Nausea, Vomiting, and Retching: Complex Problems in Palliative Care

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ABSTRACT Patients with advanced cancer commonly experience nausea, vomiting, and/or retching (NVR) as a result of the malignant process and its treatment. Recently, increasing attention is being focused on end-of-life care, which includes relief or reduction of symptoms such as NVR.

Pre-chemotherapy preparation and patient education in the palliative care setting are essential to preventing acute and delayed distress from NVR, as well as anticipatory symptoms. Careful assessment of chemotherapy-related symptoms should distinguish between the three phenomena rather than taking a global approach. Strategies for preventing anticipatory nausea, for instance, may differ significantly from those designed to reduce frequency of vomiting.

Management of anticancer treatment-related NVR should incorporate both pharmacologic and nonpharmacologic approaches, whenever appropriate, with the overall goal of improving and/or maintaining the patient’s quality of life. (CA Cancer J Clin 2001;51:232-248.)

INTRODUCTION

Nausea, vomiting, and retching (NVR) are among the most common and distressing symptoms that patients with cancer endure, both as a result of antineoplastic treatment and from the disease itself. Nausea and vomiting are the most frequently reported adverse effects of antineoplastic chemotherapy and significantly affect patients’ daily functioning, quality of life, and compliance with therapy. Effective management of these individual symptoms during initial and continued therapy profoundly influences symptom response throughout the cancer trajectory. Even mild NVR may have later sequelae, e.g., anticipatory symptoms in patients receiving chemotherapy.

Recently, increasing attention has been given to the management of NVR during the end of life, a time when many receive palliative care. Palliate, according to Merriam Webster’s New Collegiate Dictionary (1998), means “to reduce the violence of (a disease)”; in other words, to alleviate or to lessen the severity without curing. In 1990, the World Health Organization expanded this definition: “Palliative care is the active total care of patients whose disease is not responsive to curative treatment.” Palliative care, traditionally associated with end-of-life care, is a program of active,
compassionate care primarily directed toward improving the quality of life for the dying.\textsuperscript{12} Newer aggressive therapies demand the integration of palliative services throughout the illness trajectory.\textsuperscript{13} Although technological therapeutic advances have extended life and can provide relief for symptoms of disease, numerous complications, side effects, and lifestyle changes are associated with these advances. These changes and symptoms can impair quality of life for cancer patients and families.\textsuperscript{8,9,14-16}

**SIGNS VERSUS SYMPTOMS**

Many studies have addressed quality of life in oncology patients, focusing specifically on symptom control.\textsuperscript{2,4,17-21} While chemotherapy and radiation therapy may no longer be indicated for curative effect in those with advanced disease, they may provide dramatic palliation of pain, constipation, obstruction of gastrointestinal and airway passages, and other symptoms. Nevertheless, such treatment may continue to produce the dreaded symptoms of NVR. Although the severity of NVR in patients receiving radiotherapy is lower than that associated with chemotherapy regimens, the duration may be considerably longer.\textsuperscript{22}

Inability to distinguish among distinct phenomena may lead to confusion in patient assessment and clinical or research outcomes. Accurate terminology and an understanding of the symptom experience of these three phenomena (i.e., nausea, vomiting, retching) are essential for reliable, valid assessment and measurement. Without accurate assessment instruments, terms such as “signs” and “symptoms” are often used inappropriately.

Signs, such as vomiting and retching, are objective and definitive, obvious to the observer and patient and not dependent on the patient's impressions.\textsuperscript{23} Symptoms, such as nausea, arise from subjective components and dimensions unique to the individual. Symptoms may or may not be related specifically to a medical problem, may have a strong psychosocial element, and can be continuous or intermittent. The distress produced by adverse symptoms—despite their subjective qualities—affects patients’ self-care, coping abilities, and quality of life.\textsuperscript{24}

Although people may experience seemingly identical symptoms, the cause of the symptoms and each person’s response to the symptoms may vary. Regardless of the frequency, duration, or severity of a symptom, the distress resulting from it may escalate over time. In many instances, such distress becomes greater with the continuing symptom experience.\textsuperscript{14,25} An accurate assessment of the individual’s symptoms provides the basis for custom-designed management and patient education that promotes and enhances coping and self-care behaviors.\textsuperscript{26,27}

**SYMPTOM COMPONENTS AND DIMENSIONS**

Symptom occurrence refers to the frequency, duration, and severity with which a symptom occurs.\textsuperscript{28} Symptom distress, an entity that is different from symptom occurrence, has been defined as the degree of physical or mental upset, anguish, or suffering experienced from the specific symptom.\textsuperscript{24} Symptom experience is the patient's perception of and response to the occurrence and distress of a symptom.\textsuperscript{14,25} This response may include changes in behaviors, beliefs, or feelings.\textsuperscript{29}
Nausea, Vomiting, and Retching

Nausea, vomiting, and retching are distinct concepts. However, terms to describe them often are used interchangeably, which may result in imprecise assessment, measurement, and education. To obtain an accurate assessment, the health care professional should use terms in conversation, queries, and data collection that are readily understood by patients.

