Patients with cancer often experience substantial symptom burden, which can begin at or before diagnosis, and typically increases as the end of life approaches. This may include psychological distress as well as physical symptoms from the underlying cancer, ongoing treatment, or both. Comprehensive cancer care not only encompasses interventions that prolong survival but also measures that optimize symptom control and improve quality of life. However, effective symptom palliation can be challenging because symptoms frequently occur in clusters, the treatment of one symptom can result in another as a side effect, and appropriate management often requires input and collaboration from a variety of health disciplines. Although evidence for many currently used symptom treatments is lacking, this is an area of rapid development, with new studies allowing for treatment that is increasingly evidence-based. In this review, we provide a general overview of current approaches and a brief update on new developments for the pharmacologic management of pain, dyspnea, and nausea, which are three of the most common treatable cancer-related symptoms.

PAIN

Background

Pain is one of the most prevalent symptoms experienced by patients with cancer. It is estimated that 30% to 50% of patients undergoing active anticancer therapies and 75% to 90% of those with advanced cancers will experience severe pain necessitating medical intervention at some point during their disease trajectory. However, management of pain is complex because its causes are diverse and it can adversely affect numerous domains of quality of life, including physical functioning, activities of daily living, psychological and emotional well-being, and social interactions. Furthermore, pain can be influenced by the type of cancer, extent of disease, patient age and gender, and comorbidities. Therefore, effective cancer pain management involves not only a comprehensive initial assessment in terms of potential etiology and pathophysiology but also ongoing evaluation, so that changes over time and effectiveness of therapies can be adequately characterized. Specific features of the pain, including its severity, quality, location, frequency, and interference with function, should be carefully considered when making decisions about management.

Types of Pain

Pain can be broadly classified into three main types: (1) nociceptive, (2) neuropathic, and (3) psycho-
Pharmacologic management of cancer symptoms

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The Analgesic Ladder

In an effort to provide a general framework for the effective management of pain, the World Health Organization (WHO) published the three-step “analgesic ladder.” Initially introduced in the mid-1980s, it continues to be relevant and is integrated into a number of clinical practice guidelines. Briefly, the analgesic ladder proposes a stepwise approach to pain control and the choice of analgesic drugs based on pain intensity. For mild pain, acetaminophen and nonsteroidal anti-inflammatory drugs (NSAIDs) plus adjuvant analgesics are recommended; weak opioids (eg, codeine, tramadol) are used for moderate pain; and strong opioids (eg, morphine, oxycodone, hydromorphone, fentanyl, and methadone) are recommended for severe pain. Five additional principles should be underscored: (1) oral administration is preferred; (2) around-the-clock dosing should be prescribed for chronic pain; (3) drug choices are based on pain severity; (4) treatment must be individualized due to the inherent variability of analgesic responses among patients; and (5) constant attention must be given to assessments and re-evaluations. While the analgesic ladder was not developed based on empirical scientific evidence, it nevertheless offers a systematic approach to cancer pain management.

Opioids

Opioids remain the mainstay of treatment for cancer pain, due to their relative safety and reliability, variety in routes of administration, and efficacy in managing different types of pain. All opioids act by binding to specific pain receptors, namely, mu (μ), kappa (κ), and delta (δ) receptors, which are present throughout the body. In general, there is no clear evidence to support superior effectiveness or tolerability of any opioid agent over another, although there are a few notable exceptions. In renal failure, for example, morphine and codeine are contraindicated because their respective active metabolites can accumulate and contribute to increased toxicity;tramadol, hydromorphone, and oxycodone can be used with caution; and fentanyl or methadone are preferred.

Conveniently, patients who are opioid-naive are offered an oral non-opioid plus opioid combination drug first, such as acetaminophen plus codeine. For individuals presenting with moderate to severe pain at the outset, a reasonable strategy would be to start with a low dose of 5 to 10 mg of immediate-release oral morphine (or equivalent doses of oxycodone or hydromorphone; Table 1) every 4 hours. Sustained-release oral morphine of 15 mg every 12 hours is another option that can often enhance convenience and patient compliance but should be used selectively due to the longer duration of a single dose and possibility of toxicity. Methadone has been used as a first-line opioid and has the advantage of being less expensive than other opioids. Although an appropriate initial dose has not yet been established, one trial demonstrated that there was a greater opioid-related drop-out rate in patients receiving 7.5 mg methadone every 12 hours than morphine 15 mg every 12 hours, and that 5 mg twice daily is likely a safer initial dose. After selecting a starting dose of an opioid, dose adjustments are invari-

