urge to defecate at all (suggesting colonic inertia). Has the patient been having any abdominal discomfort, cramping, nausea or vomiting, pain, excessive gas, or rectal fullness? Does the patient regularly use laxatives or enemas? The "Rome criteria" (romecriteria.org) helps in assessing and defining constipation but does not take into account quality of life.

A physical examination should include the abdomen (distension, firmness, tenderness, the presence or absence of bowel sounds). A digital rectal examination should be performed to assess the presence of hard stool in the vault and rule out impaction. It may reveal the presence of hemorrhoids, fissures, fistulas or decreased tone and sensation (indicating incipient cord compression in the patient with advanced cancer). Caution should be exercised in performing a rectal examination on patients with known neutropenia or thrombocytopenia.

Diagnostic tests. Abdominal films are helpful to assess bowel gas pattern and rule out ileus or bowel obstruction. A "Constipation Score" may also be obtained from a flat abdominal x-ray.[44] The film is divided into four quadrants by drawing a large X. This identifies the four areas of the colon (ascending, transverse, descending, and sigmoid). Each quadrant is assigned a score from 0 to 3 based on the degree of stool in the lumen. A score of 0 indicates no stool, a score of 1 indicates "less than 50%" occupancy, a score of 2 indicates "greater than 50% occupancy," and a score of 3 indicates complete occupancy of the lumen with stool. Scores may range from 0 to 12 and score of 7 or greater indicates severe constipation. The usefulness of this score is that it makes constipation visible as an "action item" on the chart for health care workers to work on and follow-up. Air fluid levels and no air in the rectosigmoid on x-ray may warrant a computed tomography (CT) scan, which would provide further information about a possible obstruction.

Management

The management of constipation can be divided into general nonpharmacologic interventions and pharmacologic measures.

Nonpharmacologic. The general interventions involve patient education on the various causes of constipation, the elimination of medical and dietary factors contributing to constipation, and encouraging adequate fluid intake and increased dietary fiber. High fiber intake is contraindicated in patients at increased risk for bowel obstruction, such as those with a history of bowel obstruction or status postcolostomy. In a study of geriatric patients,[45] the administration of natural laxative mixtures (raisins, currants, prunes, dates and prune concentrate) was found to more beneficial than stool softeners, lactulose and other laxatives in terms of cost, ease of administration and pro-

duction of more natural and regular bowel movements. The role of natural laxatives in the palliative care setting has not been explored.

Pharmacologic. Therapeutic medical interventions for constipation include the administration of laxatives and rectal enemas. Oral laxatives include bulk agents, osmotic agents, contact cathartics, agents for colonic lavage, lubricants, prokinetic drugs, and opioid antagonists. Because opioids are associated with constipation in the majority of patients, a bowel regimen should be initiated at the time opioids are initially prescribed and should be continued for as long as the patient takes opioids. Lower doses of opioids, or weaker opioids such as codeine, are just as likely to cause constipation, and clinicians should therefore base laxative prescribing and titration on bowel function rather than dose or type of response.[46] Other drugs with prominent constipating effects used frequently in the palliative care population include those with anticholinergic effects, such as antispasmodics, antidepressants, phenothiazines, haloperidol, and antiemetics such as ondansetron. Autonomic neuropathy induced by chemotherapy may also result in constipation.

Oral laxative agents may be divided into those that soften the stool and those that stimulate gut peristalsis. By increasing stool bulk, stool softeners also stimulate gut peristalsis. Similarly, by enhancing intestinal fluid secretion, bowel stimulants also improve stool consistency. There is no single correct approach to laxative prescribing in palliative care. The small number of randomized studies conducted in this patient group have shown conflicting results and differed in their designs and endpoints, and are therefore not helpful.[47–49] Most recommendations are extrapolated from other fields of medicine. Although there are various recommendations in the literature on initiating patients on a bowel regimen, the most important point to remember is that regimens should be individualized and titrated to response. The various oral laxatives and their mechanism of action are presented in Table 2.

In the palliative care setting, initial regimens often include a stool-softening agent, such as docusate, combined with a stimulant, such as senna, given once or twice per day and titrated according to response. The combination allows for lower dosing of the stimulant, which may be associated with abdominal colicky pains.[50] For patients with no response, lactulose may be administered every 6 hours until a large bowel movement occurs. Intractable cases may require a bisacodyl suppository, a milk-and-molasses enema, or a Fleet enema. Proximal impaction may require magnesium citrate or other osmotic agents.

