Palliative Care and the Management of Common Distressing Symptoms in Advanced Cancer: Pain, Breathlessness, Nausea and Vomiting, and Fatigue

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INTRODUCTION

Most patients with cancer experience symptoms, the prevalence and severity of which vary according to cancer type, stage, treatment(s), and comorbidities.1-4 In advanced cancer, 35% to 96% of patients experience pain, 32% to 90% experience fatigue, and 10% to 70% experience breathlessness (Fig 1).2

Patients typically experience more than one symptom at any one time.5 Those with metastatic cancer and breathlessness (as a marker of advanced disease) have, on average, 14 symptoms.6 Grond et al5 found that 94% of those referred to a cancer pain clinic experienced additional symptoms, with 15% reporting at least five. Symptoms can be caused by the cancer itself, direct or indirect consequences of the cancer, early or late adverse effects of treatment, and/or comorbid conditions.7 The last two causes are becoming increasingly common as treatments advance and the population ages. Accurate symptom assessment and diagnosis are essential for effective treatment.8 Good symptom management is associated with improved patient and family quality of life, greater treatment compliance, and may even offer survival advantages. With population growth and aging, the proportion of patients with multiple symptoms—both related and unrelated to their cancer—is anticipated to increase, supporting calls for a more routine and integrated approach to symptom management. This article presents a summary of the literature for the use of symptom assessment tools and reviews the management of four common and distressing symptoms commonly experienced by people with advanced cancer: pain, breathlessness, nausea and vomiting, and fatigue. We also discuss the role of palliative care in supporting a holistic approach to symptom management throughout the cancer trajectory.

SYMPTOM ASSESSMENT TOOLS

Many symptom assessment tools are available for patients with advanced cancer, as exemplified by a survey of palliative care professionals (n = 331), in which 99 tools for clinical practice and 94 for research were identified.21 These assessment tools differ in various aspects, such as symptom selection, the inclusion of global quality-of-life questions, measurement of function, type of assessment scales (ie, visual analog numeric rating scale), and validation for research and/or clinical practice. Commonly cited tools for both clinical practice and research are the Edmonton Symptom Assessment System Revised (ESAS-r),22,23 the Palliative Care Outcome Scale (POS),24,25 and the Palliative Performance Scale.26

The incorporation of patient-reported outcome measures (PROMs) into routine clinical practice is supported by evidence that they improve symptom assessment and monitoring over time, help identify patients’ unmet needs or concerns, and assist clinicians with decision making and treatment planning.27-31 Examples of PROMs for patients with advanced cancer include the ESAS-r23 and the POS.25 The ESAS-r replaces the original ESAS that was first developed by Bruera et al22 in 1991. ESAS-r is a self-report...
tool, designed to capture multidimensional symptom profiles over time. It uses 11-point numeric rating scales to measure the intensity of nine symptoms (pain, tiredness, nausea, depression, anxiety, drowsiness, appetite, well-being, shortness of breath), and includes the option of measuring an additional patient-specific symptom. ESAS-r is validated for self- and proxy-reporting, has guidance on interpreting its numeric rating scale,23 and has transcultural adaptation for use in low- and middle-income countries.32

The POS was initially developed in 1999 as a tool to measure the palliative care needs of patients and their families. It has 10 items covering physical symptoms (n = 2), psychological symptoms (n = 2), spiritual considerations (n = 1), social needs (n = 4), and carer concerns (n = 1), with each item scored using a 0 to 4 (Likert) scale, with numeric and descriptive labels. The POS also includes a free text section, where patients are asked, “If any, what have been your main problems in the last three days?”33 A number of adapted POS versions now exist, including those specific to certain populations, for example, MyPOS for patients with myeloma.34 Transcultural adaptations are also available for more than 13 countries.35,36 All POS versions are validated for self- and proxy-reporting and have a clinical decision support tool to aid use.37

For older patients with advanced cancer, Van Lancker et al38 developed and validated the Assessment Symptoms Palliative Elderly, a 36-item instrument to assess symptom frequency and intensity. Although longer than ESAS-r and POS, the tool places a greater emphasis on assessing function, social symptoms, and psychological issues, all of which are prominent areas of concern for older patients with cancer.