Table 1. Approximate Equi-analgesic Doses

<table>
<thead>
<tr>
<th>Opioid</th>
<th>Equivalent Dose (oral)</th>
<th>Parenteral: Oral Conversion Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morphine</td>
<td>10</td>
<td>1:2–3</td>
</tr>
<tr>
<td>Codeine</td>
<td>60</td>
<td></td>
</tr>
<tr>
<td>Hydromorphone</td>
<td>2</td>
<td>1:2–3</td>
</tr>
<tr>
<td>Tramadol</td>
<td>50</td>
<td></td>
</tr>
<tr>
<td>Oxycodone</td>
<td>5</td>
<td></td>
</tr>
</tbody>
</table>

NOTE. Doses are approximate, and are pragmatically based on commercially available formulations. At high doses, it is suggested to reduce the calculated dose by 30% to account for possible limited cross-tolerance.

10 Nociceptive pain typically results from somatic or visceral tissue injury; it is most commonly described as sharp, cramping, or stabbing in quality. In contrast, neuropathic pain stems from abnormal sensory function of the peripheral or central nervous system; pain that is reported as burning, numbing, or electrical in nature frequently suggests a neuropathic mechanism. Importantly, patients with neuropathic pain can present with additional neurological manifestations, such as sensory changes, muscle weakness, or autonomic dysfunction. Psychogenic pain due predominantly to the disease of cancer or other comorbid psychiatric diseases rarely occurs in isolation, but pain can certainly be aggravated by psychological distress. Conversely, psychological distress including depression often occurs as a consequence of pain, and treatment of the pain may alleviate the depression. Clarifying the type of pain and determining whether it is primarily disease-related or treatment-related are important, because this information can help to guide therapy and inform prognosis. Pain that is mainly due to the underlying cancer, for example, may respond quite effectively to antitumor therapies, such as radiation, chemotherapy, combined modality chemoradiotherapy, or even surgery in some cases.

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16 It nevertheless offers a systematic approach to cancer pain management.
ably required, and telephone follow-up should occur within a few days of starting a new regimen. It is always best to start with a lower rather than a higher initial dose to prevent toxicity; breakthrough pain is treated with short-acting doses of the same opioid agent, at 10% to 20% of the total 24-hour dose of the long-acting opioid.26

One of the advantages of opioids is that they can be administered via several routes. While the oral route is preferred due to its convenience and flexibility, many patients will require other routes of delivery at some point during their disease course. This is especially pertinent for patients with oral mucositis, odynophagia, dysphagia, nausea, or bowel obstruction, all of which can render oral agents either difficult to administer or less effective. In such cases, transdermal, rectal, subcutaneous, or intravenous formulations may be considered. Transdermal fentanyl, for example, is increasingly used for cancer pain,27 although it should not be used in opioid-naive patients due to its very long half-life. The usual starting dose is 12 μg per hour, which is equivalent to approximately 30 mg of oral morphine per 24 hours (Table 1).27 For incident pain, various routes of fentanyl and sufentanil are currently under investigation, including oral transmucosal, intranasal, and nebulized formulations. Although trials show promise in terms of the quicker action of the transmucosal route compared to oral morphine,28,29 these agents should not be used in opioid-naive patients, and further studies are necessary to determine safety, including potential for addiction.

### Nonsteroidal Anti-inflammatory Drugs

Because opioids can be associated with various side effects (Table 2), the comprehensive management of cancer pain frequently integrates the use of other analgesics to reduce the dose of opioids necessary to achieve sufficient pain control. NSAIDs represent a diverse group of drugs that reduces pain by inhibiting cyclo-oxygenase (COX) 1 and 2, thereby decreasing the production of prostaglandins.30,31 There is not one particular NSAID with more analgesic or anti-inflammatory properties than another, but selective COX-2 inhibitors are associated with fewer gastrointestinal (GI) toxicities than nonselective COX 1 and 2 inhibitors.30,31 This is especially relevant in oncology because many patients with cancer receive concomitant drugs (eg, chemotherapy, corticosteroids), which may also cause GI toxicities that can be potentiated with co-administration of NSAIDs. When used carefully either as a single agent or in combination with opioids, NSAIDs have a well-established role in the treatment of cancer pain. Added to an existing opioid regimen, these agents can improve pain control, allowing for a reduction in the opioid dose and minimizing opioid-related toxicities.30,31 A meta-analysis of patients on patient-controlled analgesia showed that NSAIDs significantly decreased nausea and vomiting by 30% and sedation by 29%, although there was no effect shown for pruritus, urinary retention, or respiratory depression.32