Language and cultural diversity must be considered when assessing or measuring patient responses to these three distinct symptoms. These terms or symptoms may have different meanings or expressions among people of different ethnic, cultural, or geographical backgrounds. According to one Midwestern survey, for example, “nausea” was not understood by two-thirds of medical, surgical, and gynecologic patients queried. The expression “sick at stomach,” on the other hand, was the most common patient descriptor of nausea, and the expression “throw up” was consistently interpreted as vomiting. The three symptoms—nausea, vomiting, and retching—are independently defined below:

Nausea

Nausea is a nonobservable phenomenon of an unpleasant sensation experienced in the back of the throat and the epigastrium that may or may not culminate in vomiting; it is synonymously described as feeling “sick at stomach.” It is usually determined through self-report but also may have some objective elements, depending on intensity.

All patients, and particularly those with uncontrolled concomitant symptoms, have difficulty describing the nature of the extremely unpleasant sensations they experience as nausea. Patients commonly describe nausea as a vague unpleasantness located in the region of the throat, upper gastric region, or abdomen. Some degree of anorexia or loss of appetite usually accompanies nausea. Although anorexia may be the result of the nausea, careful assessment of these subjective symptoms is essential to differentiate the two terms. Expressions often used by patients to characterize nausea are “distressing,” “overwhelming,” “may cause a desire to vomit,” “all-consuming,” and “fish at sea.”

Vomiting

Vomiting is the forceful expulsion of the contents of the stomach through the oral or nasal cavity. Both the occurrence and the frequency of vomiting may be objectively measured. The amount of distress (physical or mental anguish, suffering, or discomfort) from vomiting, however, is subjective.

Although frequently confused with nausea, vomiting or emesis is an observable phenomenon best described as “throwing up.” Other terms for this phenomenon are “puking,” “hurling,” “upchucking,” “pitching,” and “barfing.” “Driving the white porcelain bus” is a descriptor recently coined by younger individuals. Vomiting is objective, but the degree of associated distress can only be reported by the individual.

Retching

Retching is the attempt to vomit without bringing anything up. Both subjective and objective measurements of this phenomena are possible and useful. Patients readily differentiate the frequency of occurrence and the actual distress experienced from the sensation of retching. Retching may be described by such terms as “gagging,” “dry heaves,” and “attempting to vomit without results.”

NVR: CONTRIBUTING FACTORS

In addition to known neuropathophysiological pathways, other contributing factors contributing to NVR include the emetogenic
qualities of the chemotherapy drug/combin-
tation, its dosage, route, time of day, and length
of administration. Additional factors include
other therapies (e.g., radiation, surgery), anx-
ity, previous episodes of these symptoms (e.g.,
motion sickness, pregnancy), gender, and age.
Younger patients, particularly under age 30,
are reported to have a more intense symptom
experience with NVR and concomitant
symptoms than older patients on similar
chemotherapeutic regimens.31 Among other
potential causes of emesis are metabolic
abnormalities, electrolyte imbalance, brain
metastasis leading to increased intracranial
pressure, opioids and other emetogenic drugs,
and infections. Patients with advanced cancer
may experience NVR from a combination of
several of these factors.

Neuropathophysiology of Chemotherapy-
Related NVR

Vomiting results from an intricate succes-
sion of physiological events mediated by affer-
ent enervation, humoral factors, and somatic
visceral musculature that are ultimately coor-
dinated by the emetic or vomiting center
located in the medulla. Afferent input to the
emetic center originates primarily from four
sources: The cerebrocortical pathway, which
is stimulated by learned associations; the
chemoreceptor trigger zone (CTZ) that is
located in the area postrema in the cortex and
is sensitive to chemical stimuli from the cere-
brospinal fluid and blood; the vestibular path-
way, which activates the emetic center via
body positional changes (as in motion sick-
ness); and the peripheral pathway, which is
activated by neurotransmitter receptors found
in the gastrointestinal tract where the vagus
nerve communicates with the emetic center.

The CTZ, the gastrointestinal tract, and the
cerebral cortex have been identified as sources
of afferent input to the emetic center.32,33
When efferent impulses are sent from the
vomiting center to the salivation center,
abdominal muscles, respiratory center, and
cranial nerves, vomiting occurs. The
mechanoreceptors in the bowel wall may be
stimulated by the stretch, distortion, or direct
invasion of the gastrointestinal tract by tumor.
Similar receptors are located in visceral caps-
ules and in parietal serosal surfaces and pro-
vide afferent input to the emetic center via
the vagus and splanchnic nerves.