Use of technology is likely to be an important and key component to implementing PROMs into routine clinical practice.39 Examples where integration has been successful include home asthma telemonitoring systems40 and Web-based support platforms for patients with insulin-dependent diabetes.41 In an oncology setting, Velikova et al42 found that regular repeated assessment of health-related quality of life of patients with cancer (using touchscreen computers in outpatient clinics) improved patients’ emotional well-being and resulted in more frequent discussions of chronic nonspecific symptoms. Similarly, in a randomized trial of 766 patients with metastatic cancer, Basch et al30,31 found that those receiving care incorporating routine patient-reported electronic monitoring of symptoms had greater improvements in health-related quality of life (34% v 18%), fewer emergency department visits or admissions to hospital (34% v 41% and 45% v 49%, respectively), and longer quality-adjusted survival (mean, 8.7 months v 8.0 months) compared with those receiving usual care. In a study of patients with lung cancer, Denis et al43-45 investigated the E-MOSAIC intervention, which used real-time electronic monitoring of PROMs, with measures completed weekly by participants on a palm-based device (ClinicalTrials.gov identifier: NCT00477919). They found that weekly reporting of symptoms resulted in improved survival compared with those receiving usual

FIG 1. Minimum-maximum symptom prevalence (%) for patients with cancer (n = total number of patients involved in the studies for each symptom). Adapted from systematic review findings of Solano et al.1

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care (median survival, 22.4 months vs 16.7 months). Compared with the control group, those in the intervention group also had greater improvements in symptoms, communication, and coping, but not overall quality of life.46

SYMPTOM MANAGEMENT

High-quality symptom assessment and management are fundamental to providing holistic, patient-centered care that results in positive outcomes for patients and their families. Despite their ubiquity, most symptoms experienced by patients with advanced cancer can be effectively managed using pharmacologic and/or nonpharmacologic approaches; symptom assessment and management is therefore an expected core skill of all clinicians involved in caring for patients with cancer. The following section reviews the latest evidence for the management of four symptoms commonly experienced by patients with advanced cancer: pain, breathlessness, nausea and vomiting, and fatigue.

Pain

Despite its ubiquity and the availability of management guidelines, more than 30% of patients with cancer receive inadequate analgesia for pain.47 Identifying the pain modality (nociceptive, neuropathic, or combined) helps direct effective therapy, with the WHO analgesic ladder providing a therapeutic framework.48

Nonpharmacologic treatments in the management of cancer pain include physical (massage, aromatherapy, transcutaneous electrical nerve stimulation, and acupuncture) and cognitive modalities (relaxation, distraction, and imagery exercises).49 Evidence to support the effectiveness of aromatherapy,50 transcutaneous electrical nerve stimulation,51 and acupuncture52 for reducing pain intensity in patients with cancer is lacking. For massage, study findings have been mixed, although most positive effects are not sustained beyond the intervention period or immediately after it.49 For cognitive modalities, evidence supports immediate reductions in pain intensity; however, similar to the finding for massage, evidence to support sustained reductions in pain are lacking.53,54

For the pharmacologic management of mild to moderate pain, nonopioid analgesics, such as acetaminophen and nonsteroidal anti-inflammatory drugs, remain widely used in clinical practice. Opioids for mild to moderate pain are added at step two of the WHO analgesic ladder. Codeine phosphate and/or tramadol are commonly used, although this is supported by limited evidence. Two recent Cochrane reviews found only weak evidence to support their use,55,56 and some authors have suggested bypassing step two of the WHO analgesic ladder and proceeding directly from step one to step three.57,58 Opioids, specifically morphine, remain the first-choice analgesic for moderate to severe cancer-related pain. A 2017 review of nine systematic reviews, (incorporating 152 individual studies) examining any opioid for cancer-related pain found that, on average, 19 of 20 patients with cancer with moderate or severe pain who receive opioids and can tolerate them will have their pain reduced to mild or no pain within 14 days.59 Opioids should be given orally where possible and titrated individually to the lowest effective, tolerable dose.58 Either immediate- or modified-release preparations can be prescribed regularly, with immediate-release preparations also available as required for breakthrough pain.60 No evidence of superiority across opioids for moderate to severe pain exists; morphine remains the first-line opioid of choice in international guidance because of its familiarity, availability, and cost.58 Fentanyl and buprenorphine are recommended in renal impairment (estimated glomerular filtration rate < 30)61 when morphine is contraindicated.51 Despite limited evidence, switching between opioid preparations is common practice when the first-line opioid chosen is ineffective or poorly tolerated.52 Adverse effects from opioid therapy are common and predictable.59 Constipation, nausea, and vomiting are most commonly reported, and guidelines recommend the use of laxatives with all opioid prescriptions.58