Opioid antagonists. Recent research on peripherally acting opioid antagonists, including methylnaltrexone,[51] suggests that these drugs might be useful in the management of opioid induced constipation. In a double-blinded randomized trial, subcutaneous methylnaltrexone produced an 80% laxation response within 4 hours of dosing. No opioid withdrawal was experienced and the commonest side effects were transient cramping and flatulence.[52] Another peripheral opioid antagonist, alvimopam, is orally administered, has a high affinity for opioid receptors, poor systemic absorption, and has been shown to be successful postoperatively in reducing ileus and shortening length of stay.[53]

Tegaserod is a promotility agent, which acts as an agonist at serotonin type 4 (5-HT_4) receptors in the gastrointestinal (GI) tract. It normalizes impaired motility in the GI tract, inhibits visceral sensitivity, and stimulates intestinal secretion. Tegaserod is approved by the Food and Drug Administration (FDA) for short-term treatment only of constipation-predominant irritable bowel syndrome in patients under 65 years of age. It may be useful in palliative care, but more research is required.

CHRONIC NAUSEA AND VOMITING

Nausea and vomiting affect between 40% and 70% of patients in the palliative care setting.[54,55] These symptoms cause great distress and significantly impact the quality of life of patients.[56–58] The reported prevalence of these symptoms varies, depending on patient characteristics and the assessment methods used for diagnosis. Nausea is more common than vomiting.

For research purposes, chronic nausea is often defined as nausea lasting more than 4 weeks, however, in the population with advanced illness, nausea is defined as chronic when it lasts more than 1 week in the absence of well-identified, self-limiting causes (such as chemotherapy or acute effects of radiation). Chronic nausea has many etiologies, is often multifactorial, and re-

TABLE 2. ORAL LAXATIVES COMMONLY USED FOR CONSTIPATION

Type of laxative	Preparation, starting doses	Mechanism of action	Comments
Lubricant	Liquid paraffin, mineral oil 5–10 mL	Lubricates stool surface, allowing easier passage	Associated with adverse effects, including malabsorption of fat soluble vitamins, lipoid pneumonia, leakage of oily fecal material Preparations of 25% paraffin and magnesium hydroxide considered safer
Bulk forming	Methycellulose, psyllium, fibercon 3–4 g	Increases colonic residue, stimulating peristalsis	Psyllium undergoes bacterial degradation: may contribute to bloating and flatus. Needs to be taken with plenty of water
Surfactant	Docusate sodium 100 mg	Ionic detergents soften stool by allowing water to interact more effectively with stool. Also increases secretion of water, sodium, chloride into jejunum and colon.	Used alone or in combination with senna or bisacodyl. Its efficacy as a laxative by itself is not well established.
Osmotic-poorly absorbed sugars	Lactulose 15 mL = 20 g	Draws water into the lumen by osmotic effects Bacterial degradation lowers intestinal ph and thereby stimulation peristalsis	Gas and bloating are common side effects secondary to bacterial degradation
	Polyethylene glycol and electrolytes (Colyte, Golytely) 2 sachets in 250 mL	Non absorbable, nondegraded polymer prepared in isoosmotic solution: exerts softening effect on stool, increases weight and accelerates transit	Can provide oral treatment for fecal impaction. Can only be used in patients who can tolerate large volumes of fluid
	Polyethylene glycol 3350 (Miralax)		Miralax does not include electrolytes; packaged for regular use as laxative
Osmotic-saline	Magnesium hydroxide 2–4 g	The high osmolarity of the compounds attracts water into the lumen of the entire gut. The fluid accumulation alters the stool consistency, distends the bowel, and induces peristaltic movement.	Use: Mostly as a bowel preparation to clear the bowels for rectal or bowel examinations. Drugs and dosages:
Anthraquinones	Senna 187 mg	Converted by colonic bacteria to active form: directly stimulate the myenteric plexus in colon to induce peristalsis.	Very popular in palliative care patients. Often combined with docusate or lactulose. Associated with colicky abdominal pains
Polyphenolic	Bisacodyl 5 mg	Hydrolysed by endogenous esterases: stimulates secretion and motility of small intestine and colon	Side effects as with senna. Requires dose titration to avoid colicky abdominal pains

quires chronic treatment.[59] Nausea and vomiting may be caused by the underlying disease, its treatment, or certain medications (for example, opioids used for chronic pain).