Neurotransmitters, e.g., dopamine, acetyl-
choline, histamine, and serotonin (5-HT), are
involved in the emetogenic pathways stimu-
lated by chemotherapy and radiation. The
gastrointestinal tract, the CTZ, and the emetic
center are rich in receptors for these neuro-
transmitters. The serotonin or 5-hydroxy-
tryptamine type-three (5-HT₃) receptors are
found in peripheral tissues, the nucleus of the
solitary tract, and the CTZ where the major-
ity of vagal afferents enter the brain. Both
chemotherapy and radiation can cause release
of serotonin from enterochromaffin cells in
the gut. Since the largest concentration of 5-
HT₃ receptors in the central nervous system
(CNS) is in the nucleus of the solitary tract
and the area postrema where the CTZ is
located and where vagal afferents enter the
brain, it is postulated that 5-HT₃ antagonists
may ameliorate nausea and vomiting by inter-
action with these central receptors.34

Recently, another ligand-receptor pair has
been found to play an important role in
NVR. The neurokinin receptors, are current-
ly classified as neurokinin1 (NK-1), neu-
rokinin2, and neurokinin3 receptors. Their
preferred ligands, known as neurokinins or
tachykinins are 11-amino acid peptides that
include Substance P, Neurokinin A, and
Neurokinin B.36 Of these, only the NK-1
receptor, stimulated by substance P, is involved
with emesis.37

While all of these receptors and transmit-
ters are involved in the neuropathophysiology
of nausea and vomiting, as may be adrenergic
and opioid receptors, further research is needed to determine possible interactions and/or the specific role of additional receptors and mechanisms.36

Psychological Factors

The NVR symptom experience associated with the first antineoplastic treatment can have a profound impact on patients who will require long-term palliative care. Unless the symptoms of NVR have been prophylactically managed during the initial therapy (i.e., first cycle of the first course), the actual or perceived threat of the disease, its treatment (chemotherapy or radiation), and discomforts relating to treatment, can arouse a variety of emotional and physiological responses.14,36,39

Patient Expectations

Patients are active agents whose goals and behaviors are largely determined by their perceptions and expectations of the illness. In a study designed to investigate chemotherapy-related NVR in treatment-naive patients, a statistically significant relationship (P = 0.015) was found between the patients’ expectations of NVR symptom occurrence and their expectations of symptom distress. No significant relationship was reported between the expectation of the symptom and the actual symptom experience.27 The discrepancies found between the expectation of nausea and vomiting and the actual occurrence of these symptoms suggest that patients did not have accurate pretreatment expectations. Numerous studies have demonstrated that an accurate preparatory schema and realistic expectations can reduce negative mood states and improve coping behaviors.27,38,40,41,42 These findings suggest that appropriate patient pretreatment preparation and effective early symptom management can help avoid fear, uncertainty, and distress; develop improved coping methods; and improve patients’ quality of life.

Anticipatory symptoms of NVR are conditioned responses that commence prior to the administration of chemotherapeutic regimen. For approximately 30% of chemotherapy-naive patients who experience treatment-induced NVR, anticipatory symptoms occur by the fourth treatment.44–48 Anticipatory symptoms exacerbate post-treatment NVR. Despite recent pharmacological advances in the management of chemotherapy-related NVR, further research is critical to prevent the adverse impact of these anticipatory symptoms on the patient’s quality of life throughout the illness trajectory.

Age and Gender

Women are more likely to experience chemotherapy-induced NVR than are men. Moreover, evidence that older aged patients tend to tolerate chemotherapy better than younger patients was first attributed to the less aggressive treatment regimens administered to the elderly. Today, however, older patients frequently receive aggressive therapy.48,49 A comparison of two groups of patients (younger than 65 and older than 65 years of age) with breast cancer who were receiving similar chemotherapy protocols found that with only one exception, younger patients consistently reported greater problems with NVR.31 Since women 50 years of age or younger are more likely to experience NVR, they are also more prone to anticipatory NVR.50 A recent review found that up to 90% of pregnant women experience NVR.51 Women who were queried prior to their initial chemotherapy treatment about their past experiences of NVR (e.g., with stomach flu, motion sickness, surgical procedures, pregnancies) and reported high levels subsequently described more episodes of NVR than did those with less remarkable NVR histories.27
Postoperative NVR continues to be difficult to manage despite the introduction of new antiemetic drugs. Experiences with NVR during pregnancy and/or postoperatively are examples of the influence of pre-treatment schema on post-chemotherapy NVR and have specific implications for pre-treatment preparation and early symptom management in these women.

Alcohol Effect

Although NVR are common side effects of cisplatin-containing chemotherapy regimens, patients with a history of chronic, heavy alcohol intake experience fewer symptoms with cisplatin than do those who have not been heavy drinkers. Although emesis is more easily controlled in patients with chronic heavy alcohol use, these patients still require effective antiemetic regimens.

Concomitant Symptoms

The symptom experience (symptom occurrence and symptom distress) of patients with cancer varies throughout the disease trajectory. The malignancy itself, its treatment, concurrent disorders, or nonspecific factors may contribute to additional and/or more severe NVR. Seriously ill patients with cancer have a high symptom burden. A recent study (N = 1,556) concluded that patients who have nausea and dyspnea experience more pain than patients without these symptoms. The causal associations among these symptoms are unknown. Although relief of pain may ameliorate dyspnea and nausea, consideration must be given to the possibility that improved management of dyspnea and nausea may relieve pain.

Other prevalent symptoms that affect quality of life among patients receiving end-stage palliative care are asthenia, anorexia, constipation, confusion, and mood changes (e.g., anxiety, depression). Constipation (with resultant colonic stretch) or increased intra-abdominal pressure may stimulate the mechanoreceptor pathways to the emetic center thus triggering vomiting.