### Adjuvant Analgesics

The term adjuvant analgesics refers to medications that were originally developed for indications other than cancer-related pain but were subsequently found to be useful in its management.33 Examples include antidepressants, anticonvulsants, corticosteroids, and bisphosphonates. First-line adjuvants used for neuropathic pain are listed in Table 3. These include secondary amine tricyclic antidepressants (nortriptyline, desipramine), selective serotonin and norepinephrine reuptake inhibitors (duloxetine, venlafaxine), calcium channel α2-δ ligands (gabapentin, pregabaline), and topical lidocaine (for localized peripheral neuropathic pain).34-36 Similar to NSAIDs, combining opioids with adjuvants enhances neuropathic pain control and necessitates lower doses than if each agent is used individually.34,37,38 Adjuvants should always be given an adequate trial (Table 3) and titrated up until the pain is controlled, dose-limiting side effects occur, or the maximal effective dose is reached. If there is no response, a trial of another adjuvant in a different class should be initiated; if there is a partial response, a second adjuvant may be added. In a recent trial, combined gabapentin and nortriptyline was more efficacious than either drug given alone.39 It is important to note that the nature of the neuropathic pain—burning, numbing, or electrical—does not predict for level of response to any of these agents.

For cancer-related bone pain, bisphosphonates can play a significant role as adjuvant analgesics. While their onset of action may be slow, numerous trials have demonstrated their palliative benefit for this purpose.40,41 When instituted early in the course of bone metastases, they also can prevent fractures and decrease the risk of bone complications, such as hypercalcemia.40,41 Osteonecrosis of the jaw, while rare, is the most debilitating side effect; it is best avoided with

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**Table 2. Side Effects of Opioids**

<table>
<thead>
<tr>
<th>Side Effect</th>
<th>Side Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Constipation*</td>
<td>Hallucinations</td>
</tr>
<tr>
<td>Urinary retention</td>
<td>Fatigue</td>
</tr>
<tr>
<td>Nausea</td>
<td>Xerostomia*</td>
</tr>
<tr>
<td>Vomiting</td>
<td>Myoclonus</td>
</tr>
<tr>
<td>Sweating</td>
<td>Peripheral edema</td>
</tr>
<tr>
<td>Impotence</td>
<td>Hyperalgesia</td>
</tr>
<tr>
<td>Pruritus</td>
<td>Respiratory depression</td>
</tr>
<tr>
<td>Sedation</td>
<td>Drowsiness</td>
</tr>
</tbody>
</table>

*Occur in nearly all patients.
<table>
<thead>
<tr>
<th>Agent</th>
<th>Starting dose and Titration</th>
<th>Duration of Adequate Trial</th>
<th>Adverse Effects</th>
<th>Precautions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Secondary amine tricyclic antidepressants</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nortriptyline</td>
<td>25 mg every hour, increasing by 25 mg every 3–7 days, until pain relief or 150 mg daily</td>
<td>6–8 weeks with 2 weeks at maximum tolerated dose</td>
<td>Drowsiness, confusion, orthostatic hypotension, dry mouth, constipation, urinary retention</td>
<td>Contraindicated in glaucoma, symptomatic prostatism and significant cardiac disease</td>
</tr>
<tr>
<td>Desipramine</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duloxetine (D)</td>
<td>(D) 30 mg on demand, increasing to 60 mg on demand after 1 week, then until pain relief or 60 mg twice daily</td>
<td>(D) 4 weeks</td>
<td>Drowsiness, confusion, orthostatic hypotension, dry mouth, constipation, urinary retention</td>
<td>Contraindicated in glaucoma, symptomatic prostatism and significant cardiac disease</td>
</tr>
<tr>
<td>Venlafaxine (V)</td>
<td>(V) 37.5 mg on demand, increasing by 75 mg each week, until pain relief or 225 mg daily</td>
<td>(V) 4–6 weeks</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Calcium channel α2-δ ligands</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gabapentin (G)</td>
<td>(G) 100–300 mg every hour or 100–300 mg three times per day, increasing by 100–300 mg three times per day every 1–7 days, until pain relief or 1,200 mg three times per day</td>
<td>(G) 3–8 weeks during titration and 2 weeks at maximum dose</td>
<td>Dose-dependent dizziness and sedation</td>
<td>Dosage reduction required in renal insufficiency</td>
</tr>
<tr>
<td>Pregabalin (P)</td>
<td>(P) 50 mg three times per day or 75 mg twice daily, increasing to 300 mg daily after 3–7 days, then by 150 mg daily every 3–7 days, until pain relief or 200 mg three times per day or 300 mg two times per day</td>
<td>(P) 4 weeks</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Topical lidocaine</td>
<td>3 patches daily for a maximum of 12–18 hours</td>
<td>3 weeks</td>
<td>None</td>
<td>None</td>
</tr>
</tbody>
</table>
meticulous oral hygiene and ensuring that dental procedures, such as tooth extractions, are instituted prior to commencing bisphosphonate treatment. Corticosteroids are another example of an adjuvant analgesic that can be used to relieve bone pain. These agents are also useful to relieve headaches associated with brain metastases, back pain from spinal cord compression, and abdominal pain from bowel obstruction. In addition, they may improve anorexia, nausea, vomiting, and general sense of well-being. However, their effectiveness is generally limited to a few weeks; for this reason and because of their numerous side effects, their use should generally be limited to the acute management of pain rather than its long-term control.