More than 20% of patients with cancer experience neuropathic pain.63 Although anticonvulsant or antidepressant medications are considered standard treatment of nonmalignant neuropathic pain, evidence for their effectiveness in cancer is mixed. A meta-analysis of four randomized controlled trials (RCTs) found no analgesic benefit from adding pregabalin or gabapentin to opioids in patients with cancer-related pain.64 By comparison, Jongen et al65 found antdepressants and anticonvulsants effective and well tolerated in patients with confirmed cancer-related neuropathic pain, and in a separate double-blind crossover RCT, an opioid-sparing effect was found with the addition of pregabalin to opioid therapy.66 As such, neuropathic pain agents remain recommended in international pain guidelines and should be considered an appropriate adjunct to opioids for patients with neuropathic pain.58 Ketamine has not been shown to be effective for patients with cancer-related neuropathic pain, although it may have a role in a specific subsection of patients with hyperalgesia.67,68 A Cochrane systematic review found a lack of evidence to support the use of methadone as an adjuvant for cancer-related neuropathic pain.69 Limited data suggest that it may have a role in patients with cancer-related pain unresponsive to morphine or other opioids.70 Its complex pharmacology necessitates use by specialist physicians.

There is mixed evidence to support bisphosphonates for cancer-related bone pain. One systematic review found that 22 of 28 RCTs did not identify any analgesic benefit.71 However, a meta-analysis of studies including only patients with multiple myeloma (n = 8) found a difference in amelioration of pain with use of bisphosphonates compared with placebo or no treatment (pooled risk ratio, 0.75; 95% CI, 0.60 to 0.95), although the overall quality of evidence was found to be low.72 By comparison, radiotherapy has been shown to be highly effective in the management of
cancer-related bone pain. A meta-analysis found that almost a third of those treated with radiotherapy experienced total resolution of pain at 4 weeks, with a single fraction of 8 Gy being effective.73 Specialist pain interventions, for example, nerve blocks, should be considered in patients with moderate to severe pain refractory to standard pharmacologic treatments.58

**Breathlessness**

Breathlessness is a common symptom that becomes increasingly prevalent as disease progresses.74,75 Refractory breathlessness (that which persists despite optimal treatment of the underlying condition) is associated with a shortened life expectancy,6,77 can be especially frightening for patients and families,78,79 and often results in use of acute hospital services.80,81 Despite increased understanding of the mechanisms of breathlessness, new and effective treatment options remain elusive.84 Thus, clinicians also experience distress when faced with refractory breathlessness because of the limited availability of effective interventions.5,78,79

Management should start with optimizing the treatment of any underlying causes of breathlessness, especially bronchoconstriction. Nonpharmacologic treatments should then be considered, in particular, positioning and breathing techniques, mobility aids, and muscle strengthening.85 The importance and potential effectiveness of simple aids, such as a hand-held fan, should also not be overlooked.86 For pharmacologic treatments, the European Respiratory Society and American Thoracic Society have both concluded that beyond oxygen and opioids, there is no robust evidence for other pharmacologic agents.88,89 Oxygen has a clear and accepted role for patients with hypoxia. However, in patients with mild or nonhypoxemic breathlessness, the benefit derived from oxygen is similar to medical air, and there are limitations to its use (eg, safety, cost).88,89 Relevant systematic reviews of effectiveness and clinical trials are available for opioids, oxygen, and benzodiazepines.88,90-95 Although opioids by mouth and injection can reduce breathlessness, their effects are modest or small, and the optimal dosing, titration, and potential issues arising from long-term use (eg, safety, tolerance, dependence, misuse) remain to be determined.90,96 The evidence from Cochrane reviews does not support a role for benzodiazepines, except as second- or third-line treatment if opioids fail, because there is no overall evidence of benefit and some evidence of possible harms.94

Holistic breathlessness services combine tailored nonpharmacologic and pharmacologic breathlessness management,97 typically with input from multiple specialties and professions (eg, medicine, nursing, physiotherapy).98 Such services represent an evidence-based means for early integration of palliative care on the basis of need rather than prognosis.99 They are highly valued by patients and their carers and overall can lead to significant improvements in distress due to breathlessness and aspects of psychological health, including depression.97 In a single-blind randomized trial, Higginson et al88 assessed the effectiveness of a new breathlessness support service compared with usual care for patients with advanced disease and refractory breathlessness. The service comprised an initial outpatient clinic appointment with respiratory medicine and palliative care clinicians during which time patients were also provided with a breathlessness pack that included information, management, and pacing guidance, a hand-held fan or water spray, a poem (a short mantra to help breathing and relaxation during crises), and an individualized crisis management plan. Approximately 2 to 3 weeks later, patients received a home visit by a physiotherapist and/or occupational therapist to assess their need for aids and adaptations, as well as to reinforce self-management of breathlessness and provide additional guidance on pacing and exercises. A second and final outpatient appointment with a palliative care specialist followed and allowed any additional actions to be incorporated and a discharge plan to be developed.98 The study found significant improvements in breathlessness mastery in the breathlessness support service group compared with the control group (mean difference, 0.58; 95% CI, 0.01 to 1.15), as well as improvements in overall survival for patients with chronic obstructive pulmonary disease and interstitial lung disease but not cancer.98