Tumor Burden

Tumor enlargement that impinges on adjacent anatomical structures in the gut may cause severe NVR by activating mechanoreceptors in the bowel wall. Some common conditions caused by tumor enlargement that contribute to NVR include delayed gastric emptying, gastric outlet or bowel obstruction, gastritis, hepatic or renal failure, hypercalcemia, hyponatremia, and increased intracranial pressure. Delayed gastric emptying may be due to physiological problems, e.g., anticholinergic effects of drugs including opioids, or to mechanical resistance (partial or complete) to emptying. Ascites, hepatomegaly, and duodenal or pancreatic tumors are some of the causes of such mechanical resistance. Usually such conditions require pain control, hence careful assessment is critical to determine whether the NVR is associated with analgesic agents.

Limited data are available concerning the impact of tumor burden on chemotherapy-related NVR, yet such data could have important clinical implications. In one study of the impact of tumor burden on NVR in ovarian cancer patients (N = 101) who were receiving their initial chemotherapy treatment, individuals with large (greater than 2 cm) tumors had more delayed emesis (days two to seven).
and more acute nausea than those with minimal tumor burden (smaller than 2 cm). Persistent, delayed nausea and vomiting are more evident in patients 55 years or older with large residual tumors.60

The predictors for no delayed emesis were an antiemetic drug combination that included dexamethasone, minimal tumor burden, low neuroticism, and no history of motion sickness. Although these findings were from chemotherapy-naïve subjects with known tumor burden, the data raise questions about the role of tumor burden on the NVR symptom experience of subjects in the palliative care phase.

Other Drugs that Cause NVR

In addition to antineoplastic chemotherapy, opioids, non-steroidal anti-inflammatory drugs, digoxin, anticoagulants, and anticholinergics are some of the drugs that may induce NVR. These symptoms are caused by chemical action at the CTZ, by serotonin release in the gastrointestinal tract, through gastrointestinal irritation or stasis, or by a combination of these mechanisms.59 Opioids activate the CTZ and may cause gastric stasis that leads to NVR. The area postrema has one of the highest densities of opioid receptors.61 NVR may be caused by gastrointestinal irritation from non-steroidal anti-inflammatory drugs. Some evidence indicates that reduced clearance of plasma morphine, morphine-3-glucuronide, and morphine-6-glucuronide concentrations may be a causal or aggravating factor in the nausea and vomiting and cognitive function profile of palliative care patients with significant renal function impairment.68

ASSESSMENT OF NVR

Assessment is an ongoing process that begins with the initial patient contact and continues through the illness trajectory. It is crucial that researchers and clinicians distinguish nausea from vomiting and both of those from retching, rather than taking a global approach to all symptoms. Interviews, questionnaires, or self-report instruments must use words that have the same meaning to all participants. A balance must be maintained between the need to obtain accurate data about specific symptoms and burdening the patient or family with numerous, intrusive questions. Assessment tools that can be completed and reviewed quickly utilize less patient energy and nursing time. Although most palliative care patients may have experienced NVR during earlier antineoplastic therapies, the clinician or researcher must avoid words or suggestions that may influence the patient to focus on the symptoms. During the initial contact, the patient’s prior symptomatology, methods of management, and expectations need to be assessed. Input from family members and significant others may be helpful.

Patient journals, logs, or daily diaries (Fig. 1), completed by the patient or caregiver, provide useful assessment information. These introspective self-report tools also help family caregivers and patients develop experience in problem-solving, a greater sense of control, and improved self-care. Review of such logs can offer health care providers insight into patterns of symptom occurrence, self-care strategies used by the patient (including individualized pharmacologic and nonpharmacologic interventions), and situational or concomitant events.

Several comprehensive instruments that include assessment of one or more of the components of NVR are available to help evaluate concomitant symptomatology.14,25,62-67 Some such as the Adapted Symptom Distress Scale (ASDS) measure several concepts in addition to NVR.54-67 Others, such as the Symptom Distress Scale68 and The Memorial Symptom Assessment Scale67 measure either a
**Self-Care Journal Sample**

Sample journal entries are shown below. Remember that details are important; if in doubt, include it.

| Date   | Time     | How I Felt Before Self-Care Activity | Self-Care Activity | Result |
|--------|----------|---------------------------------------|---------------------|--------|
| 1/15   | 4:30 pm  | Restless; feel sick at stomach         | Had backrub listening to relaxing music | 1      |
| 1/15   | 8:00 pm  | Feeling better; had a stool            | Drank 1 c. of Ensure, Prepared for sleep, Took Benadryl *PO* | 2      |
| 1/16   | 8:00 am  | Hungry                                | Took stool softener; Ate cream of wheat and toast | 1      |
| 1/16   | 10:30 am | Tired; Jabbing abdominal pain          | Analgesic patch changed; Napped in recliner | 1      |
| 1/16   | 12:30 pm | Stomach feels empty                    | Sipped hot tea; Ate chicken soup          | 1      |
| 1/16   | 4:00 pm  | Bitter taste in mouth                  | Oral care: Sucked on lemon drop           | 1      |
| 1/16   | 6:30 pm  | Hungry but don’t wish to smell hot foods | Enjoyed cottage cheese, fruit salad, and applesauce; Drank 1/2 c. Carnation bkft | 1      |
| 1/16   | 8:30 pm  | Sleepy/tired                           | Warm bath and went to bed, Took Benadryl *PO* | 2      |
| 1/17   | 8:00 am  | Stomach feels good                     | Ate toast, fruit, and yogurt              | 2      |
| 1/17   | 10:30 am | Feel bloated, constipated              | Took stool softener                       | 2      |
| 1/17   | Noon     | Thirsty                                | Drinking tea                             | 1      |
single component or are global measures of the concepts. Only instruments specifically assessing NVR are included in Table 1.