Mechanisms

The pathophysiology of chronic nausea and vomiting is complex, with many aspects not fully understood. Much of what we know today is based on research done on patients receiving chemotherapy or radiation, and in the postoperative setting. Two distinct sites in the brain stem (medulla) are critical for the control of emesis: the vomiting center (VC) and the chemoreceptor trigger zone (CTZ).[60] The VC, located in the lateral reticular formation of the medulla, is the physiologic control center. It is not a discrete anatomic

site, but represents interrelated neuronal networks, including the nucleus tractus solitarius (NTS) and the dorsal motor nucleus of the vagus (DMV).[61,62] The NTS is the site where numerous afferent neuronal pathways from various sources converge.[63] These sources include: (1) cortical pathways from higher cortical centers that respond to sensory stimuli (pain, sight, smell) and psychogenic stimuli (memory, conditioning, fear), (2) vestibular pathways that respond to vertigo and visuospatial disorientation, (3) peripheral pathways (via the vagus and splanchnic nerves) from the gastrointestinal tract, visceral capsules and the parietal serosal surfaces, and (4) neuronal connections from the chemoreceptor trigger zone.

The CTZ, located in the area postrema of the medulla (near the fourth ventricle), also receives afferent input from peripheral sites (GI tract) via the vagus and splanchnic nerves. Unlike the VC, the CTZ is functionally located outside the blood–brain barrier and is therefore able to sample emetogenic toxins, metabolic abnormalities, such as uremia or hypercalcemia, or drugs in the blood and spinal fluid.[64] It cannot, however, initiate emesis independently and does so only via stimulation of the NTS.

Once the vomiting center (NTS) receives signals from the various afferent sources mentioned above, the information is processed and the DMV puts out an appropriate vasomotor efferent response (respiratory, salivatory, gut, diaphragm, and abdominal muscles) inducing nausea, retching or vomiting, depending on the intensity and duration of received signals.[65] Figure 5 summarizes the interrelationship between the two centers and the various afferent inputs discussed thus far.

Much of the progress in antiemetic therapy has been attributed to the identification of neurotransmitters and their receptors along the course of the vomiting pathway.[66] The vomiting process is initiated when neurotransmitters stimulate receptors located in the vomiting pathway. The most well recognized neurotransmitters are serotonin ($5-HT_3$), substance P, dopamine, histamine, and acetylcholine. The GI tract, the CTZ, and the VC are rich in receptors for these various neurotransmitters.[67] Histamine and acetylcholine act on histamine-1 (H_1) and muscarinic (M) cholinergic receptors respectively, which have been identified in the NTS and appear to play a predominant role in motion sickness.[68]

Medications that block these receptors include antihistaminics, such as diphenhydramine and cyclizine, and anticholinergic agents, such as scopolamine. Dopamine exerts its effect on dopamine receptors (D_2), which are abundant in the CTZ.[69] D_2 receptor antagonists, such as phenothiazines (such as chlorpromazine and prochlorperazine), butyrophenones (such as haloperidol), and metoclopramide, are known to be useful in chemotherapy-related emesis. At high doses, metoclopromide has weak $5-HT_3$ antagonistic actions in addition to its antidopaminergic effects. A number of $5-HT_3$ antagonists have been developed in recent years and have proven to be highly effective in chemotherapy-induced nausea. Substance P is a regulatory neuropeptide belonging to the tachykinin family of peptides. It mediates its actions through neurokinin (NK-1) receptors, which are abundant in the CTZ, NTS, and GI tract (vagal afferents).[70,71]

The higher centers of the brain are involved in psychogenic mechanisms that exert an influence on the vomiting pathway by stimulating the CTZ and NTS. In patients with anticipatory chemotherapy-induced nausea and vomiting (CINV), the action of chemotherapy agents on higher centers of the brain leads to conditioned responses to sensory stimuli (pain, sight and smell) and emotional stimuli (memory, anticipation, and fear). Autonomic failure, leading to delayed gastric emptying, produces early satiety, and nausea. This is common in patients with advanced cancer and also found in other chronic illnesses.[72]

Assessment

Nausea is a subjective symptom, the definition and expression of which may vary from person to person. Some patients may even use the term nausea to describe early satiety, bloating, or reflux symptoms. The causes of chronic nausea can be multifactorial and the symptoms dynamic. Nausea is commonly accompanied by other symptoms, such as pain, sleep, appetite, fatigue, anxiety, and depression, and it is important to assess for these simultaneously, because these symptoms may either contribute to or worsen nausea, thereby adding to the overall distress experienced by patients.