**Nausea and Vomiting**

Nausea, defined as the unpleasant subjective feeling of wanting to vomit or retch, and/or vomiting,100 are experienced by as many as 68% of patients with cancer at some point during their illness; during the last 6 weeks of life, the prevalence of nausea and vomiting is 40% or more.101 Poorly controlled nausea and vomiting is associated with physical, cognitive, and psychosocial distress, and can contribute to patient and family fears of death from dehydration and/or starvation.102,103

Nausea and vomiting secondary to antineoplastic agents or radiation therapy should be anticipated and managed according to ASCO antiemetic, or equivalent, clinical practice guidelines.104 The latest ASCO antiemetic update includes evidence-based recommendations and information on the appropriate use of olanzapine, neurokinin 1 receptor antagonists, and use of subcutaneous 5-hydroxytryptamine-3 receptor antagonists.104

Much less trial evidence is available for the use of antiemetics in patients with advanced cancer and nausea and vomiting unrelated to antineoplastic agents or radiation therapy.105,106 Instead, an etiologic or mechanism-based approach to choosing an antiemetic is commonly recommended.107 This approach requires clinicians to take a detailed history and perform a focused examination to determine the most likely underlying cause(s) of the patient’s nausea and vomiting. In the advanced cancer population, the most common underlying causes of nausea
and vomiting are chemical abnormalities (eg, renal or liver failure, hyponatremia, hypercalcemia); drugs (eg, opioids, antidepressants, antibiotics); infection; and impaired gastric emptying, as well as visceral and serosal causes of delayed gastrointestinal transit (bowel obstruction, gastric bleed, enteritis, constipation).\textsuperscript{108-111} Once the most likely underlying cause of the patient’s nausea and vomiting is determined, an appropriate antiemetic can then be selected based on the pathophysiology and receptors implicated (Table 1).\textsuperscript{108}

Unless contraindicated, antiemetics should be prescribed regularly and with a low threshold for being administered parenterally. If, despite titration, treatment with a single agent remains ineffective, a second-line antiemetic should be commenced. The addition of a second-line antiemetic is preferred over switching, because cancer-related nausea and vomiting is often multifactorial, involving multiple neurotransmitters and receptor sites. Currently, only limited and low-quality evidence exists for the use of corticosteroids,\textsuperscript{112} olanzapine,\textsuperscript{113} and cannabinoids\textsuperscript{114,115} for nausea and vomiting that is not secondary to antineoplastic agents or radiation therapy. Nonpharmacologic measures, such as dietary advice,\textsuperscript{116} psychological services,\textsuperscript{117} and acupuncture/acupressure,\textsuperscript{118} may offer some benefit when used alongside standard pharmacologic approaches, although again, evidence of their effectiveness for nausea and vomiting unrelated to antineoplastic treatment is limited.

### Fatigue

Fatigue is “a subjective, unpleasant symptom which incorporates total body feelings ranging from tiredness to exhaustion creating an unrelenting overall condition which interferes with individuals’ ability to function to their normal capacity.”\textsuperscript{119(p527)} The severe and unrelenting nature of fatigue negatively affects patients and those close to them.\textsuperscript{120,121} It is highly prevalent, affecting three quarters of patients with advanced cancer, perhaps related to the proinflammatory state that plays a role in its pathogenesis.\textsuperscript{122} Other contributing factors include anemia, malnutrition, neuro-endocrine impairment, and muscle dysfunction.\textsuperscript{123} Assessment of fatigue can be via single-item tools (eg, 0 to 10 numeric rating scale), unidimensional (eg, Functional Assessment of Cancer Therapy: Fatigue), or multidimensional (eg, European Organisation for Research and Treatment of Cancer QLQ-FA13 and Chalder Fatigue Scale) scales (for a comprehensive review, see Minton and Stone\textsuperscript{124}).