To ensure accurate and comprehensive assessment, the instrument to measure NVR must be chosen carefully. The following criteria are important:

- Use self-report tools rather than observational assessment whenever feasible.
- Use instruments with known psychometric properties (i.e., reliability and validity).
- Look for clarity, precision, cultural sensitivity, and understandable wording in the self-report instrument.
- Choose an instrument with an easy-to-read format.
- Ascertain and describe the specific symptoms and the components to be measured.
- Determine a time frame for recall of the symptom experienced.
- Consider the purpose for which the instrument is intended, e.g., characterizing a patient population (demographics, type of cancer, type of treatment) or type of symptom (e.g., chemotherapy-related [acute or delayed], anticipatory, chronic).
- Consider the ease of scoring and type of score (e.g., total instrument, subscale scores for each individual symptom or component).

We believe that global assessments without information about the individual symptoms have hindered progress in understanding NVR and development of effective interventions. Pharmacologic and nonpharmacologic interventions do not exert equivalent effects on these unique symptoms. Accurate measurement of these individual symptoms is crucial to determine symptom patterns and make comparisons.

**PHARMACOLOGIC MANAGEMENT OF NVR**

The symptoms of nausea and vomiting are most frequently managed with antiemetic drug therapy. Antiemetics need to be chosen based on the causes and types of the nausea. Several classes of antiemetics are currently used in the management of NVR (Table 2). Adequate symptom management may require combination drug therapy.

### 5-HT<sub>3</sub> Receptor Antagonists

The development and successful use of 5-HT<sub>3</sub> receptor antagonists have significantly changed the management of NVR. These drugs are very effective in both elderly and young patients, can be administered every 24 hours, and their effectiveness is increased when given in combination with dexamethasone. Granisetron, ondansetron, and dolasetron are well-tolerated agents that are widely used in the US for preventing acute NVR associated with chemotherapy or radiation therapy, but studies have failed to support their benefit in the management of delayed NVR. Nevertheless, the value of 5-HT<sub>3</sub> receptor antagonists to relieve the NVR associated with radiation therapy and acute emetogenic chemotherapy is well documented. Their role in the management of chronic nausea is less well documented.

The effectiveness of ondansetron in a palliative care setting was also demonstrated in a 1998 study by Currow et al. Eighty percent of patients with nausea and 71% of patients with vomiting were improved. Symptom control was achieved in eight of 10 palliative care patients admitted with either nausea and/or vomiting.

Although the 5-HT<sub>3</sub> receptor antagonists (e.g., granisetron, dolasetron, ondansetron) represent a major improvement in the management of chemotherapy-induced NVR, clinical experience indicates that the antiemetic efficacy of 5-HT<sub>3</sub> antagonists (given as single agents or in combination with dexamethasone) is not always maintained over multiple chemotherapy cycles. Moreover, emesis protection in the acute phase is adversely influenced by failure in the delayed...
| Instruments to Measure Nausea, Vomiting, and Retching | Dimensions | Type | How Administered | Reliability/Validity | Strengths/Weaknesses |
|-----------------------------------------------------|------------|------|------------------|----------------------|---------------------|
| Duke Descriptive Scale (DDS)                         | Nausea and vomiting, with frequency, severity, and activity combined | Check scale | Patient Interview Nurse Observation Other health care worker | Unreported | Low ceiling may limit information |
| Visual Analog Scales (VAS)                           | May be devised for individual symptoms and their components: frequency; duration; severity; distress | A line, usually 100 mm long, with reliable anchor descriptors at extremes | Self-report | Unreported; Reliability is strength with stable phenomena | Subjects’ inability to discriminate between grades of sensation; requires more administrator time; inaccurate when marked by another or subject in supine position; unstated time frame |
| Morrow Assessment of Nausea and Emesis (MANE)        | Post-treatment nausea and vomiting: onset; severity; intensity; duration | 16-item, 5-point Likert scale (onset); 6-point Likert scale (severity-intensity) | Self-report | Test/Retest Reliability: 0.61-0.78 Construct Validity: 0.72-0.96 | Primarily used with antiemetic studies; long (> 24 hour) time frame |
| Morrow Assessment of Nausea and Emesis Follow-up (MANE-FU) | Anticipatory nausea and vomiting (frequency) | 17-item, 5-point Likert scale (severity-intensity) | Self-report | Content and convergent validity supported | Assess anticipatory nausea |
| Rhodes Index of Nausea and Vomiting Form-2 (INV-2)   | Nausea, vomiting, retching, and the components of each symptom: frequency; amount; duration; severity; distress | 8-item, 5-point Likert scale | Self-report | Split half Reliability: 0.83-0.99 Cronbach’s Alpha: 0.98 Construct Validity: 0.87 | 12-hour time frame; Measure distress of symptom; totals symptom experience scale; subscales for triad and occurrence and distress; used with varied groups |
| Rhodes Index of Nausea, Vomiting, & Retching (INVR)  | Nausea, vomiting, retching, and the components of each symptom: frequency; amount; duration; severity; distress | 8-item, 5-point Likert scale | Self-report | Split half reliability: 0.83-0.99 Cronbach’s alpha: 0.98 Construct Validity: 0.87 | More user-friendly; more easily read; larger print; 12-hour time frame; measure distress of symptom; totals symptom experience scale; subscales for triad and occurrence and distress |
| Functional Living Index Emesis (FLIE)                | Effects of nausea and vomiting on: physical activity; social and emotional functions; eating | 18-item, 7-point Likert scale | Self-report | Content and criterion validity; internal consistency supported | Ease of use; provides information about the effect of nausea and vomiting on functional status |
Morrow et al. compared two groups of patients, one (N = 300) treated before 5-HT\textsubscript{3} receptor antagonists became available and one (N = 300) treated with 5-HT\textsubscript{3} receptor antagonists. Although patients in the 5-HT\textsubscript{3} receptor antagonists group did have a significant reduction in the frequency of post-treatment vomiting.\textsuperscript{6} In fact, patients who received the 5-HT\textsubscript{3} receptor antagonist reported an increase in duration of post-treatment nausea and vomiting compared with the non 5-HT\textsubscript{3} group.