A validated multidimensional assessment tool, such as the Edmonton Symptom Assessment system (ESAS), should be used to record the intensity of symptoms at initial assessment, and then at regular intervals afterward to gauge response to treatment.
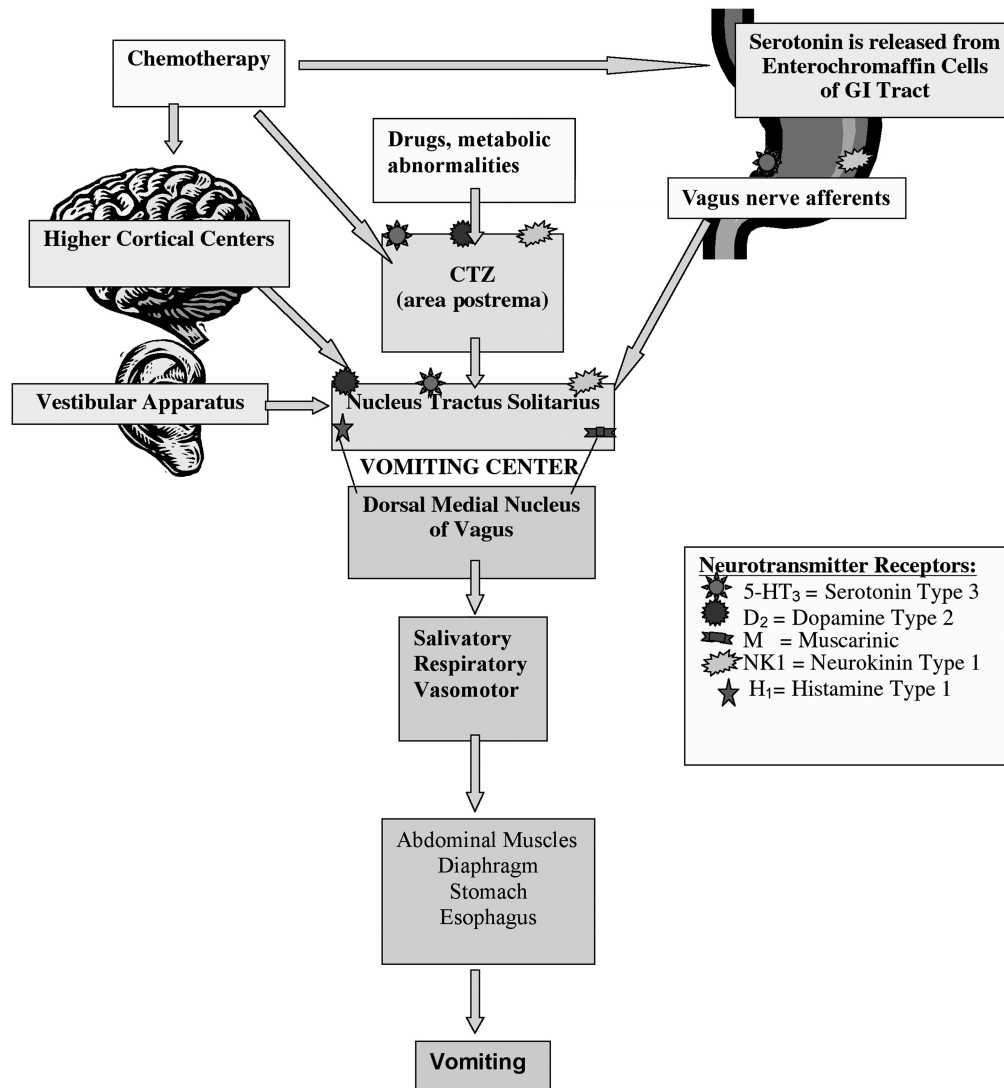
FIG. 5. Neuronal pathways in nausea and vomiting. GI, gastrointestinal; CTZ, chemoreceptor trigger zone.