**DYSPNEA**

**Background**

Unlike objective measures of breathing that include oxygen saturation and respiratory rate, dyspnea is defined as an uncomfortable, subjective awareness of breathing. Although dyspnea in cancer patients is most frequently caused by either primary lung cancer or pulmonary metastases, its etiology can be diverse and may also include congestive heart failure, pneumonia, pulmonary embolism, pleural effusion, anemia, chest muscle weakness, psychological distress, or any conditions associated with abdominal wall distension, such as ascites or severe, uncontrolled constipation. Importantly, dyspnea is experienced by many terminally ill cancer patients near the end of life, even in the absence of obvious cardiopulmonary pathology.

**Assessment of Dyspnea**

It is first essential to determine whether a patient’s dyspnea is secondary to a cause that is amenable to disease-specific treatments. Conditions such as pneumonia, pulmonary embolism, and anemia may be reversed with appropriate antibiotics, anticoagulation, and transfusions, respectively, and thus provide a meaningful palliative benefit to patients with advanced cancer. Because dyspnea is subjective, relying on physical findings can be misleading. The sensation of dyspnea is not always associated with signs of tachypnea or obvious use of accessory muscles. Conversely, patients may not feel short of breath even when such signs are apparent. Therefore, the most reliable component of the evaluation, whenever possible, is to ask patients directly how short of breath they feel.

**Oxygen Therapy**

Research has demonstrated the benefit of oxygen therapy for relief of dyspnea in patients with advanced cancer and hypoxemia. Palliative oxygen for non-hypoxemic patients is also widely prescribed, but its benefit in this situation is not supported by the available evidence. A meta-analysis of the few studies that have been conducted exclusively in patients with cancer (n = 134, four studies) demonstrated no benefit from oxygen therapy compared to medical air in mildly hypoxic or non-hypoxic patients. A recent international randomized controlled trial of 239 patients with life-limiting illness (16% had cancer), refractory dyspnea, and $P_{O_2} > 55$ again found no additional symptomatic benefit for relief of dyspnea with oxygen compared to room air by nasal cannula. Of note, patients did receive substantial benefit from both interventions, and trials investigating different flow rates of room air are indicated. When benefits did occur, they occurred in the first 72 hours of therapy; thus if oxygen is prescribed, it should be discontinued if there is no effect within 3 days. It has been proposed that oxygen therapy can stimulate the V2 branch of the trigeminal nerve, which itself may have a central inhibitory effect on dyspnea. Patients with dyspnea often report relief from air by fan directed at the face, and cold air directed on the cheek has been found to decrease dyspnea induced in healthy participants. This is an inexpensive intervention that warrants further investigation.

**Opioids**

For symptomatic control of dyspnea in patients with advanced cancer, opioids are the one class of agents with the most evidence of effectiveness, and are recommended in current palliative care practice guidelines. Their benefit in improving cancer-related dyspnea has been demonstrated in several randomized controlled clinical trials. However, the optimal choice of opioid—in terms of type of agent, starting dose, and route of administration—remains poorly defined. Most randomized controlled trials have used morphine, and most studies in patients with cancer have used the subcutaneous route, although in clinical practice the oral route is most often used. Several recent studies have confirmed that both in populations already on opioids and those who are opioid-naive, there was no evidence of respiratory depression during treatment of dyspnea with low-dose opioids. Nebulized opioids have appeared promising in some nonrandomized studies, but their efficacy has not been consistently demonstrated, and there is a lack of randomized trials in this area. One randomized study comparing nebulized morphine to subcutaneous morphine did not find a difference between the two...
groups, but this study was underpowered. Larger randomized studies are needed before a conclusion can be reached as to whether the aerosolized route is appropriate. In the meantime, oral or subcutaneous administration of opioids continues to be the treatment delivery of choice for the control of dyspnea in patients with advanced cancer.