**NK-1 Receptor Antagonists**

NK1 receptor antagonists have proven particularly effective in phase III trials in preventing delayed NVR associated with chemotherapy. None are yet FDA approved. Interestingly, these antagonists are active against emetogenic stimuli, e.g., apomorphine.

| TABLE 2 |
|---|
| **Antiemetic Drugs**\textsuperscript{42,74,75} |
| **Drug** | **Route/Dosage/Schedule** |
| **Serotonin Receptor Antagonists** |  |
| Dolasetron | Oral (PO): 100 mg/once; Intravenous (IV): 100 mg (1.8 mg/kg)/once |
| Granisetron | PO: 1-2 mg/once; IV: 8 mg/once |
| Ondansetron | PO: 16-24 mg/once or 8 mg every 12 hours X 2 doses; IV: 8 mg (0.15 mg/kg)/once |
| **5-HT\textsubscript{3} Receptor Antagonists** |  |
| PO: 10-25 mg/4-6 hours; sustained release 10 or 15 mg/q 10-12 hours; RECTAL (R): 25 mg/4-6 hours; IV: 20-40 mg/infuse over 30 minutes q 3-4 hours; INTRAMUSCULARLY (IM): 5 mg/ml |
| PO: 10 mg/q 4-6 hours; R: 10 mg/q 6-8 hours; IM: 10 mg/2ml |
| PO: 250 or 100 mg/q 6-8 hours; R: 200 mg/q 6-8 hours; IM: 200 mg/2ml |
| **Enthiazines** |  |
| PO: 5, 10, or 25 mg/q 4-6 hours; sustained release 10 or 15 mg/q 10-12 hours; RECTAL (R): 25 mg/4-6 hours; IV: 20-40 mg/infuse over 30 minutes q 3-4 hours; INTRAMUSCULARLY (IM): 5 mg/ml |
| PO: 10 mg/q 4-6 hours; R: 10 mg/q 6-8 hours; IM: 10 mg/2ml |
| PO: 250 or 100 mg/q 6-8 hours; R: 200 mg/q 6-8 hours; IM: 200 mg/2ml |
| **Butyrophenones** |  |
| PO: 0.5, 1, 2, or 5 mg/q 4-6 hours; IV: 0.5-2 mg/titrate as needed |
| PO: 1.25-2.5 mg/titrate as needed |
| **Substitute Benzamides** |  |
| PO: 5 or 10 mg/q 6 hours; IV: 1-3 mg/kg/piggy back pre-chemotherapy and q 2-3 hours for 3 more doses |
| PO: 10 mg/before meals and at bedtime |
| **Cannabinoids** |  |
| PO: 2.5, 5, or 10 mg/q 4-6 hours |
| **Cortico Steroids** |  |
| To prevent delayed symptoms-PO: 2-4 mg/4x/day x 2 days, 3x/day x 2 days, 2x/day x 2 days, once/day x 2 days, then stop; for acute emesis prior to chemotherapy-PO: 20 mg/once; IV: 20 mg/once over 5 minutes |
| **Benzodiazepines** |  |
| PO: 1 or 2 mg (maximum 3 mg) every 2-3 hours as needed; IV: 0.5-3 mg/ml (0.025-.04 mg/kg)/to mild-moderate sedation |
Phenothiazines

The phenothiazine class includes several different drugs that may be administered orally, rectally, intramuscularly, or intravenously. The dosing schedule, which can vary from every four to six hours to every 10 to 12 hours, depends on the route of administration and preparation. These agents are particularly effective for delayed nausea when used together with corticosteroids in combination antiemetic regimens. Although the phenothiazines are effective in the management of delayed symptoms, they may cause several side effects, including drowsiness, hypotension, and extrapyramidal symptoms, especially in older patients.