Both nonpharmacologic and pharmacologic treatments for fatigue are available. These should be considered once treatment of any underlying/reversible causes of fatigue have been optimized. Proactive monitoring and protocolized management of physical symptoms can improve general fatigue, as well as affect activity levels and motivation.\textsuperscript{125} The use of exercise for fatigue is supported both during and after anticancer treatment (standardized mean difference [SMD], \(-0.27; 95\%\ CI, -0.37\) to \(-0.17\)).\textsuperscript{126}

### Table 1. Etiology-Based Guidance for Antiemetic Prescribing

| Nausea and Vomiting Etiology | Mechanism and Receptors Implicated | First-Line Drug Options |
|------------------------------|-----------------------------------|-------------------------|
| Nausea and vomiting unrelated to antineoplastic agents or radiation therapy | See specific ASCO guidance: [https://www.asco.org/practice-guidelines/quality-guidelines/guidelines/supportive-care-and-treatment-related-issues](https://www.asco.org/practice-guidelines/quality-guidelines/guidelines/supportive-care-and-treatment-related-issues) | |
| Chemical/metabolic | Stimulation of CTZ (D2) | Haloperidol |
| Drugs (not antineoplastic, eg, opioids) | Stimulation of CTZ (D2) | Haloperidol |
| Impaired gastric emptying/gastric stasis | Gastroparesis (D2) | Metoclopramide |
| Visceral/serosal causes of delayed gastrointestinal transit | Malignant bowel obstruction (stimulation of CTZ [D2]) and/or stimulation of peripheral pathways (muscarinic acetylcholine receptor, H1) | Cyclizine |
| Cranial causes | Activation of meningeal mechanoreceptors secondary to meningeal irritation with or without increased ICP | Cyclizine (with or without dexamethasone for increased ICP) |
| Vestibular causes | Stimulation via vestibulocochlear nerve (muscarinic acetylcholine receptor, H1) | Cyclizine |

NOTE. Treat reversible/underlying causes of nausea and vomiting where appropriate/possible. Prescribe most appropriate first-line antiemetic (on the basis of likely etiology) regularly and as needed; review at least every 24 hours. Consider parenteral administration if oral absorption in doubt.

Abbreviations: CTZ, chemoreceptor trigger zone; D2, dopamine type 2; H1, histamine type 1; ICP, intracranial pressure.
with consistent secondary effects on depression and sleep quality, although most studies are limited to patients with primary breast cancer receiving adjuvant chemotherapy or patients with prostate cancer. The strongest evidence is for aerobic exercise (eg, walking, cycling). Resistance training may have an additional role in cancers where cachexia is highly prevalent, for example, lung and pancreatic, although studies for these groups are fewer in number and smaller.

Evidence is relatively weaker and less consistent for other nonpharmacologic treatments, although arguably more applicable, being limited to those with advanced, incurable disease. There is restricted support for psychosocial interventions, including cognitive behavioral or expressive group therapies (SMD, −0.25; −0.50 to 0.00), although benefit has been found after cancer treatment. Educational interventions involving information giving with reinforcement or problem-solving led to small improvements in fatigue intensity (SMD, 0.28; 95% CI, 0.09 to 0.48), but the anxiety-relieving effect is stronger. There is insufficient evidence for complementary and alternative medicines, including acupuncture and hypnosis.

Once nonpharmacologic treatments have been used, the psychostimulant methylphenidate can be considered. In 2011, a meta-analysis of five psychostimulant trials, four of which related to methylphenidate, found an overall SMD for psychostimulant use of −0.28 (95% CI, −0.48 to −0.09). However, more recent and larger RCTs have found methylphenidate to be ineffective for the management of cancer-related fatigue, with evidence of benefit limited to patients with narcotic-induced fatigue and/or depression. Evidence for modafinil is mixed, with two trials concluding either no benefit or benefit only with severe fatigue. For patients with anemia, including during chemotherapy, the hemopoietic growth factor erythropoietin reduces fatigue (SMD, −0.36; 95% CI, −0.46 to −0.26), whereas evidence for darbepoetin is less consistent. Single trials support short-term use of dexamethasone, although efficacy and safety beyond 2 weeks are undetermined. There is currently no evidence of benefit from L-carnitine supplementation, progesteroidal steroids, or paroxetine.

In summary, most patients with advanced cancer experience symptoms throughout the disease trajectory, often with greater intensity as death approaches. If poorly managed, such symptoms can have a considerable impact on patients’ ability to function, quality of life, ability to comply with anticancer treatments, and use of health care resources. All clinicians involved in the care of patients with cancer should be competent in symptom assessment and management. For complex, multiple, and/or refractory symptoms, patients may benefit from additional support services, such as those provided by specialist palliative care. Multidisciplinary palliative care teams have been shown to improve patient outcomes and current ASCO guidelines therefore recommend that patients with advanced cancer should receive dedicated palliative care services, early in the disease course, and concurrent with active treatment. At a service level, managers and policymakers should consider incorporating routine screening of symptoms into usual care structures, with evidence that symptom assessment tools can improve patient outcomes and possibly even survival.

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