Other Pharmacologic Therapies

Because a substantial number of patients with cancer-related dyspnea also have a prior history of smoking, many will benefit from interventions directed at managing reversible airflow obstruction caused by emphysema or chronic bronchitis. This may include the use of β-agonists or anti-cholinergics. Corticosteroids also may be useful in this situation, as well as in the treatment of lymphangitic carcinomatosis. Although benzodiazepines are frequently prescribed for dyspnea, there is scant evidence substantiating their use in patients without concomitant anxiety. A recent systematic review identified seven studies evaluating the effectiveness of benzodiazepines for dyspnea in cancer and COPD, and found a slight but nonsignificant trend towards a beneficial effect. One study conducted in patients with terminal cancer and life expectancy of less than 1 week where patients received 2.5 mg of subcutaneous morphine 4-hourly, midazolam 5.0 mg 4-hourly, or both, found that the combination regimen provided the greatest relief of dyspnea. However, all of these patients were previously using opioids, and had a performance status of 4 by Eastern Cooperative Oncology Group criteria. Until there is further evidence, it is reasonable to prescribe benzodiazepines for ambulatory patients who have dyspnea that is exacerbated by concomitant anxiety. Phenothiazines have similarly been used for dyspnea, although it is unclear whether their action is specifically on dyspnea or on the anxiety associated with it, and there have been no trials in patients with cancer.

There has been recent interest in the use of nebulized furosemide for dyspnea. A recent review article retrieved 42 studies; however, most of these evaluated pulmonary function rather than dyspnea, and were conducted on patients with asthma rather than cancer. Overall, a positive influence using doses of 20–40 mg was shown on dyspnea andphysiological measurements, although most studies were very small. The mechanism of action remains unknown, although animal and in vitro models have suggested several mechanisms, including activation of pulmonary stretch receptors and inhibition of vagal irritant receptors. The results thus far are encouraging and further adequately powered randomized studies are warranted, although currently this therapy cannot be recommended given the limited evidence.

Finally, cancer patients may occasionally experience dyspnea as a result of anemia, which can be a manifestation of the underlying cancer or a side effect of the cancer treatment. In this setting, definitive management of the malignancy with combinations of surgery, chemotherapy, and/or radiation may ultimately improve anemia in the long term and also ameliorate any related dyspnea. However, for rapid relief of symptoms, red blood cell transfusions are the most effective. Although erythropoiesis-stimulating agents (ESA) were shown to be effective in raising hemoglobin levels and decreasing transfusion requirements, its use for cancer-associated and chemotherapy-induced anemia has become controversial because of data linking ESA use to an excessive risk of thromboembolic events. In light of this evidence, transfusions appear to be the best option for cancer patients suffering from anemia-related dyspnea.

NAUSEA AND VOMITING

Background

Patients with advanced cancer may experience severe nausea and vomiting as a result of their cancer (e.g., bowel obstruction from GI cancer) or their ongoing treatment (e.g., chemotherapy, radiation to the GI tract, opioids). Although the two symptoms frequently occur together, nausea may be present without vomiting and vice versa. The awareness of nausea, the inability to take in fluids and food, the associated acidic and bitter tastes, and the smell of vomitus can be extremely distressing. Although nausea has many potential etiologies, chemotherapy-induced nausea and vomiting (CINV) is one of the most common. Because a fair number of patients remain on systemic therapy during the late stages of their disease, CINV can continue to be a major issue, even near death. The incidence of CINV is related to the actual chemotherapy drug; these can be divided into four categories, based on the anticipated degree of nausea and vomiting (Table 4).
involves combination regimens. The lining of the stomach and intestine, the chemoreceptor trigger zone in the 4th ventricle of the brain, the vestibular apparatus, and the cerebral cortex are all involved in the intricate pathophysiology of nausea and vomiting. Stimulation of one or more of these areas is mediated through various neurotransmitters, including serotonin, dopamine, acetylcholine, histamine, and substance P. For purposes of prevention and management, three distinct types of CINV have been described: (1) acute nausea and vomiting may start as early as 1 hour following chemotherapy, but more often begins 4 or more hours later; (2) delayed nausea and vomiting usually occur more than 1 day after chemotherapy; and (3) anticipatory nausea and vomiting typically happen prior to treatment as a conditioned response to significant nausea and vomiting during previous chemotherapy treatments. The latter is a learned response and thus is not mediated by the usual emetogenic neurotransmitters.