Metoclopramide and Other Drugs

Substituted benzamides, such as metoclopramide, are effective for mild-to-moderate nausea and vomiting. A recent retrospective assessment of a metoclopramide-based antiemetic regimen for chronic nausea in advanced cancer patients who were admitted to a Palliative Care Unit (N = 100) revealed that 32% presented with “nausea” upon admission; during the average admission, 98% developed “nausea.” Utilizing a standardized procedure for the antiemetic treatment of existing nausea, the report suggests that although nausea is very frequent, it can be controlled in the majority of such patients using safe and simple antiemetic regimens. The study found metoclopramide effective in controlling the nausea in most of the patients.

Other drugs with antiemetic effects include butyrophenones, antihistamines (histamine H1 receptor antagonists, e.g., diphenhydramine), corticosteroids, and cannabinoids. Medications that block dopamine receptors (phenothiazines, metoclopramide, butyrophenones) prevent or reduce the emetic response associated with mild to moderately emetogenic chemotherapeutic regimens. Thus, butyrophenones, e.g., haloperidol and droperidol, are used effectively in some antiemetic drug combinations.

Although the benzodiazepines are only as minimally effective as antiemetics, they can be particularly useful when anxiety is associated with nausea and vomiting. The efficacy of benzodiazepines, e.g., lorazepam and alprazolam, may be derived from their sedative, anxiolytic, and amnesic properties, which enhance the effectiveness of antiemetic regimens.

Antihistamines, such as cyclizine and promethazine, and anticholinergics, particularly hyoscine, also exhibit antiemetic effects. An advantage of these drugs is that some can be administered with a transdermal patch as well as orally or parenterally.

Corticosteroids are useful in heightening the effects of antiemetic agents. Mystakidou et al. found that adding dexamethasone to tropisetron-containing combinations, or tropisetron alone, increased their anti-emetic effectiveness and that these combinations were more effective than chlorpromazine and dexamethasone.

The use of cannabinoids for the management of NVR has been limited, although some studies have shown reduction of nausea and vomiting. A study of the antiemetic drug prescribing preferences of practicing adult oncologists revealed that cannabinoids (either as marijuana smoke or as oral tetrahydrocannabinol) were ranked ninth in order of

Antiemetics need to be chosen based on the causes and types of the nausea. Adequate symptom management may require combination drug therapy.
preference for the treatment of mild to moderate nausea and vomiting, and sixth for more severe symptoms associated with chemotherapy.76 Gonzalez-Rosales and Walsh79 found dronabinol in combination with prochlorperazine, for example, was effective in treating unresponsive nausea and vomiting in a patient with widespread metastatic disease.

Guidelines for the management of chemotherapy-induced NVR have been published by several organizations, such as the American Society of Clinical Oncology80 and the American Society of Health System Pharmacists.81 The most current practice guidelines, released in March 2001, were developed by the National Comprehensive Cancer Network (NCCN), and a “lay-language” version for patients has been jointly developed by NCCN and the American Cancer Society (available online at www.nccn.org and www.cancer.org).

These treatment guidelines designed by multidisciplinary teams as consensus documents, when used with accurate self-report assessments, can be helpful for health professionals involved in the management of patients receiving palliative care.

NONPHARMACOLOGIC MANAGEMENT OF NVR

Nonpharmacological interventions can be used alone, in combination, or as adjuvant therapy with pharmaceutical agents to manage NVR. Although research on the nonpharmacological management of NVR is limited, these interventions can be effective in controlling nausea and vomiting by relaxing the patient and, when used in conjunction with antiemetics, can reduce the dose and frequency drug requirements.

Diet and Environment

Before antiemetics are prescribed, potentially nauseating stimuli in the patient's environment should be reduced or eliminated. This may include minimizing sights, sounds, or smells that can initiate nausea.38,39 Unpleasant odors should be eliminated along with smells from cooking. Attractively prepared food should be presented as small meals rather than large ones. Cool, carbonated beverages and bland foods served at room temperature seem to be best tolerated. Foods may taste differently during chemotherapy and need to be selected or changed accordingly.70,82,83 Sweet, fatty, highly salted, and spicy foods should be avoided. Experimenting with sour foods such as lemons, sour pickles, or sour hard candy is also helpful.