History. Other aspects of nausea should be assessed, such as duration, frequency of vomiting episodes, and the ability to keep fluids down, because patients may require alternative routes for medications, hydration, and the replacement of electrolytes. Patients should routinely be questioned about the frequency of bowel movements, because in this population chronic constipation is frequently present and it contributes to nausea. Table 3 summarizes findings on history and physical examination that provide clues to the etiology of nausea and vomiting.

In patients with cancer, it is important to obtain details of the sites of tumor involvement and spread, as well as the treatment history. In patients with intra-abdominal involvement, nausea with or without vomiting is often seen as caused by liver metastasis, bowel obstruction from mechanical obstruction by tumor, or peritoneal carcinomatosis. Nausea may be present secondary to primary or metastatic brain involvement by tumor, or leptomeningeal disease. Radiation therapy to the spine or abdomen may be followed by nausea and vomiting. Delayed CINV may be present. This refers to symptoms that occur 24 hours after chemotherapy administration and that may last for as many as 6 to 7 days.[73]

A large number of medications are associated with nausea, and a detailed medication history is essential. The common offenders include opioids, nonsteroidal anti-inflammatories, anticholinergics, and antibiotics. Patients should be questioned about recent use of steroids, because abrupt inadvertent discontinuation with-

TABLE 3. CLUES TO ETIOLOGY OF NAUSEA AND VOMITING FROM HISTORY AND PHYSICAL EXAMINATION

Findings	Possible etiology
Pattern of infrequent large volume vomitus which relieves nausea	Bowel obstruction—partial or complete Gastric outlet obstruction
Symptoms of nausea or vomiting related to movements	Vestibular dysfunction Mesenteric traction
History of polyuria and polydipsia	Hyperglycemia Hypercalcemia
Associated changes in mental status	Brain metastasis Hyperglycemia Hypercalcemia Hyponatremia Uremia
Papilledema	Raised intracranial pressure as with brain metastasis
Orthostatic blood pressures, absence of heart rate variability with valsalva, syncopal episodes	Autonomic insufficiency
Decreased frequency of bowel movements	Constipation
History of a mood disorder or anxiety	Anxiety
History of Treatment Radiation	Delayed chemo-induced, nausea & vomiting
Chemotherapy	Medication, radiation
Other (e.g., antibiotics)	
Epigastric Pain, anemia; melena	Peptic ulcer disease (use of NSAIDs or corticosteroids)
Distended abdomen, shifting dullness, fluid wave	Ascites

NSAIDS, nonsteroidal anti inflammatory drugs.

out taper could lead to addisonian crisis, presenting with nausea, vomiting, abdominal pain, and hypotension. Patients with human immunodeficiency virus (HIV) may have nausea, which is a side effect of all the drugs of the highly active antiretroviral therapy (HAART) regimen.

Emotional experiences and any history of anxiety disorder should also be explored in the history.

The physical examination may provide clues to the etiology of nausea. Patients who are severely cachectic, with evidence of muscle wasting and decreased skinfold thickness, may have postural hypotension and gastroparesis as a result of autonomic failure. Papilledema indicates raised intracranial pressure. The abdominal examination may reveal masses, hepatomegaly, and ascites. Rectal examination should be done to rule out fecal impaction.

Diagnostic tests include evaluation of renal function, serum electrolytes and glucose, liver functions, and calcium levels. Imbalances may contribute to or be the result of nausea and vomiting. Uremia, liver dysfunction, hypercalcemia, hyponatremia and hypokalemia are associated with nausea and emesis. Abdominal x-rays may show bowel obstruction or fecal impaction. CT scan or magnetic resonance imaging (MRI) of the brain may be indicated when brain metastasis is suspected from history or physical examination (papilledema, mental status changes, neurologic focal signs).

Management

Appropriate management of nausea and vomiting depends on formulating pharmacologic strategies, taking into account the most likely underlying cause(s) of symptoms, and inferring the pathophysiologic mechanism responsible. Unfortunately, because of the lack of well-designed studies, there is a paucity of data on this subject and current management is based on expert opinion rather than evidence. Most palliative care specialists have favored a "mechanistic" approach to antiemesis treatment, where initial medication choice is based on the likely mechanism and neuropharmacology of the emetic pathway. Two prospective audits of current practice have showed response rates of 80%–90% when following this approach.[74,75] An alternative approach of empiric treatment has been recommended by some, and in studies was found to be highly effective.[76–79] There have been no head to head comparisons of these approaches.