Management

Delineating the type of CINV that a patient is experiencing is important because this can guide management. Several classes of agents are commonly used in the treatment of CINV: (1) anti-serotonergics, (2) anti-dopaminergics, (3) neurokinin receptor antagonists, and (4) corticosteroids. The first two classes of antiemetics are most effective for the control of acute nausea, whereas they have minimal effect on delayed nausea. Granisetron and ondansetron are examples of anti-serotonergics, while examples of anti-dopaminergics include prochlorperazine, metoclopramide and haloperidol. Conventionally, the anti-serotonergics are reserved for use with chemotherapy that has moderate to high emetogenic potential, such as cisplatin, cyclophosphamide and anthracyclines. Neurokinin receptor antagonists (eg, aprepitant) and corticosteroids (eg, dexamethasone) have been shown to have a definitive, albeit modest, effect during the delayed phase of nausea. Management of anticipatory nausea and vomiting can be more challenging and its prevention should be a key priority. Once established, however, benzodiazepines may be useful due to their anxiolytic and amnestic properties. Psychotherapy with a particular focus on behavioral or cognitive interventions also can be considered.

Nausea Unrelated to Chemotherapy or Radiation Treatment

In patients with advanced cancer, the prevalence of chronic nausea that is not associated with chemotherapy can be up to 70%. The cause is most often multifactorial, with etiologies that include gastroparesis, treatment with opioids or other emetogenic agents, partial obstruction, hypercalcemia, constipation, oral infections, or brain metastases. Investigations should be conducted to rule out potentially reversible or treatable causes. In cases where it is not possible to identify or specifically correct the underlying etiology, empiric therapy with antiemetics should be offered, usually beginning with a single medication targeting the suspected mechanism of nausea and vomiting. The dose should be optimized before a second medication with a different mechanism of action is added. Correction of dehydration, hypokalemia, and metabolic alkalosis will sometimes also effectively resolve the symptom.

There have been two recent systematic reviews of management of nausea unrelated to cancer treatment. Both found that the evidence supporting existing consensus-based guidelines for management of nausea and vomiting in advanced cancer is sparse. It is generally suggested to treat nausea based on the neuropsychology of the putative emetic pathway. However, given the multifactorial nature of most chronic nausea, an empirical method of choice based on trial-and-error is recommended. Antiemetics common in existing guidelines with a lack of rigorous studies investigating other widely prescribed agents such as haloperidol, cyclizine and methotrimeprazine, but they are inexpensive, well-tolerated, and recommended in existing guidelines. More research is necessary before expensive agents such as the serotonin antagonists, olanzapine and 5HT3 receptor antagonists can be routinely recommended; constipation is a particular concern for 5HT3 receptor antagonists in view of the frequent occurrence of this symptom in patients with advanced cancer and its possible contribution to the nausea.

Opioid-induced nausea deserves particular mention due to its occurrence in up to 30% of patients, especially young women. The cause is thought to be due to direct effects of opioids on the chemoreceptor trigger zone and the vestibular apparatus. Anti-emergencies such as haloperidol or metoclopramide are generally used as first-line agents. Fortunately, patients generally develop tolerance to this opioid-related side effect within 1 week of initiating therapy, at which point the antiemetics can be discontinued. For some patients in whom the symptom is persistent or refractory, changing to a different opioid also may be effective. Nausea that emerges after chronic opioid use is most likely mediated through diminished gut motility or constipation that causes obstruction. Management is best directed at increasing gut motility with prokinetic agents or relieving constipation with laxatives.
SUMMARY

Advanced cancer symptoms, such as pain, dyspnea, and nausea, may be related either to the underlying disease or to its treatment, and can contribute to poor quality of life. The successful management of these symptoms requires a solid knowledge base regarding their pathophysiology, careful clinical assessment to target potential underlying causes, and the use of a combination of medications and interventions. The growing number of trials in this area increasingly allows for an evidence-based approach, with proven treatments replacing those for which there is consistently no evidence of benefit. Such an approach will maximize effect, reduce toxicities from ineffective treatments, and improve the overall well-being of patients with cancer.

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