Since patients with advanced cancer may not feel hungry or thirsty, their preference or desire not to eat must be recognized and respected. Ingestion of food may cause NVR and concomitant abdominal symptoms such as pain, abdominal distention, constipation, or diarrhea. Excessive intake of proteins and lipids may induce NVR, because of cachexia-associated changes in the metabolism. Caregivers for these patients should focus on avoiding hunger, thirst, NVR, edema, and dyspnea. Small amounts of carbohydrates and water often constitute the optimal diet for these patients.82,83

Acupuncture/Acupressure

The use of acupuncture and acupressure to relieve NVR has been effective in several series. An NIH Consensus Conference reported the efficacy of acupuncture for adult postoperative and chemotherapy-related nausea and vomiting.84 Fan et al.,85 in a study of 200 patients, found acupressure at the P6 (Nei-Guan) point was an effective prophylaxis for postsurgical nausea and vom-
iting, and concluded that it was a good alternative to conventional antiemetic treatment. Stein et al.86 found that acupressure was an effective nonpharmacologic method to reduce intraoperative nausea during elective cesarean section in the awake patient. Aikins87 reviewed 10 randomized trials that looked at the effects of acupressure, ginger, and pyridoxine on nausea and vomiting with pregnancy and found evidence of benefit, although the data on acupressure alone are equivocal.

Dundee and colleagues found that P6 acupuncture is an effective adjuvant to conventional antiemetic therapy for patients receiving cytotoxic drugs.88,89 Dibble and colleagues90 conducted a randomized clinical trial in women undergoing chemotherapy for breast cancer and found that finger acupressure decreased nausea.

There has been very limited research using acupressure with terminally ill patients. Brown et al.91 found that acupressure wrist bands were not effective in reducing nausea and vomiting in a small sample of hospice patients. Difficulty obtaining complete data, however, was a major limitation of this study.

Music Therapy

Relaxation and hypnosis do not work magic, but serve as adjuncts to medication and other comfort measures. Frank92 investigated the effects of music therapy and guided visual imagery on anxiety and the degree and duration of nausea and vomiting. Results showed that the patients’ perceived degree of vomiting was significantly reduced, and suggested that the duration of vomiting was also decreased. Another study of 33 patients found that music was helpful as an adjunctive therapy in decreasing nausea and vomiting associated with high-dose chemotherapy.93

Progressive Muscle Relaxation

According to Bayuk,94 relaxation techniques, including progressive muscle relaxation training, guided imagery, and hypnosis have been shown in several research studies to be helpful in alleviating the nausea and vomiting, as well as the anxiety, experienced by cancer patients receiving chemotherapy. Cotanch and Strom,95 for example, found that progressive muscle relaxation may be effective in reducing nausea, vomiting, anorexia, and emotional distress that frequently accompany chemotherapy.

Morrow96 reported that progressive muscle relaxation training was effective in decreasing the frequency of chemotherapy-related nausea and vomiting. In a study of women with breast cancer, relaxation techniques significantly reduced nausea and vomiting before and after chemotherapy.97 Results from a study by Arakawa98 in 60 Japanese patients receiving chemotherapy verified the effectiveness of progressive muscle relaxation in reducing NVR. There has been no published research using progressive muscle relaxation in palliative care. However, the positive results noted with chemotherapy patients indicate that it may be a useful strategy for the palliative care setting, as well.

Guided Imagery

Frank99 reported that patients who underwent guided imagery had a significantly lower perceived degree of vomiting and a decrease in the duration of vomiting. Scott et al. compared a clinical relaxation program that included guided imagery with a standard antiemetic drug protocol for chemotherapy.100 The drug protocol was more effective in reducing the number of episodes of nausea and vomiting; however, the total duration of nausea and vomiting was four hours shorter with the relaxation program. Troesch et al.100 examined the effec-
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The effectiveness of adding guided imagery to a standard antiemetic drug regimen in patients receiving chemotherapy. The guided imagery group experienced symptoms later than did those in the control group, although the differences were not significant. Those in the guided imagery group reported feeling significantly more prepared, relaxed, and in control than subjects in the control group.

Although data regarding nonpharmacological measures for managing NVR are limited, there is support for their use either alone or as a supplement to pharmacological agents. They are noninvasive, can frequently be practiced by the patient alone, and enhance feelings of control.

CONCLUSIONS

The goal of palliative care is to achieve the highest quality of life for patients with progressive disease. Part of achieving that goal involves the complex management of the separate symptoms of NVR. Understanding of NVR has been hindered by the use of global assessments, insufficient use of reliable and valid instruments, and inadequate recognition of the components of the symptom experience. Expert ongoing assessment of the patient’s symptom experience prior to beginning therapy and throughout the illness trajectory is crucial. Despite pharmacological advances, such as development of the 5-HT3 receptor antagonists and combinations with corticosteroids, delayed NVR, refractory emesis (following first-line antiemetic therapy), anticipatory NVR, and chronic NVR continue to adversely affect patients’ quality of life. Without adequate assessment of the symptom experience and appropriate intervention, symptom occurrence and symptom distress may increase, causing additional problems and affecting patients’ quality of life.

The potential causes of NVR in cancer patients are numerous, especially in those with advanced or metastatic disease. Although studies in this population have been limited, patients with advanced disease report NVR prevalence rates ranging from 10% to 70%. Randomized studies that look at the cancer experience among different ethnic groups are needed. Reliable and valid self-reporting is essential as a scientific basis for the study of effective interventions for NVR, with the overall goal of improving patients’ quality of life.

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