Pharmacologic. Metoclopramide, dexamethasone, haloperidol, hyoscine butylbromide, and cyclizine are the most commonly used antiemetics worldwide.[80]

Phenothiazines and butyrophenones. Agents from this group are effective antiemetics, exerting their effect by acting centrally at the CTZ, predominantly as D2 antagonists. These agents do not increase GI motility and so are often used in patients presenting with bowel obstruction.[81]

Haloperidol, a narrow-spectrum agent, is predominantly a D_2 antagonist with negligible anticholinergic activity. The oral bioavailability is approximately 65%. It is highly protein bound and is not cleared by the kidney, making it safe in the presence of renal failure. Initial doses range from 0.5–2 mg orally/intravenously/subcutaneously and can be repeated at 4-hour intervals. In the elderly, doses of 1 mg every 12 hours are usually effective.[82] It is an ideal agent in patients with nausea and delirium, and has been successfully combined with 5-HT$_3$ antagonists in cases of intractable nausea.[83] When used subcutaneously, it is recommended to keep the concentration of haloperidol below 1.5 mg/mL to avoid precipitation of haloperidol crystals.[84]

The broader spectrum agents, such as chlorpromazine, prochlorperazine, and promethazine, have dopaminergic, cholinergic, and histamine receptor antagonism. Side effects include extrapyramidal reactions, hypotension, urinary retention, constipation, dry mouth, and sedation. Prochlorperazine has a low oral absorption (14%) and is usually administered via the rectal or parenteral routes. Promethazine has a slightly better oral bioavailability (25%) than prochlorperazine.

Substituted benzamides. This group includes metoclopramide and cisapride. Metoclopromide is predominantly a dopaminergic antagonist at low doses; however, at doses greater than 120 mg per 24 hours it becomes a 5-HT$_3$ receptor antagonist acting centrally in the CTZ or the gut. It has prokinetic activity via the cholinergic system in the myenteric plexus. Local acetylcholine release, mediated by the 5-HT$_4$ receptor, appears to play an important role in reversing gastroparesis and bringing about normal peristalsis in the upper GI tract. Antiemetic doses are greater than those required for prokinetic effect. Anticholinergic medications, including tricyclic antidepressants, will antagonize the prokinetic effect. Because of its

short half-life (3 hours), a continuous infusion of metoclopramide can be effective when intermittent administration fails to control nausea.[85] Side effects include akathisia and extrapyramidal reactions (more likely in younger patients), which may not be dose dependent.

Cisapride is a significantly more potent 5-HT$_4$ receptor agonist than metoclopromide, and it also acts on the lower GI tract. Unfortunately, cisapride can cause potentially fatal cardiac arrhythmias, has multiple drug interactions and is only available through the manufacturer.

Antihistaminics and anticholinergics. Antihistaminics, such as cyclizine, promethazine, and dimenhydrinate, are useful antiemetics, particularly if a vestibular component to the nausea is identified. Drowsiness is a major side effect. Antimuscarinic/anticholinergic agents include tertiary and quaternary ammonium salts. Tertiary derivatives, including atropine and scopolamine, are lipophilic, cross the blood–brain barrier and may cause sedation and confusion. Glycopyrrolate, a quartenary compound, has little central nervous system (CNS) penetration and is therefore preferred. Anticholinergics have been used to reduce symptoms of nausea and abdominal colic when associated with mechanical bowel obstruction.[86]

Cannabinoids. The proposed mechanism of action of dronabinol is through brainstem cannabinoid receptors.[87] Several studies have demonstrated its efficacy as an antiemetic agent for the treatment of chemotherapy-induced nausea and vomiting.[88–91] In a study of patients with acquired immune deficiency syndrome (AIDS)-related cachexia, dronabinol showed significant improvement in nausea, appetite, and mood, without weight gain.[92] Side effects, such as somnolence, confusion, and perceptual disturbance are common, particularly in the elderly. Euphoria is more common than dysphoria in younger patients. Larger studies are needed to assess the value of canabinoids as antiemetics in patients with advanced disease.

Serotonin antagonists. Although serotonin antagonists are widely used and effective in the management of CINV and radiotherapy-induced emesis, there are few published clinical trials on the use of these drugs in managing chronic nau-

sea in patients with advanced cancer. A recent systematic review[93] suggested that the previously limited use of 5-HT$_3$ antagonists in palliative care practice may need to be reconsidered, however, trials comparing serotonin antagonists and metoclopramide have either had methodological problems[94] or used inadequate doses of metoclopramide[95] (e.g., 10 mg three times per day). There have been some reports of its effectiveness in patients with postoperative nausea[96] and refractory nausea.[97,98]

Neurokinin-1-receptor antagonists. In clinical studies, neurokinin-1 (NK-1) receptor antagonists have shown efficacy in reducing both acute and delayed CINV when added to other antiemetics.[99–101] The potential role of NK-1-receptor antagonists in the treatment of chronic nausea and vomiting of advanced cancer is currently unknown.

Thalidomide. Initially used an antiemetic, mild anxiolytic, and hypnotic in the 1950s, thalidomide was withdrawn from the market because of severe teratogenesis when used by pregnant women. In recent years there has been renewed interest in this drug. In addition to its central antiemetic and sedative effects, thalidomide has been found to have immunomodulatory, antipyretic, possible antiangiogenic, antidiaphoretic, and analgesic actions.[102] In a study of 37 cachectic patients with advanced cancer,[103] thalidomide in low doses (100 mg) resulted in improvement in appetite, nausea, and sensation of well-being. Further research is needed to evaluate its effects on chronic nausea.

Corticosteroids. Corticosteroids have powerful nonspecific antiemetic effects that are not well understood. They may act by modulation of prostaglandin release.[104] In patients with nausea secondary to brain tumors or increased intracranial pressure, corticosteroids reduce peritumoral edema. They may also be helpful in the management of pain which often coexists with nausea. In patients with CINV, corticosteroids, such as dexamethasone and methylprednisolone, have been found to be effective antiemetic agents and offer a clear advantage over placebo for protection against emesis in both the acute and delayed phases.[105–107] Corticosteroids are often added to medications such as metoclopramide in order to improve symptom control in advanced cancer. A recent multicenter double-blinded parallel trial[108] demonstrated that after 48 hours of metoclopramide treatment, dexamethasone produced a faster onset of antiemetic effect, but was not significantly better than placebo in improving intensity of nausea over an 8-day period. Possible reasons include a significant placebo effect or a delay in response to metoclopramide (1 week of treatment may be required before full benefit is achieved).

Nonpharmacologic interventions. In patients with nausea or emesis caused by mechanical obstruction, surgical procedures, such as percutaneous gastrostomy, colostomy, intestinal bypass, or laparotomy for obstruction secondary to tumors or adhesions, may be considered for improving symptom control. Based on current evidence, there is no consensus on the indications for conservative versus surgical treatment of patients with advanced cancer.[109–112] The consideration for surgical interventions should be individualized, weighing risks and benefits of the procedure.[113] Published data show operative mortality to range from 9% to 40% and complication rates to vary from 9% to 90%.[114–122] In most published reports symptom control and patient comfort are not described, and there is lack of uniformity on the assessment of quality of life.[123] Newer endoscopically placed stents[124] for gastric outlet obstruction offer the advantage of lower cost, the possibility of an outpatient procedure, and low risk of complications. Abdominal paracentesis or a permanent intraperitoneal catheter[125] may be helpful in the patient with nausea and ascites that does not respond to conventional therapy.

Behavioral and complementary therapies. Most of the research on psychological and nonpharmacologic interventions has been conducted in chemotherapy or postoperative patients. Acupuncture and acupressure have been shown to augment the effect of antiemetics during chemotherapy and to reduce postoperative nausea and vomiting. Transcutaneous electrical nerve stimulation (TENS) has also been shown to enhance the effect of antiemetic drugs, and its effects may be mediated by endogenous opioid peptides.[126] A meta-analysis of 19 randomized trials[127] found equivalent benefit of nonpharmacologic treatment of nausea in postsurgical patients compared to traditional therapy. This benefit was not found in children. The modali-

ties studied were acupuncture, electroacupuncture, TENS, acupoint stimulation, and acupressure. Similar analysis has not been performed for patients with advanced disease. Other studies have included progressive muscle relaxation and guided mental imagery during periods of chemotherapy, and have shown beneficial effects.[128–130] Cognitive therapy has been found to be effective in providing relief of psychological morbidity associated with physical symptoms in advanced cancer.[131] Adaptation of these techniques to palliative care patients with nausea warrants research.

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